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ABSTRACT BOOK

XXII CONGRESSO

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Roma, 17-20 novembre 2012

Erfige Palace Hotel

Associazione Italiana Radioterapia Oncologica

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Main Program

SIMULTANEOUS INTEGRATED BOOST: RADIOBIOLOGICAL AND CLINICAL IMPLICATIONS

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The employ of a "boost" dosage to small fields in radiotherapy clinical practice is ancient as the 2D technique. The first rationale is always the aim to reduce the dose delivered to healthy tissues without loosing the chance of primary tumor local control. The main biological evidence is the clinically inferred inhomogeneity in tumor cell density. For microscopic disease in regional lymphonodes a lower dose is required for tumor control than for macroscopic primary tumor. The boost fields for the macroscopic tumor can be combined at the end of the large fields for microscopic disease treatment schedule as "sequential boost". Further the boost fields can be combined after daily or weekly large fields treatment session as a "concomitant boost" or can be delivered combined after every large fields treatment session including in the planning calculation the dose for the boost fields as "simultaneous boost". More recently the use of IMRT, associated with significant dosimetric improvements, as compared to conventional 3D, allows the simultaneous delivery of different dose levels to different target volumes within a single treatment fraction as "Simultaneous Integrated Boost" (SIB). As a result of this approach the high-risk volume can be treated with fewer fractions compared to conventional schedules with the reduction of nominal dose balanced by a reduction of overall treatment time (OTT). By this way the reduction of OTT by SIB set the acceleration of the treatment schedule as a Simultaneous Modulated Accelerated Radiation Treatment (SMART). The rationale of SIB should be summarized as a technical approach to manage the heterogeneity of tumor burden sites, a biological approach to increase the efficacy of the dose delivered to the target by shortening overall treatment time and delivery treatments with altered fraction doses and also a physical approach to obtain a high conformation of dose distribution to spare healthy tissues. The linear quadratic model (LQ) describes the observation that a change in dose per fraction has less effect on early responding tissue and rapid proliferative tumors than on late responding tissues. Such a model is essential to evaluate not only normal tissue and tumor response within the target volume but also normal tissue damage outside the target volume where the local dose per fraction can be well below 2Gy (the standard fraction dose in clinical practice). Therefore the validity of SIB approach depends on different factors strongly linked to the radiobiological basis of radiation effects on tumor cells, acute and late responding healthy tissues. The impact of OTT on tumor response is based on the assumption that the reduction of treatment duration minimizes the risk of tumor colognes proliferation during the last phase of treatment. Commonly to increase the tumor control probability a dose escalation with conventional fractionation is performed, but is always associated with the prolongation of OTT, some of the potential gain may be lost as a consequence of tumor-cell repopulation. On the other and for tumors with a high α/β ratio, less sensitive to fraction dose modification, decrease in total dose achieved with SIB may lead to a reduction in tumor control probability. However, this negative effect may be compensated by the shorter overall treatment times often used for the moderate hypofractionation (fraction size to boost site higher than 2Gy) and acceleration of SIB. Tumor hypoxia gives a contribution to tumor cells resistance to radiation. The SIB strategy might allow overcoming inhomogeneity of hypoxic and oxygenated cells within tumor volume, giving higher fraction dose to the more radio-resistant hypoxic clonogens. The managing of altered fractionation regimens by the use of SIB strategy can't forget the radio-sensitivity that marks healthy tissues. For both acute and late responding normal tissues the SIB strategy give the advantage of a great conformation of the dose around the target with a spare from higher doses for tissues around the target. However functional and healthy tissues are also strongly involved in the tumor

volume and the fractionation strategy has to face their radiobiological differences. For the late responding tissues, with a slow cellular turnover, for an increment in the dose fraction size the radiobiological expectation is that the therapeutic ratio between tumors and late-responding normal tissues will be lower, compared with conventional fractionation given in the same overall time. On the other and managing acute responding tissue as mucosa cell damage and regeneration might be twofold, because shortening the OTT do not give the time to acute responding tissue to regenerate the damage induced by radiation but on the other a reduction of OTT might be so substantial to not allow a clinical appearance of DNA radiation induced damage during the treatment time. In clinical practice most of data are coming for treatment of head and neck neoplasm, were the cell repopulation represent a high risk of relapse. SIB is largely employ in nasopharyngeal tumors were the IMRT is strongly recommended as appropriate treatment. From the evidence of the good local control achieved with "concomitant boost", many investigational protocols are running on breast cancer treatment. There are little evidence but many ongoing schedules also for the treatment of gastrointestinal district as rectum and anal canal cancers. The SIB is investigate also in the field of palliation of brain metastases with aim of increase the dose to the lesions site maintaining the conventional palliative fractionation dose to whole brain. The SIB can be a smart biological tool to investigate altered fractionations tailored on different diseases and different anatomical sites with the clear advantages of a great sparing of normal tissues and a good compliance for patients that undergo to shorter daily sessions and often shorter overall treatment time. As all the technology advanced technique require a quality assurance in terms of planning and treatment delivery. First of all the target definition for SIB delivery should be an integration of functional and appropriate morphological imaging. The reproducibility of the planned dose is essential to investigate a technique with steep gradient of dose around the target and with such radiobiological implications. Is to be considered investigational in most of the diseases.

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INTEGRATED APPROACHES IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Lung cancer remains a major public health problem worldwide because of its high incidence, rapid progression, and poor outcome. In locally advanced non-small cell lung cancer (LA-NSCLC) neoadjuvant setting is the best way to explore personalised treatment strategy. Trimodality therapy (radiation, chemotherapy and surgery) has been investigated in two famous randomized trials. INT 1039 published by Albain1 compared concurrent radiochemotherapy followed by surgery to definitive chemoradiation in stage IIIA patients. Progression-free survival was significantly improved for patients who underwent surgery (13 *vs* 10.5 months), but there were no significant differences in 5-year overall survival rates (27% *vs* 20%). An exploratory hypothesis- generating analysis of this trial suggested that patients undergoing pneumonectomy fared poorly when compared with the matched cohort of chemoradiotherapy patients and patients who underwent a lobectomy may fare better than those treated with concurrent chemoradiotherapy. A recent phase III trial also compared the benefit of surgery or radiation therapy after induction chemotherapy for stage IIIA NSCLC patients. The European Organization for the Research and Treatment of Cancer (EORTC) conducted a trial in which patients received 3 cycles of platinum-based chemotherapy followed by randomization to either surgery or 60 Gy of thoracic radiation2. There was no difference in median, progression free, or overall survival outcome between the 2 arms. Even if these phase III trials failed to show a survival benefit to surgery in the management of N2 patients, several observations arise from literature regarding type of surgery (pneumonectomy *versus* lobectomy), radiotherapy technique and patients selection. However, in both trials local tumour progression was approximately reduced by 50% by the addiction of surgery3 so intervention remains an attractive treatment option. Neoadjuvant chemoradiation delivered with a combination of cisplatin and etoposide (which is the old standard association) in selected patients offers a nodal clearance of 37% with a pathologic Complete Response (pCR) ranging from 14 to 17%, 4-6. A retrospective study published by Higgins and colleagues 7 showed a mediastinal pathological complete response (pCR) of 35% after preoperative chemotherapy *versus* 65% after preoperative chemoradiation (p=0.01). On multivariate analysis a mediastinal pCR was associated with improved DFS and LC but not OS. More recently, some third generation compounds have been added to cisplatin or carboplatin to improve these results. Different trials explored the adding of taxanes to radiotherapy and platinum compounds, but the reported results are generally poor with a pCR ranging from 3.8 to 11% with both paclitaxel or docetaxel 8-11. Gemcitabine (2-2'-difluorodeoxycytidine) is a well known cytotoxic drug and a potent radioenhancer. *In vitro*, the radiosensitization is dose and time dependent, also at a noncytotoxic concentration, and it is greatest when exposure to drug precedes radiation. Its radiosensitization activity has been correlated with the ability to deplete dATP pools through the inhibition of the ribonucleotide reductase by the difluorodeoxycytidine diphosphate 12. Adding a full dose of cisplatin to weekly gemcitabine in the neoadjuvant setting, results in a pathologic CR rate of around 30% with a nodal clearance in 50% of patients 13. Nowadays, in

metastatic setting, chemotherapy compounds are generally given according to tumor histology 32 with pemetrexed as an active drug in non-squamous histology *vs* gemcitabine as more effective in squamous one's. Both drugs have a radioenhancer effect 12,15 and could be administered concurrently with radiation 16-17. Actually few data are available according to this issue and generally refer to retrospective analysis 18. In locally-advanced unresectable NSCLC standard treatment is chemoradiation and concurrent modality offers the best results. Two new articles confirm this affirmation. At JCO May 2010 Auperin at al 19 reported a new meta-analysis which undertook systematic searches for trials, followed by central collection, checking, and reanalysis of updated individual patient data (1205 patients). Concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control. There was a significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; p =.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; P =.01); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; P =.69). The benefit was also confirmed in elderly patients (more than 70 years) with good performance status. In January 2010 Cochrane Lung Cancer Group 20 published an update of the reviews in 2004 incorporating additional trials and more mature data. It demonstrates the benefit of concurrent chemoradiation over sequential treatment with a 10% absolute survival benefit at 2 years (HR 0.74, 95% CI 0.62 to 0.89). Authors underlined that patient selection is an important consideration in view of the added toxicity of concurrent treatment. Uncertainty remains as to how far this is purely due to a radiosensitising effect and whether similar benefits could be achieved by using modern radiotherapy techniques and more dose intensive accelerated and/ or hyperfractionated radiotherapy regimens. In 2011, Curran reported the updated results of RTOG 9410 21 comparing sequential arm with concurrent and concurrent/hyperfractionated ones. 601 patients were randomized and survival data at 11 years reported. Concurrent arm obtained the better survival in comparison with both sequential and concurrent/hyperfractionated arm. Another confirmation of no benefit of altered fractionation is the CHARTWEL trial 22 in which no significant survival benefit is reported. Even if concomitant treatment is considered the gold standard 23, the question of which drug is the best solution for concurrent radiochemotherapy is still open. As previously reported, the role of histology in drug selection is an actual issue and a phase III trial are testing this hypotesis (PROCLAIM Trial). Nowadays, the debate around the role of induction and consolidation chemotherapy is not closed. Both solutions demonstrated no survival improvement in comparison with concurrent radiochemotherapy 24-26. However, induction chemotherapy to chemoradiation (with a maximum of 2-3 cycles) has theoretical advantages such as: 1) decrease in tumor volume; 2) decrease in irradiated volume and 3) identification of a good prognostic group before chemoradiation. So, it could be an useful approach in order to reduce target volume and consequently reducing toxicity and escalating radiotherapy dosage. The nationally accepted standard radiation prescription dose has remained at the same level (60–63 Gy) for more than 30 years27. Doses in this range provide inadequate local control28. Results from studies of stereotactic radiation therapy for lung cancer estimate that biologically equivalent doses of 100 Gy are needed to achieve local control for the small-volume stage I lung cancers treated with that technique29. In stage III disease, RTOG 9311 employed 3DCRT to safely escalate a fractionated radiation dose to 83.8 Gy in patients who did not receive concurrent chemotherapy30. The RTOG 0117 reported the feasibility of escalated total dose (74Gy) with concurrent chemotherapy31. These encouraging results served as projection expectations for the high-dose radiation arms of the current RTOG 0617, which is a phase III intergroup trial (RTOG 0617/ NCCTG N0628/ CALGB 30609) testing 74 Gy *versus* 60 Gy with concurrent chemotherapy for patients with inoperable stage III NSCLC. The recent years have seen significant gains in the understanding NSCLC biology and growth factors signalling with the development of target therapies. Significant advances have also be made in radiation dosimetric planning, tumour imaging and treatment delivery techniques that allow to assess and account for uncertainties.

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BREAST AND LUNG TUMORS

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Breast tumors

Effects of radiotherapy after breast conserving surgery on recurrence rate and breast cancer death: It is well known that postoperative radiotherapy (RT) after breast conserving surgery (BCS) reduces the risk of local recurrences and has a smaller but statistically significant impact on overall survival. The Early Breast Cancer Trialist's Collaborative Group published on Lancet in 2005 an overview of 11 trials, showing an absolute risk reduction for isolated local recurrences of 16,1% in N0 patiients and of 30% in N+ patients at 5 years, and a reduction of the risk of death at 15 years ranging from 5.1% (N0) to 7.1% (N+). In 2011 the same group published the results of a meta-analysis of individual patient data for 10801 women in 17 randomised trials (Lancet 2011, 378: 1707-1716). The analysis confirmed that after breast conserving surgery, radiotherapy halves the risk of disease recurrence and reduces the breast cancer death rate by about a sixth. These proportional benefits vary little between different groups of women. By contrast the absolute benefits of radiotherapy vary substantially and they can be predicted at the time when treatment decisions need to be made.

Partal breast irradiation: The deeper knowledge of factors which impact on individual risk of recurrence after BCS has pushed forward the ongoing studies on partial breast irradiation. Now we can define with greater appropriateness patients with a low risk of recurrence, and select those in which a more conservative approach of radiotherapy can be tested. The group from European Institute of Oncology published recently their results with intraoperative radiotherapy (IORT) in 1822 patients trea-

ted outside the ELIOT protocol. The 5 years ipsilateral breast recurrence rate in the group of patients which meets the ASTRO criteria for "suitable" group is 1,5%, while the recurrence rate is 4,4% in the "cautionary" group and 8,8% in the "unsuitable" group. These results give further evidence to the efficacy of PBI, irrespectively from the technique employed, in selected groups of patients. The publication of the results of the ELIOT trial is pending. These data, together with those which will come from the several ongoing randomised studies (NSABP-RTOG, RAPID, IRMA, IMPORT ecc.) will help us to identify patients in which PBI can be used safely.

Treatment of the axilla: The publication in 2011 of the ACOSOG Z 0011 trial changed radically the management of patients with clinically negative axillary nodes. The study showed that in patients with early (< 2)sentinel node metastases at sentinel node biopsy (SNB), axillary lymph nodes dissection (ALND) does not modify survival (5 years disease free survival: 82,2 with ALND, 83,9% with SNB). No patients were permitted to have irradiation of the axilla. Tangential fields can however provide incidental dose to level I-II axillary nodes, and the impact of this dose to disease control in the axilla is unknown. Further efforts must be made to define subgroups of patients (e.g.: small tumors, low grade, estrogen receptor positive tumors) in which a more conservative axillary surgery is appropriate.

Postmastectomy radiotherapy in patients with 1-3 positive lymphnodes: The indication for adjuvant postmastectomy radiotherapy (PMRT) in patients with 1-3 positive lymphnodes is a controversial issue. In the 2005 review of the Early Breast Trialist's Collaborative Group, a survival benefit from PMRT was documented and in a recent consensus report from St. Gallen 2009 the use of PMRT was recommended in young patients with high risk disease In 2011 the Danish Breast Cancer Group Radiotherapy Committee published recently an analysis of different studies of PMRT, and strongly recommended PMRT also in patients with 1-3 positive lymphnodes, since in all studies patients submitted to PMRT showed a significant improvement in local and regional recurrence rate (relative risk reduction 15-30%) and, to a lesser extent (1-10% risk reduction), in overall survival compared to patients treated with mastectomy only. Also in this case we need to identify subgroups of patients at higher risk, to avoid overtreatment of a consistent portion of women.

Non Small Cell Lung Cancer (NSCLC)

Early stage tumors (T1-T2, N0): Stereotactic radiotherapy (SRT) can be now defined a standard technique in the treatment of early NSCLC with a poor performance status. These results have closely matched those obtained with surgical resection. Currently there is a lot of enthusiasm regarding the development of SRT in operable patients. The Japan Clinical Oncology Group has completed a phase II trial comparing 48 Gy/4 fraction to surgery. Other such study are the Dutch ROSEL study and the STARS study. The results of randomised trials in early operable NSCLC comparing surgery with SRT are eagerly awaited. A better knowledge of fraction size according to the site of the tumor, the more and more widespread use of image guided radiotherapy, the possibility to manage respiratory motion (4D CT, gated irradiation, breath control techniques), give us the means to perform SRT safely also in central tumors and in tumors larger than 3 cms.

Locally advanced disease (stage IIIA and IIIB): Concomitant radiochemotherapy is still to be considered the standard treatment in good performance patients with locally advanced NSCLC. In recent years there has been undoubted progress in the development of targeted agents for NSCLC. In this molecular era there is limited understanding of how best to combine targeted agents with radiotherapy and in general good quality clinical studies with a combination of radiotherapy and targeted agents are lacking. Dose escalation has confirmed to increase local control in NSCLC. Modified fractionation, as accelerated hyperfractionation, could improve local control, since most NSCLC have a doubling time of less than 1 week. Prolonging the duration of treatment could therefore be detrimental because it results in accelerated tumor repopulation. A meta-analysis of studies of accelerated radiotherapy published recently on JCO showed that the use of modified radiotherapy has led to a 12 to 13% reduction of the risk of death in patients with lung cancer, resulting in a 5 years absolute benefit of 2,5% in NSCLC. In order to exploit the advantages of modified radiotherapy without increasing unacceptably acute and late toxicity, optimal RT techniques must be employed. There is now evidence that moderately hypofractionated radiotherapy with a significant shortening of the treatment (e.g.: 60-66 Gy in 4-5 weeks) can be performed together with chemotherapy without an increase of late toxicity when all the possible advantages of recent technology are exploited (PET scan for the definition of target volume, IMRT, volumetric IGRT, 4D CT, gated irradiation, breath control techniques). Further studies are however needed to confirm that "high tech" radiotherapy with higher dose per fraction can improve survival in locally advanced NSCLC.

LEZIONE DI AGGIORNAMENTO: GRANDANGOLO IN RADIOTERAPIA ONCOLOGICA

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A comprehensive review of published Literature during year 2012 has purposed, mainly focusing on Reviews and Randomised Controlled Trials (RCTs) fairly relevant to radiation oncology of prostate and head and neck cancers. As far as prostate cancer (PC) is concerned, consistent interest has been reserved to the association of radiotherapy (RT) and Androgen Deprivation Therapy (ADT). A recently published phase III study investigated the potential of adding RT (65-69 Gy, conventionally delivered) to ADT *vs*. ADT alone in a selected group of locally advanced or confined, high-risk, PC patients (pts). In both arms hormonal treatment consisted of long-term (i.e. lifelong) ADT, achieved with orchiectomy or luteinising hormone-releasing hormone (LHRH)

agonist. After a median follow-up (FU) of six years and 1205 randomized pts, adding RT resulted in a significant increase of overall survival (OS) compared to ADT alone (7-year OS of 74% *vs*. 66%, respectively) with HR 0.77 (95% CI 0.61-0.98) favoring integrated treatment. Moreover, combined treatment significantly improved disease-specific survival (DSS) and biochemical control (BC), without significant impact on toxicity. On the basis of these results and warranting investigation of other features, like ADT duration and potential ADT long-term toxicity (mainly cardiovascular), authors advice combined strategy to be always discussed in less-favorable disease pts [1]. Similar conclusions emerge from a recent metanalysis on data from ten RCTs from 1988 to 2011, with 6555 pts treated with RT +/- ADT. Authors considered all RCTs comparing RT with or without any ADT in localized or locally advanced PC, including ADT given before, during or after RT, but excluding those studies for which ADT was given in both arms. Data confirmed a significant survival advantage of ADT both on OS and disease-free survival (DFS). Subgroup analysis revealed a major advantage from use of long-term (up to three years) Goserelin over other strategies, with HR of 0.72 (95% CI 0.60-0.87) with respect to OS, when compared to RT alone. Complete hormonal blockade was not shown to be superior to Goserelin monotherapy. Although the different treatment schedules resulted in some heterogeneity in outcome analysis, authors definitely underlined the evidence-based benefit from the combination of ADT and RT in high-risk PC pts [2]. Although ADT/RT association might be considered a standard strategy locally advanced or organ-confined high-risk PC, the same conclusions cannot be extended for less advanced disease. In particular, since intermediate-risk PC pts are a very heterogeneous disease, the real role of ADT (particularly short-term ADT) combined with RT is far to be validated; furthermore, the actual evidence of a significant improvement of the outcome in this setting of pts mainly comes from trials where RT doses (up to 70 Gy) would be judged unacceptable by modern standards. The question raises whether ADT is still necessary when dose-escalated RT techniques are employed. In the attempt of clarifying this issue, Zumsteg and Zelefsky analyzed the evidence for and against short-term ADT in the contest of Dose-escalation for intermediate-risk pts, further suggesting an appropriate risk-adaptive strategy based on pts clinical characteristics and number of risk factors [3]. It results evident how the concern about ADT potential toxicity is a matter of fact and hormonal-induced cardiovascular toxicity is a stringent issue. Dana-Farber Cancer Institute investigators recently performed an up-to-date metanalysis of published RCTs in order to determine whether ADT would be associated with excessive cardiac deaths, and PC specific mortality in unfavorable-risk pts. A review of 4141 pts from eight RCTs, comparing immediate ADT *vs*. no immediate ADT, has been performed. No significant risk of cardiovascular mortality was associated with immediate ADT (overall RR 0.93; 95% CI 0.79-1.10, p=0.41) either in trials of long-term ADT (RR 0.91; 95% CI 0.75-1.10) or in trials of 6 months or less duration (RR 1.00; 95% CI 0.73-1.37). Moreover, ADT use resulted in reduced PC mortality (RR 0.69; 95% CI 0.56-0.84) and all-cause mortality, as well [4]. In order to optimize RT-associated ADT, it is very important the early identification of pts in whom short-course ADT would be insufficient for cure, so requiring longer ADT, as well as the identification of potentially-resistant pts to be considered for new drugs. In this purpose, the assessment of prostate-specific antigen (PSA) as a surrogate of PC-specific mortality would play a role. In a series of 734 men enrolled in two RCTs, where a significant benefit of 6 months of ADT on survival was reported, the assessment of two potential early surrogate for PC-specific mortality based on PSA concentrations was investigated. In particular, lowest PSA concentration (*PSA nadir*) and that immediately after RT (*PSA end*) were reviewed; well-defined criteria were used to assess whether *PSA nadir* and *PSA end* concentrations of more than 0.5 ng/mL were surrogate endpoints for PC-specific mortality. Results showed that both endpoints acted as surrogate for that specific outcome. Pts with *PSA end* values exceeding 0.5 ng/mL should be considered for long-term ADT since more likely to be cured from prolonged duration; on the opposite pts with *PSA nadir* values exceeding 0.5 ng/mL should be considered for a switch to other drugs specific for potentially castration-resistant pts [5]. As pointed out [3], RT Dose-escalation plays a crucial role in achieving a adequate biochemical control in both low-, intermediate- and high-risk PC pts, suggesting that this strategy should nowadays be offered to all pts regardless of risk status; however, evidence-based impact on OS and PC-specific mortality has not been confirmed so far. That's why Viani et al. recently updated their previous report, comparing the benefit of high-dose (HDRT) conformal RT (i.e. more or equal than 74 Gy, conventionally-delivered) with conventional RT (CDRT) in terms of OS, PC-specific mortality and BC. Authors reviewed data from 2508 pts in five RCTs comparing different RT schedules for localized PC, excluding trials with hypofractionation or brachytherapy, but not ADT. After a minimum FU of 5 years pooled analysis showed significant reduction of PC mortality and improved BC with HDRT compared to CDRT, with absolute risk reduction of PC-specific mortality and biochemical failure rate at 5 years of 1.7% and 12.6%, respectively. No difference in OS was shown between groups. According to authors, that difference between PC-specific mortality and OS was explained by the fact that in HDRT group more deaths from causes other than PC occurred [6]. It's not possible to avoid mentioning of hypofractionated schedules since this approach in PC treatment strategy has become more and more diffuse either with conformal irradiation or, more frequently, with the widespread use of intensity-modulated RT (IMRT). So far, the majority of studies on hypofractionation mainly investigated the toxicity profile of this approach and definitive results about oncologic outcomes in comparison to conventionally-fractionated schedules are warranted. Actually, data on acute toxicity well compare to conventional RT, enforcing the evidence of a safety profile of well-delivered hypofractionated schedule. Similar conclusions have been reached

by researchers from Royal Marsden who recently reported on preliminary safety results of CHHiP Trial, where pts were randomized in a 1:1:1 ratio to receive conventional RT of 74 Gy *vs*. two hypofractionated arms of 60 Gy and 57 Gy in 20 and 19 fractions, respectively [7]. With a median FU of 50 months, 457 pts have been have evaluable for interim analysis, showing comparable rates of bowel and bladder toxicity at two years from RT (RTOG Grade 2 or worse rates of 4.3%, 3.6%, 1.4% in the 74 Gy, 60 Gy, 57 Gy group, respectively). Interestingly, acute bowel and bladder side-effects seemed to peak sooner (almost three months earlier) in the experimental arms than in the control arm; nevertheless, late-effects did not seem to significantly differ among groups. Finally, it's worthwhile mentioning two relevant reviews on IMRT and functional outcomes after RT, as well. Prostate Cancer Working Group of IMRT Indications Expert Panel (Royal College of Radiologist, Ontario Cancer Care) proceeded an exhaustive evidence-based analysis of existed data of comparison between IMRT and conformal RT in definitive and postoperative PC irradiation. On the basis of published evidence, authors concluded how IMRT should actually be recommended over conformal RT in definitive treatment of PC, providing to deliver doses greater than 70 Gy. No clear evidence has been found to recommend IMRT in postoperative setting too, due to insufficient data and future research are requested [8]. The second review deals with functional outcomes and with all complications following RT; a critical analysis of the last ten years of Literature has been performed, focusing not only on widely discussed subjects like rectal and bladder effects, but specific attention has reserved to erectile dysfunctions and health-related quality of life, providing a comprehensive tool for clinical management [9]. As expected, in head and neck cancers (HNC) the main interest has been focused on the integration of RT to chemotherapy (CT), as this approach is actually considered the gold standard treatment in the locally-advanced disease. Some concern still exists about the possible role of unconventional RT fractionation schedules in achieving satisfying disease control and comparable outcomes than concomitant radio-chemotherapy (RT-CT). In this setting, very interesting results emerged from the GORTEC 99-02 study which compared, in a three-arm randomized trial, conventional RT-CT (70Gy/7weeks plus 3 courses of carboplatin-based CT) *vs*. accelerated RT-CT (70Gy/6weeks plus 2 courses of carboplatin-based CT) *vs*. very accelerated RT (64.8Gy/3.5weeks without CT). Far from expected were the results with no benefit in terms of progression-free survival (PFS) coming from accelerated RT-CT compared with conventional RT-CT (HR of 1.02, 95% CI 0.84-1.23; p= n.s); moreover, PFS of very accelerated RT alone resulted lower than either conventional RT-CT (HR of 0.82, 95% CI 0.67-0.99, favoring conventional RT-CT) or accelerated RT-CT (HR of 0.83; p= n.s.). As a consequence, authors concluded that CT still has a substantial effect when given concomitantly with RT and acceleration of local treatment, although intense, actually cannot compensate for the absence of CT [10]. Even with some caveats like the absence of any stratification for human papillomavirus (HPV)-status and the use of "traditional" CT schedules (Taxanes not contemplated), these results enforce the evidence in favor of RT-CT integration with conventional irradiation schedules, warranting for more robust results coming from the integration of new drugs or unconventional treatment schedules. The role of RT intensification has also been explored in a different contest of accelerated irradiation, without CT but with the potential benefit on hypoxia prevention by mean of carbogen inhalation and nicotinamide [11]. 345 laryngeal cancer pts were thus randomized between accelerated RT (68 Gy / 38 days), given alone or with carbogen and nicotinamide. As a whole, no significant benefit was observed in the experimental arm either on local control, or organ preservation; however, a better regional control was observed for pts with significant hypoxic tumors, for whom a 5-year regional control of 93% was achieved with integrated treatment, compared to 86% of RT alone. These recent data and previously published reports as well, do not completely help us to clarify at what level the "edge" on treatment intensification might be put and, more importantly, if this limit would automatically lead to an improvement of overall outcomes. RT acceleration, whether or not combined to concurrent CT, seems not to improve the results which have been already achieved with conventionally-delivered concomitant RT-CT. The role of biological drugs is far to be validated in terms of outcomes and toxicity. In this feature a crucial point will probably be the appropriate selection of pts, since the assessment of HPV-status has emerged as a relevant prognostic factor [12]. It is likely that in selected well-prognosis pts a deintensification of treatments would be necessary in order to balance efficacy and toxicity. Actually, we keep on increasing our knowledge about predictors of acute and late toxicity after RT-CT [13] and relationships between dosimetric constraints and functional outcomes have highlighted the potential for assisting in prognosis and treatment [14]. A great deal of emphasis has been reserved so far to cutaneous and mucosal reactions and greatest efforts have been spent on order to improve organ preservation. In this setting a recent area of interest is focusing on the problem of disphagia and on the whole pattern of therapeutic procedures aimed to overcome nutritional problems. It is possible that some of these procedures, like percutaneous endoscopic gastrostomy (PEG) would be overweighted and a prediction model for a safe PEG application may be useful [15]. Moreover, an exhaustive review about swallowing mechanism and physio-patology of dysphagia in HNC treatment has been highly appreciated, with the purpose to join specific recommendations to be adopted for RT patients [16]. As for prostate cancer, the Head and Neck Cancer Working Group of IMRT Indications Expert Panel (on behalf of Royal College of Radiologist) proceeded an evidence-based analysis of existed data of comparison between IMRT and two-dimensional RT in HNC irradiation. Based on 1555 pts in 15 papers, findings favored IMRT compared with traditional RT when the avoidance of the adverse outcomes are the main purposes; so far, insufficient data support IMRT if oncologic outcomes only is the main purpose. Future investigation on IMRT role in

recurrent HNCs, as well as its use in integrated treatments, are warranted [17].

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NEW TRENDS IN THE TREATMENT OF CNS MALIGNANCIES AND LYMPHOMAS

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Novel insights for the treatment of malignant brain tumors that could have major impact on daily clinical practice in the next years have been reported in the past months. New findings that could change the standard of care in anaplastic oligodendroglial tumours come from the long-term follow-up results of the EORTC 26951 and RTOG 9402 phase III trials presented at the ASCO 2012 Meeting. Anaplastic oligodendrogliomas account for approximately 5 to 10% of all primary malignant brain tumours and the standard treatment is surgery followed by radiotherapy. In the EORTC 26951 trial, 368 patients with newly diagnosed anaplastic oligodendroglial tumors were randomized between radiotherapy alone (59.4 Gy in 33 fractions) or followed by 6 cycles of standard PCV [procarbazine, CCNU (lomustine) and vincristine] chemotherapy. Median progression free survival after radiotherapy plus PCV was significantly longer compared to radiotherapy alone (24.3 months *versus* 13.21 months). Median overall survival was also significantly prolonged in the combined arm (42.3 months *versus* 30.6 months). 1p/19q co-deleted patients (n = 76) treated with radiotherapy plus PCV had improved overall survival compared to radiotherapy arm (median overall survival not reached *versus* 113 months). In the 224 patients without 1p/19q co-deletion the difference in overall survival was non-significant (25 months *versus* 22 months in the radiotherapy arm). There was a slight trend towards improved overall survival in MGMT methylated and IDH mutated tumors *versus* unmethylated and IDH wild type tumors. The authors concluded that the addition of PCV to radiotherapy increases progression free survival and overall survival and that patients with 1p/19q co-deletion appear to benefit most from the addition of chemotherapy. These findings were confirmed by the long-term follow-up results of the RTOG 9402 trial, also presented at the ASCO Meeting. In this phase III study, 291 patients with anaplastic oligodendrial tumors were randomly assigned to PCV followed by radiotherapy *versus* radiotherapy alone. For codeleted tumors median survival was 14.7 years in the combined arm *versus* 7.3 years in the radiotherapy arm. For non codeleted tumours there was no difference in overall survival between the 2 groups (2.6 years *versus* 2.7 years). Taken together these studies establish radiochemotherapy treatment as a new standard of care for patients with anaplastic oligodendroglial tumors carrying 1p/19q co-deletions and underline the prognostic and predictive role of the 1p/19q loss. Questions remain regarding the optimal timing of radiotherapy and chemotherapy and whether temozolomide could be equivalent to PCV. Another important issue in brain tumors regards the optimal management of elderly people with high grade gliomas. The most appropriate treatment is still controversial and a standard of care has not yet been established. Two previous randomized trials

showed the superiority of radiotherapy over best supportive care and the equivalence of conventional fractioned radiotherapy (60 Gy in 30 fractions) and hypofractionated radiotherapy (40 Gy in 15 fractions). More recently, the results of two clinical trials comparing radiotherapy alone with temozolomide alone have been published. The trial from the Neuro-oncology Working Group (NOA) of the German Cancer Society, NOA-08, compared standard post-operative radiotherapy at a dose of 60 Gy in 6 weeks to dose-dense temozolomide (100 mg/m^2) in a 1 week on/1 week off schedule in 373 patients with anaplastic astrocytoma or glioblastoma aged 65 years or older and with a KPS ≥60. Temozolomide alone showed non-inferiority compared to radiotherapy alone, with a reported median overall survival of 8.6 months in the temozolomide group and 9.6 months in the radiotherapy group, respectively. Median event-free survival did not differ significantly between the two groups (3.3 *versus* 4.7 months). O□ methylguanine-DNA methyltransferase (MGMT) gene promoter methylation was associated with longer overall survival than was unmethylated status (11.9 months *versus* 8.2 months). Event-free survival was longer in patients with MGMT promoter methylation who received temozolomide than in those who underwent radiotherapy (8.4 months *versus* 4.6 months), while the opposite was found in patients unmethylated (3.3 months *versus* 4.6 months), suggesting a predictive role of MGMT promoter methylation. The Nordic trial compared temozolomide alone (200 mg/m^2 day 1-5 every 28 days for up to 6 cycles) to standard radiotherapy (60 Gy in 2 Gy fractions over 6 weeks), or short-course hypofractionated radiotherapy (34 Gy in 3.4 Gy fractions over 2 weeks) in 342 patients 60 years or older with newly diagnosed glioblastoma. In comparison with standard radiotherapy, median overall survival was significantly longer with temozolomide (8.3 months *versus* 6.0 months), but not with hypofractionated radiotherapy (7.5 months). For all patients who received temozolomide or hypofractionated radiotherapy (n=242) overall survival was similar (8.4 months *versus* 7.4 months). For age older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy. Patients treated with temozolomide who had tumour MGMT promoter methylation had significantly longer survival than those without MGMT promoter methylation (9.7 months *versus* 6.8 months), but no difference was noted between those with methylated and unmethylated MGMT promoter treated with radiotherapy. Both trials revealed that in elderly patients with high grade gliomas temozolomide could represent an alternative to radiotherapy, especially in the subset of patients with MGMT promoter methylation. What remains unclear is the role of temozolomide in unmethylated patients. More data that could help define the role of MGMT as well as the role of temozolomide in combination with radiotherapy, are expected by the ongoing EORTC (26981-22981)/NCIC CTG phase III trial who is comparing hypofractionated radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma. The management of Hodgkin's lymphoma (HL), continues to evolve. Current management of HL involve initial treatment with chemotherapy or combined modality therapy (CMT), followed by restaging to assess treatment response. PET scans are recommended to evaluate initial staging and assess treatment response at restaging. Different trials incorporated CMT in all treatment arms and tested radiation filed size and/or dose and types and duration of chemotherapy. The HD10 trial involved four-armed randomization with a factorial analysis and compared 2 *vs*. 4 cycles of ABVD and 20 *vs*. 30 Gy IFRT in early-stage non bulky disease; the trial was designed according to non-inferiority principles with a primary end point of freedom-from treatment failure (FFTF). With a median follow up of 79 months, the arm that included two cycles of ABVD and 20 Gy IFRT was considered to be non-inferior with respect to FFTF and was associated with less severe toxicity and was thus concluded by the authors to be optimum therapy. The 8-year FFTF on this arm of the trial was 86% and 8-year survival was 95%. The HD11 trial was of a similar design and compared four cycles of BEACOPP given at baseline doses with four cycles of ABVD, followed by 20 Gy *vs*. 30 Gy IFRT in early unfavorable. At a median follow up of 82 months, the 5-year FFTF was inferior in the 4 ABVD+20 Gy arm (81% *vs*. 85%- 87%), although no difference in 5-year survival (94%-95%) was observed; the 4 ABVD + 30 Gy arm was concluded to be non-inferior to the BEACOPP regimens and was recommended as the treatment of choice due to the greater toxicity of BEACOPP. The HD14 study that was aimed at improving treatment outcomes of patients with early-stage unfavorable HL by intensifying therapy. They found that patients treated with two cycles Esc BEACOPP plus two cycles of ABVD followed by 30 Gy of IF-XRT (the 2 + 2 regimen) had an estimated 5-year progression-free survival of 95.4% compared with 89.1% for those who were treated with the standard four cycles of ABVD followed by the same dose of radiation. Chemotherapy alone has also been investigated as a treatment option for patients with early-stage nonbulky disease (stage I–II or IIIA). In the multicenter study conducted by the NCIC Clinical Trials Group and ECOG, patients with stage IA or IIA HL were randomized to receive ABVD (4–6 cycles) or subtotal lymphoid radiation therapy (STLI). With a median follow up of 11.3 years, the 12-year survival was superior in patients randomized to receive chemotherapy alone (94% *vs*. 87%; HR = 0.05; P = 0.04); in contrast, 12-year freedom from progressive disease (FFPD) was inferior (87% *vs*. 92%; HR = 1.91; P = 0.05. In a recent retrospective study, Canellos et al reported that 6 cycles of ABVD is an effective and safe treatment for selected patients with limited-stage, nonbulky disease. Most patients (69%) had stage IIA disease; 13% had stage IA and 15% had stage IIB disease. All patients included in this series experienced a clinical complete remission with chemotherapy alone. The failure-free survival rate was 92% and the median follow-up was at least 60 months. Results of these trials suggest that ABVD alone could be a reasonable choice of treatment for younger patients with favorable presentations of stage I to II nonbulky disease, especially if they experience prompt and complete response to the first 2 cycles of ABVD, to

avoid the long-term risks of radiotherapy. Clinical trials of CMT have incorporated RT fields of varying extent. IFRT was accepted as the standard in combined modality therapy programs. Recently, clinical trials have utilized even more limited fields, referred to as involved node radiotherapy (INRT). The concept of involved node irradiation (INRT) was developed initially in the EORTC/GELA and has been adopted by other clinical trials groups. In the GHSG HD17 trial, patients who are treated with combined modality therapy are randomized to treatment with IFRT or INRT. Involved node radiotherapy is attractive, since the irradiated volume is less and a smaller volume of radiation treatment must be associated with less risk for late effects. Preliminary data confirming this concept have been published. The treatment of non-Hodgkin lymphoma (NHL) varies based on the type of NHL and stage. The role of reduced volume and reduced doses is addressed, integrating modern imaging with three-dimensional planning and advanced techniques of treatment delivery. Both wide-field and involved-field techniques have now been supplanted by the use of defined volumes based on node involvement shown on computed tomography (CT) and positron emission tomography (PET) imaging. The involved-site radiotherapy concept defines the CTV based on the PET-defined pre-chemotherapy sites of involvement with an expansion in the cranio-caudal direction of lymphatic spread by 1.5 cm, constrained to tissue planes such as bone, muscle and air cavities. There is increasing evidence in NHL that traditional doses are higher than necessary for disease control and related to the incidence of late effects. The multicentre, prospective, randomized-controlled trial of Lowry et al compared efficacy and toxicity of differing radiotherapy doses in non-Hodgkin lymphoma (NHL). Three hundred and sixty one sites of indolent NHL (predominantly follicular NHL and marginal zone lymphoma) were randomised to receive 40-45Gy in 20-23 fractions or 24Gy in 12 fractions. Six hundred and forty sites of aggressive NHL (predominantly diffuse large B cell lymphoma as part of combined-modality therapy) were randomised to receive 40-45Gy in 20-23 fractions or 30Gy in 15 fractions. There was no difference in overall response rate (ORR) between standard and lower-dose arms. In the indolent group, ORR was 93% and 92%, respectively, (p=0.72); in the aggressive group, ORR was 91% in both arms (p=0.87). There was also no significant difference detected in the progression free or overall survival. There was a trend for reduced toxicities in the low-dose arms; only the reduction in reported erythema reached significance. In conclusion there was no loss of efficacy associated with radiotherapy doses of 24Gy in indolent NHL and 30Gy in aggressive NHL, compared with previous standard doses of 40-45Gy. As yet there are no large datasets validating the use of involved-site radiotherapy; these will emerge from the current generation of clinical trials. The aim of Rossier study was to assess the response rate, duration of response, and overall survival after low-dose involved-field radiotherapy in patients with recurrent low-grade lymphoma or chronic lymphocytic leukemia (CLL). Forty-three (24 women, 19 men) consecutive patients with indolent lymphoma or CLL were treated with a total dose of 4 Gy (2 × 2 Gy) using 6- 18-MV photons. Radiotherapy was given either after (n = 32; 75%) or before (n = 11; 25%) chemotherapy. The overall response rate was 90%. Low-dose involved-field radiotherapy is an effective treatment in the management of patients with recurrent low-grade lymphoma or CLL. Radiotherapy remains the most effective single modality in the treatment of lymphoma. A reduction in both treatment volume and overall treatment dose should now be considered to minimise the risks of late sequelae.

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VULVAR CANCER SURGERY: WHY, WHEN AND HOW

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In the open scene of vulvar cancer treatments surgery plays a central role, currently being the first choice and exerting a great impact on prognosis. Main goal of surgery is both to allow a correct staging of disease and supply a therapeutic result. Infact, in 1988 vulvar cancer staging system switched from clinical to surgical (Meeting Report 1988); afterwards it was revised on the base of the main emerging features affecting prognosis (FIGO 2009 Meeting Report, Pecorelli 2009): tumor size, number and size of groin lymphnode metastasis and surrounding tissues involvement are exclusively assumed from pathologic exame; according to the surgical stage any additional therapy may be scheduled. Moreover, surgery is by itself an essential therapeutic act, as long as carried out in a "radical" manner. In this respect, one of the first concerning observation was the unexpected rising in overall survival after introduction of radical vulvectomy with en bloc bilateral inguinofemoral (IF) and pelvic lymphadenectomy, instead of simple local excision (FJ Taussig 1940). More recently, the removal of more than 10 inguinofemoral lymphnodes (IFL) for each side was observed to be associated with better survival in patients with positive nodes (Courtney-Brooks 2010). It was also remarked that the removal of deep and superficial IFL improves survival if compared to simple superficial lymphadenectomy (Stehman 1992, Burke 1995). Likewise, extent of surgical margins have been shown to be strictly related to the incidence of local relapse (JM Heaps 1990). It follows that, in case of resectable disease, when patient's general conditions are favorable, radical surgery should always be performed primarily, both in early and locally advanced stages of disease and even when the surgical demolition implies a heavy burden. In addition, even in case of unresectable local advanced disease, surgery should be attempted after a neoadjuvant treatment; likewise, when metastatic disease is associated to local severe symptoms, surgery retains a palliative role. To summarize in a slogan we could answer the question "when to perform surgery" with "always if possible". In order to fulfill a safe and radical surgery some recommendations from literature should be complied and some easy norms could be summarized this way: a) Obtain microscopical tumor free margins measuring $\geq$ 8 mm in each resection, since the risk of local recurrence increases to 50% in patients with closer margins (Heaps 1990). Because of shrinkage due to sample fixation, approximately estimated as 15% of the specimen size, it is recommended to observe about 2 cm of macroscopic resection margins (Boonstra 1983) b) Avoid conservative surgery consisting in simple wide local resections when tumor is bilateral or multifocal, in favor of a radical vulvectomy (Dittmer 2012) c) Resect the soft tissues up in depth, reaching the perineal fascia d) Remove the skin bridge that connects inguinal regions to perineal area in cases of macroscopical involvement of the site or clinically massive metastatic commitment of the groin lymph nodes (De Hullu 2002) e) IF-lymphadenectomy should always include the removal of deep lymphnodes, located below the cribriform fascia and medial from the femoral vein (Hacker 2000) f) Sentinel lymph-node biopsy (SNB) should to be restricted to unifocal invasive tumors, <4 cm in diameter, after having accurately excluded nodal involvement by clinical and instrumental procedures Radical inguino-femoral lymphadenectomy should be performed in case of positive SN or when the tracer does not reach inguinal regions (van der Zee 2008) g) In case of a midline tumor (medial border < 1 cm from midline) a SN should be identified in both groins: if not or in any doubt the SNB procedure should be abandoned and lymphadenectomy performed (ISNS – 2008).

Unfortunately, surgical treatment still imposes a considerable burden in terms of local and systemic morbidity, prolonged hospitalization and mortality. This is mainly due to the type of affected patients (consider advanced age and related systemic diseases), as well as the specific issues related to the anatomical area in question (as contamination of wounds and humidity), the frequent need for massive demolition, delayed feeding and consequential development of intestinal bacterial flora, potentially reaching a septic status. Indeed, short and long-term postoperative complications are frequent and sometimes severe, including wound break down, infection, lymphocele, lymphedema, cellulitis, erysipelas and deep venous thrombosis. The main negative aspect linked to such complications is the possible detrimental influence on the therapeutical impact of surgery, being able to determine a delay on the start of adjuvant therapies, sometimes up to lose the correct indication. That's why, without losing the prior attention for an adequate and radical surgery, a commitment to modulation is mandatory in order to minimize demolition up to minimum required, especially for early disease. Over the years, many acquisitions allowed to resize the extent of surgery towards a more sparing vulvar and nodal surgery, such as: a) Replacement of the radical vulvectomy with en bloc inguinopemoral lymphadenectomy through butterfly incision (Toussig and Way 1950) by the less radical vulvectomy and bilateral lymphadenectomy through separate triple incisions, sparing the inguino-crural skin bridge (Byron 1962, De Hullu 2002), reliable in the patients without massive nodal involvement b) Introduction of the radical wide local excision instead of radical vulvectomy, in the case of small lesions (< 2cm) or more in general when the tumor/vulvar size ratio is favorable and safe distance from the resection margins is allowed (Hacker 2000) c) Evidence of safety and efficacy of clitoral-sparing surgery when tumor doesn't involve the very anterior vulva (Chan 2004) d) Omission of a nodal surgical staging (by SNB or lymphadenectomy) in the tumors with stromal invasion < 1 mm, when the risk of groin metastasis is negligible (Wilkinson 1982, Oonk 2006) e) Introduction of mono-ipsilateral inguinofemoral lymphadenectomy in patients - unfit for SNB - with unilateral tumors distant > 1 cm from the median line, with clinically negative groin lymph nodes, because of a very low estimated risk of contralateral metastasis (Homesley1993, Andrews 1994) f) Adoption of SNB as a reliable nodal staging system, sparing bilateral inguinal lymphadenectomy in almost 70% of cases (Van der Zee 2008) g) Routinary sparing of the

saphenous vein, with an estimated benefit of 30% of reduction in legs lymphedema.

On the other hand, when extensive surgery is unavoidable, it is necessary to minimize the side effects integrating plastic and reconstructive surgical techniques. The most important features of an oncoplastic approach are good long-term results, tension free closures, acceptable cosmesis, rehabilitation of the basic functions otherwise compromised (as walking and sitting), and sometimes the preservation of sensitive facilities, all in a single-stage operation. Various reconstructive techniques can be performed to repair the skin defects according to the different sizes and sites, mostly using local dermohypodermal rotation or transposition flaps or mio-cutaneous flaps (Salgarello 2005). After all, given the technical and medical complexity related to this kind of surgery it is cautiously recommended to combine perioperative protocols for local and systemic care and management: some attentions have revealed extremely important in the prevention of complications, such as improve preoperatory caloric supply and administration of probiotics, use of dynamic legs compression, fasting and parenteral nutrition in the post-op, antibiotics and anti-diarrhoic drugs, prophylaxis for thromboembolism, inflatable mattress and immobilization, carefull management of the wound, blood oxygenation by ventimask, prolonging transurethral catheter and many others (Fanfani 2006).
In conclusion, given the multidisciplinary approach and the technical skills required, above all because of the rarity of this disease, it should be recommended to address patients affected by vulvar cancer to specialized Oncological Centers, centralizing the cure in multidisciplinary controlled pathway of care and allowing data collection for advanced research.

LA RADIOTERAPIA: INDICAZIONE E RISULTATI CLINICI

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Vulvar cancer is the fourth most common gynaecologic cancer and comprises 5% of the malignancies of the female genital tract. The majority are squamous cell carcinomas (90%) and it affects elderly women with the median age at diagnosis of 65–70 years. Direct extension to adjoining structures are frequent and the disease mainly spreads through the lymphatics (mostly inguinofemoral nodes). Hematogenous spread is quite unusual. Prognosis is strongly correlated to inguinal lymph node metastases and the stage of disease. Since the disease is uncommon, no large randomized controlled trials (RCTs) are available up to now. Indeed, most treatment guidelines are based on small retrospective studies. In the past, radical vulvectomy with bilateral inguinal–femoral lymphadenectomy, was the standard operation for vulvar carcinoma with a significant improvements in survival but with considerable physical disfigurement and sexual dysfunction, and a high rate of postoperative complications including wound breakdown, infection, and lower extremity lymphedema. Currently, the policy of treatment are adopting less morbid and conservative procedures. Modified surgical approaches are feasible and safe for vulvar cancer and the sentinel node dissection procedures seems promising. Although radiation therapy plays an important role, due to limited literature, treatment guidelines are less clearly defined. Radiation therapy can be used in different settings for the management of patients with vulvar cancer: as adjuvant therapy to prevent LRR (to decrease the incidence of locoregional failures after wide local excision in patients with stage I and II tumors and to reduce the incidence of postsurgical failure in patients with stage III and IV disease); as definitive therapy for nonsurgical patients; as neoadjuvant therapy to improve the resectability and to reduce the surgical morbidity, as salvage therapy in postsurgical recurrent vulvar cancer and as palliative therapy for alleviating the distressing symptoms in incurable patients For early-stage vulvar cancer surgery is the first choice, and radiation therapy continues to play an adjuvant role: various surgical–pathologic factors are associated with a higher risk of local recurrence including: larger tumor size, deep invasion (>5mm) and lymphovascular space invasion and close or positive surgical margin. In patients with stage III and IV disease (pN+) adjuvant radiotherapy is reserved to patients with more than one pathologically positive node or extracapsular extension. The debate about the radiation therapy as an effective alternative to inguinal or pelvic lymph node dissection in patients with clinically negative nodes was addressed by several authors: radiation therapy is correlated with less toxicity and less local control respect to surgery. Due to insufficient evidence, surgery remains the standard treatment for the groin nodes in early-stage vulvar cancer. In locally advanced vulvar cancer (LAVC) the combined chemoradiotherapy is slowly evolving as a new option in the management of LAVC both as preoperative and definitive treatment, reducing surgery-related morbidity. Generally, an individual approach is preferred using combination of surgery, radiation therapy, or chemoradiotherapy in order to reduce the treatment related morbidity. Various trials have tested the feasibility of concurrent chemoradiotherapy (CCRT) using different chemotherapeutic agents. With modern, state-of-art facilities of radiation therapy like intensity-modulated radiation therapy (IMRT), one can expect better tolerance to CCRT regimes.

Conclusions: Today, the operative therapy is much less radical and more emphasized on individualized therapeutic concepts. The tendency is to leave the ultraradical surgical options which suffer from high morbidity towards less radical, minimal invasive techniques. For early-stage vulvar cancer, radiation therapy is selectively used as an adjuvant therapy in operated patients with adverse features. For LAVC, CCRT is slowly becoming a popular option both as preoperative and definitive treatment. Frequent interruptions during CCRT due to acute skin and hematological toxicity may jeopardize the results of definitive radiation therapy in such patients.. However, with modern radiation therapy facilities like IMRT, one can expect better tolerance to CCRT regimes and therefore future trials should incorporate IMRT in CCRT regimes.

LA PIANIFICAZIONE E I VOLUMI DI TRATTAMENTO

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Carcinoma of the vulva presents critical of management for its anatomical location, lymph node involvement, and its impact in elderly patients. Adjuvant radiation therapy is offered to patients with close (≤ 8 mm) or positive margins to improve local control. In addition, for patients with more than one inguinal lymph node involvement, adjuvant inguinal-pelvic RT should be used to decrease the risk of nodal recurrence and to improve survival. Moreover, in patients with advanced locoregional vulvar cancer, RT with or without combined chemotherapy could be used as neaoadjuvant or definitive treatment to allow organ preservation by replacing exenteration surgery. Very important is the definition of GTV, CTV-T, CTV-N, depending on the stage of disease. Equally important is the definition of OAR. Although a variety of techniques exist to deliver radiation therapy to the pelvis and inguinal regions simultaneously, the advantages and disadvantages of each method require careful consideration when choosing which radiotherapy technique to utilize.
The evolution of radiotherapic techniques has significantly reduced the OARs irradiation thus obtaining a lower rates of acute and late toxicity.

TOXICITY AND QUALITY OF LIFE

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Compared to the traditional treatment of vulvar cancer with surgery alone, the growing evidence of the importance of the integration with radiotherapy and chemotherapy calls for a new reflection on the toxicity and on the impact on the quality of life. The low incidence of this neoplasm makes it difficult to comprehensively estimate these aspects and all publications complain about the lack of exhaustive data. The studies published generally involve small numbers of patients and are most often retrospective, with different schedules of radiation therapy and chemotherapy, integrated with surgery or more rarely exclusive. Data on toxicity is often incompletely reported. Data related to the quality of life is more lacking, for different reasons. First, the objective difficulty of understanding and measuring such subjective, intimate and complicated aspects, influenced by variables not often studied or considered relevant in the evidence-based medicine. These considerations, common to the treatment of other gynecological malignancies, are more valid in the context of vulvar cancer because of the older age of the patients. The toxicity concerns also aspects of sexual life, affecting the quality of life and altering the body image and the self-esteem, issues that clinicians are often unfamiliar to face but which should be important to predict, to diagnose, and to cure. Articles on these topics are often contained in papers of nursing or clinical psychology. Finally, we must consider that a percentage of patients require palliative treatments at the diagnosis, and in this case the toxicity and the quality of life should be primary objectives. Because of the rarity of this neoplasm, the toxicity of integrated treatments may be better known by some systematic reviews of data published in medical issues, reported in the Cochrane Registers and in other important databases. Relating to the treatment of the inguinofemoral lymph nodes an update of the Cochrane Database Syst Rev. 2001: CD002224, was published in May 2011, which examined the randomised clinical trials comparing inguinofemoral lymph node dissection and primary radiotherapy for patients with early squamous cell cancer of the vulva.[1] No new randomized clinical trial (RCT) was identified by the updated search. Out of twelve identified papers only one met the selection criteria. From this one small RCT that included 52 women, there was a trend towards less lymphoedema (RR 0.06, 95% CI 0.00 to 1.03) and fewer life -threatening cardiovascular complications (RR 0.08, 95% CI 0.00 to 1.45) in the radiotherapy group, but increased groin recurrence rates and lower disease-specific survival rates (RR 3.70, 95% CI 0.87 to 15.80). Primary surgery was associated with a longer hospital stay than primary groin irradiation (RR 0.28, 95% CI 0.13 to 0.58). The authors concluded that until better evidence is available, surgery should be considered the first choice treatment for the groin nodes in women with vulvar cancer, despite a higher rate of complications. Data on the toxicity and efficacy of adjuvant radiotherapy on the pelvis and groins emerges from small retrospective and one randomized study recently conducted by the Gynecologic Oncology Group.[2] This protocol enrolled 114 patients randomly allocated to postoperative pelvic and groin radiation (45-50 Gy, n=59) or to ipsilateral pelvic node resection (n=55) after radical vulvectomy and inguinal lymphadenectomy. Fourteen intercurrent deaths occurred after radiation as compared with only two after pelvic node resection, narrowing 6-year overall survival (51% compared with 41%, hazard ratio 0.61 [95% CI 0.30-1.3], P=.18). However, the cancer-related death rate was significantly higher for pelvic node resection compared with radiation (51% compared with 29% at 6 years, hazard ratio 0.49 [95% CI 0.28-0.87], P=.015). Late chronic lymphedema (16% compared with 22%) and cutaneous desquamation (19% compared with 15%) were balanced after radiation and pelvic node resection. Other retrospective studies point out that a not so common risk that should be taken into account in the evaluation of the treatment plan is the hip fracture.[3] Data relating to the toxicity of radiotherapy treatments concomitant with chemotherapy are very inhomogeneous because there is not a standard schedule of treatment. The toxicity varies depending on whether the treatment is integrated with surgery or exclusive, if conventional fractionations are used, or bid, if there is a split or if not and as a function of the extent of irradiation fields. The toxicity is lower with intensity-modulated radiotherapy so that it should be favored.[4] Intensity-modulated RT appears to offer advantages by elimination of dose modulation across overlapping regions and reduction of unnecessary dose to the bladder, rectum, and small bowel. Early results with small numbers of patients show interesting results, with a low incidence of severe toxicity[5].

Also chemotherapy regimens varie widely. Drugs generally used are cisplatin, 5 fluorouracil, mitomicyn C alone or combined, with different expected toxicity. Overall we can claim that the use of mitomicyn C seems to be associated with higher incidence of morbidity and mortality. In 2004 a retrospective study on 17 patients that investigated the acute and late toxicities associated with the use of chemoradiation therapy (CRT) with 5-fluorouracil (5-FU) and mitomycin C or mitomycin C alone showed in six patients grade 4 neutropenia, in three patients life-threatening neutropenic sepsis. Severe enterocolitis was a direct cause of death in two patients. In four patients, the second cycle of chemotherapy was cancelled because of severe toxicity associated with the first cycle. One patient had grade 4 skin toxicity in the vulvar-perineal area. Six patients had grade 3 and seven patients had grade 2 acute skin toxicity. Skin toxicity necessitated the interruption of CRT in nine patients at a median dose of 32.4 Gy (range: 16.2-48 Gy). One patient developed bowel perforation and colovaginal fistula 1.5 years after completion of CRT[6]. The regimens containing only 5 Fluorouracil are burdened with a higher proportion of grade 3 or higher acute non-skin toxicities and patterns containing only cisplatin are burdened from more grade 3 or higher skin toxicity[7]. Some additional knowledge on the toxicity of radiochemotherapy may result from two Cochrane analysis. The first, published in 2011, contains data on the safety of neoadjuvant and primary chemoradiation compared to other primary modalities of treatment such as primary surgery or primary radiation. The autors selected randomised controlled trials or non-randomised studies that included multivariate analyses of chemoradiation. One RCT and two non-randomised studies that allowed for multivariate analyses met the inclusion criteria and included a total of 141 women. Adverse events were extensively reported in only one study, which found no statistically significant difference in risk of adverse events between primary chemoradiation and primary surgery due to the very small numbers in each group. In the RCT there was no observed statistically significant difference between neoadjuvant chemoradiation and primary surgery. Adverse events were not reported in the largest study of 63 women. Quality of life (QoL) was not reported in any of the included studies. All studies were at high risk of bias. The radiochemotherapy regimens varied widely[8]. The second issue published in march 2005 reports data on the safety of the combined treatment strategy using concurrent neoadjuvant chemoradiation therapy followed by surgery. The authors selected studies of curative treatment of patients with advanced, primary squamous cell carcinoma of the vulva treated with radiochemotherapy followed by surgery. Randomised controlled trials were not available. Five studies met the inclusion criteria. (Eifel 1995; Landoni 1996; Montana 2000; Moore 1998; Scheistroen 1993). Chemotherapy was given uniformly within each of the five selected studies but four different chemoradiation schedules were applied. Radiotherapy dose fractionation techniques, fields and target definitions varied. Skin toxicity was observed in nearly all patients. Wound breakdown, infection, lymphedema, lymphorrhea and lymphoceles were also common. A total of 27 to 85% of participants died due to treatment related causes or disease. The five studies showed that preoperative chemoradiotherapy reduces tumour size and improves operability but complications are considerable and informations on the effects of quality of life (QOL) are not available[9]. In general we can say that preoperative radiochemotherapy with a dose between 46 and 50 Gy with conventional fractionations, integrated with 5-fluorouracil – cisplatin based chemotherapy, followed by conservative surgery, reports a non-negligible but acceptable toxicity, with acute cutaneous reactions and surgical wound complications being the most common adverse effects, which require specific information to the patients.[10] Leukopenia is another frequent chemotherapy related acute side effect. Data on the late toxicity are insufficient. Lymphedema in particular has been evaluated in few studies after gynecological cancer treatments. In 2004, a population-based cross-sectional mail survey (56% response rate) was completed by 802 gynecological cancer survivors indipendentemente regardles of treatment strategy. Ten percent of participants reported being diagnosed with lymphedema, and a further 15% reported undiagnosed "symptomatic" lower limb swelling. Diagnosed lymphedema was more prevalent (36%) amongst vulvar cancer survivors. Overweight or obesity were important risk factors[11]. About the risk of urethral stenosis many authors propose the use of doses per fraction on the vulva not exceed 180 cGy. Another important issue is the quality of life that concerns various aspects such as sexual morbidity, a wider concept than physical toxicity because it includes sexual behavior, sexual functioning, subjective sexual satisfaction and the relationship between these aspects and depression[12]. In literature the following aspects have been investigated: the relationship between sexual morbidity and socio-demographic factors (age, degree of instruction, employment, presence of a partner), the disease status, the performance status, the fatigue, etc… generally through semistructured interviews, coming sometimes to opposite conclusions. Studies on the relationship between sexual morbidity and the type of treatment, in particular studies on patients undergoing radiation therapy are absolutely lacking. While some aspects are very complex to be treated and require a multidisciplinary approach, others are more strictly medical and should not be ignored during treatment planning and follow up. Patients often complain about the need to address these issues with their doctors.

In conclusion we can say that much has still to be explored on the topic of toxicity and the effects on the overall well-being of patients of the integrated treatments. During treatment planning and follow-up, physicians should have a particular attention to these aspects, not neglecting the importance of an informative and therapeutic dialogue with patients. Very useful, given the lack of scientific data in the literature, is the publication of personal experiences and the establishment of multicentric and multidisciplinar study groups.

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TITLE

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The imaging work-out of soft tissue tumors has now reached a well-defined role. Magnetic Resonance Imaging is un established step in the evaluation of the extension of the masses thanks to its large field of view. It sharply investigate the mass relationships with anatomical structures as nerves, vessels and articular structures. These data allow to well establish the tumor compartimentality, but the real challenge is to determine the benignancy or the malignant nature of the mass. Indeed only few tumors have typical MR features of benignancy (e.g. lipoma, angioma, neurinoma target-shaped) and a large number of masses need of biopsy. Functional imaging, as Diffusion Weighted Imaging and Dynamic-Contrast-Enhanced Imaging investigate the cellularity, the tumor matrix and the vascularization of the mass but the histological evaluation is mandatory. Contrast-Enhanced Ultra Sounds provide additional information regarding the tumor aggressiveness showing anarchic neoangiogenesis. Moreover it depict suspicious areas for greater dedifferentiation, supporting the biopsy. Contrast-enhanced Computed Tomography is really useful to evaluate large arterial vessels encasement and bone involvement. At present, the evaluation of tumor response is based on RECIST criteria and provides the assessment of the tumor size. Nevertheless the need to quantify the tumor necrosis is emerging and all imaging modalities with perfusional studies (CEUS, CT, MRI) have been proposed. The follow up is tailored depending on the anatomical site (superficial or deep masses) and on the tumor type; Ultra Sound and Magnetic Resonance Imaging are widely used with this aim.

RADIATION THERAPY FOR SOFT TISSUE SARCOMAS. NEOADJUVANT *VS* ADJUVANT TREATMENT

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One of the major issues in the management of Soft Tissue Sarcomas is to achieve optimal local treatment and its optimal integration with adjuvant chemotherapy (CT) in high-risk patients. Combined preoperative or postoperative radiation therapy (RT) and limb preservation surgery is a well established approach for extremity sarcomas. Preoperative RT presents some potential advantages, including smaller treatment volumes potentially leading to decreased late tissue morbidity, possible tumor reduction allowing more conservative surgery, and may be the preferred option, especially for critical tumour size and unfavourable locations, allowing more favourable local control and functional results (1). Pre or postoperative RT integrated with full-dose Epiribicin and Ifosfamide was feasible in the recently reported phase III Italian Sarcoma Group Trial comparing 3 *vs* 5 cycles of adjuvant chemotherapy. Early postoperative complications were higher in the preoperative CT-RT patient group, but their incidence were well comparable with historical available data (2,3). This trial demonstrated that 3 cycles of full-dose CT are not inferior to 5, resulting in highly compliant adjuvant program for the patient. Chemotherapy was given preoperatively, exploiting its potential added local benefit, possibly in combination with preoperative RT (4). Interestingly, preoperative RT-CT resulted to minimise the negative prognostic impact of close or positive margin of resection on local and distant outcome, thus allowing more conservative surgery in proximity of critical structures with improved functional results (5). Recent advances in RT planning and delivery, including IMRT and IORT, allow now more accurate radiation dose distribution to the tumour volume while sparing surrounding uninvolved structures, resulting in a potential decrease in postoperative complications when preoperative RT+/- CT is given. Reducing the RT dose to tissues that will be used as a surgical flap at surgery could improve the wound healing process and reduce the risk of postoperative complications. Moreover, selected RT dose escalation to the tumor bed at surgery with IORT, offers a favourable opportunity to increase the chances of tumor control avoiding radiation to vulnerable surgically reconstructed structures. Such innovative integrated approach (preoperative IMRT/Chemotherapy, Resection/IORT and Surgical Reconstruction) is currently ongoing at our Institute, in particular for high-risk patients. Our recently reported results in extremity sarcomas, demonstrated a

high local control rate and no difference in local recurrence rate when marginal resection was needed to spare function (role of IORT in extension of surgical margins). Importantly, a low incidence of postoperative complications has been reported (6). Preopertive IMRT combined with aggressive surgical resection and IORT is currently used at several institutions in unfavourable tumor locations, such as retroperitoneal sarcomas. This treatment strategy resulted feasible and effective with improvement of local tumor control and a potential impact on patient survival. Finally, much interest has been recently dedicated to pathological and molecular aspects of this disease. Sarcomas are not only rare but also highly heterogeneous including more than 50 distinct histotypes, with different sensitivity to CT and RT. At present, a new ISG phase III Trial in high-risk sarcomas is ongoing to compare full-dose standard *vs* histotype-tailored neoadjuvant CT within the context of an integrated strategy, including these innovative local treatment modalities. The identification of path and molecular factors that are predictive of response to treatment is currently under investigation.

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THE ROLE OF IMAGING IN RADIATION TREATMENT PLANNING FOR SOFT TISSUE SARCOMAS

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Soft tissue sarcomas (STS) constitute an uncommon and heterogeneous group of tumors of mesenchymal cell origin. Although STS comprise more than 50 different histopathological subtypes, they share several clinicopathological features and are usually considered as a group for diagnostic and therapeutic purposes, with the exception of specific particularities of some subtypes such as rhabdomyosarcoma, gastro-intestinal stromal tumors (GIST), extraosseus osteosarcoma and Ewing's sarcoma. STS can arise anywhere in the body, but most originate in the extremities, less frequently in the trunk, retroperitoneum, head and neck, and viscera [1-3]. The cornerstone of the management of STS patients is surgery but contemporary management of sarcomas often includes a multidisciplinary approach using a combination of surgery, radiotherapy (RT), and chemotherapy specific for tumor type, histologic grade and stage of disease. RT can be employed as neoadjuvant (preoperative), adjuvant (postoperative), or primary local therapy, depending on the site and type of tumor, the availability and acceptability of the surgical option, and the efficacy of chemotherapy. Neoadjuvant RT is frequently used for large, deep soft tissue sarcomas and can also be delivered prior to resection of spine or pelvic sarcomas. Adjuvant RT is utilized in many centers following resection of soft tissue sarcomas if the tumor, or the surgically contaminated tissues in patients with incomplete excision, cannot be excised with a safe margin or an intact fascial plane [4]. It is also used for patients with poor histologic response to chemotherapy, or intralesional excision of a radiographically or cytologically benign-appearing lesion later found to be sarcoma on review of final pathologic material [5]. The existence of a zone of uncertain size and location that may contain subclinical disease in proximity to the presenting site of the primary tumor presents a frequent dilemma. The local growth characteristics of STS have suggested that tumor cells may be located in the surrounding soft tissues at some distance from the main tumor mass. This risk zone, that was described as consisting of a granulation tissue-like proliferation with characteristcs including edema and neovascularity but also satellite tumor cells, need to be included in radiotherapy target volumes with an appropriate margin. Nowadays, magnetic resonance imaging (MRI) has emerged as the prevailing imaging modality in the diagnosis and evaluation of sarcomas. As a matter of fact, MRI better delineates soft tissue compared to CT but can also show high T2-weighted signal changes in the surrounding tissue representing peritumoral edema, i.e. a risk zone that could contain satellite tumor cells. Therefore, MRI is often recommended to determine more accurately the radiation target, i.e. the clinical target volume (CTV) through coregistration with planning CT images. In this case, MRI should be performed with the same patient's position of planning CT to optimize the quality of the coregistered images [1, 6, 7]. Optimal target volume definition for preoperative radiotherapy of STS patients is critical to ensure maximal local disease control and avoid unnecessary irradiation of surrounding healthy tissues, thereby reducing the risk of long-term sequelae of treatment [8]. In the case of postoperative RT, a portion of the dose is ordinarily applied to a larger volume encompassing the surgical bed with appropriately safe margins. Commonly applied doses are 45-50.4 Gy in once-daily 1.8-2-Gy fractions. This is followed by a smaller volume boost to the tumor bed. Typically, doses of 10-16 Gy are applied, resulting in a total dose of 60-66 Gy. For preoperative radiotherapy, the gross tumor volume (GTV) is defined by the tumor volume visualized using gadolinium-enhanced, T1-weighted MRI. The GTV encompasses the dominant lesion but not the peritumoral edema seen on T2-weighted scans, while the CTV is constructed by expanding the GTV in all directions by a surrounding

margin of 1.5 – 2.0 cm, except longitudinally, where the expansion is typically larger and, in the cases of extremity STS, is of about 4 cm [2]. Preoperative RT is usually delivered in once-daily 1.8-2-Gy fractions to a total dose of 45-50.4 Gy. In terms of radiotherapy technique, IMRT ± IGRT is often the treatment of choice since it is able to deliver a highly conformal dose to the gross disease planning target volume and high-risk subclinical disease regions while minimizing dose to selected, adjacent critical structures. Positron emission tomography (PET) has wide-ranging utility in sarcoma, including staging, assessment of prognosis,
monitoring response, and potentially to customize treatment regimens. A study found that FDG-PET-based GTVs contoured using a threshold value of 2 or 2.5 most closely approximated standard T1-gadolinium MRI volumes [9]. Higher threshold values lead to PET volumes much smaller than the GTVMRI. The standard deviations of the ratio of the volume of GTVPET to the volume of GTVMRI for all thresholds were relatively large. An important factor is that most of the lesions in this study were associated with non-uniform distribution of FDG. This heterogeneity could be attributed to focal necrosis and variation in histology or cellularity within the tumor. Another factor is the relatively poor spatial resolution of PET functional images. The poor correlation between the FDG-PET/CT and the MRI-defined volumes suggests that it is unlikely that FDG-PET can significantly contribute in GTV definition for RT planning in patients with STS [9, 10]. On the other hand, FDG PET provides additional prognostic information. Higher metabolic activity (maximum standardized uptake value) of the primary tumor has been shown to predict shorter survival. With integrated whole-body PET/MRI, a novel metabolic-anatomic imaging technique recently introduced into clinical practice, it could be possible to combine morphologic and functional information [10, 11]. MRI has also gained an important role in the follow-up of patients treated with radiotherapy. While MRI proved to be highly sensitive in the detection of musculoskeletal changes over time, it is not very specific because of the difficulty to distinguish local recurrence from post-RT soft tissue changes. Diffusion-weighted magnetic resonance imaging (DWI) is a recent addition to the soft tissue MRI sequences being employed at many institutions. DWI provides qualitative and quantitative functional information concerning the microscopic movements of water at the cellular level and it could be used for the differentiation of post-therapeutic change and recurrence of STS [12-14].

In conclusion, MRI better delineates soft tissue compared with CT and therefore it should be recommended to accurately outline the radiation target volumes (GTV and CTV). Functional imaging, such as FDG-PET and DWI, are still objects of study. In the future, other MRI techniques, such as perfusion studies and DWI, as well as various PET tracers could help clinicians to better identify target volume and to assess early treatment response.

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ADJUVANT EXTERNAL BEAM RADIOTHERAPY IN THE TREATMENT OF HIGH RISK THYROID CANCER: PROS

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The first approach to the management of Differentiated Thyroid Carcinoma is surgery. EBRT has been known to control unresectable thyroid cancer at least since the 1960s. In patients with a risk of recurrence, RAI therapy after total thyroidectomy can reduce that risk to a minimum. However, it is known that the risk of recurrence and death even after RAI is higher in the presence of extrathyroid extension, and RAI is less effective in controlling extrathyroid disease and extrathyroid extension. It is also know that the risks of both recurrence and death increases with increasing age. Often, this therapy is reserved for older patients with macroscopic residual disease or those with aerodigestive or massive muscle invasion and at least presumed microscopic residual disease, and patients with recurrent disease who cannot be satisfactorily managed with additional surgery and 131I. Patients younger than 45 years are generally not treated with EBRT because of their good prognosis and the possible late side effects of therapy. Although EBRT can con-

trol gross disease in the neck, the initial results of adding EBRT after resection of all gross disease were conflicting, some suggesting no benefit or even a deleterious effect; however, the majority reported an improved local failure-free rate from the addition of EBRT. In fact several retrospective studies have shown that EBRT may be an effective adjuvant therapy after surgery to prevent locoregional recurrence in patients older than 45 years with locally invasive disease. One study from the Christie Hospital (Manchester, UK) on patients with extrathyroid extension reported a local control rate of 89% if there were negative margins or microscopic residual disease after surgery and 69% if there was macroscopic residual or inoperable disease. In a study from MD Anderson (Houston, TX) on 131 patients (96% of whom had extrathyroid extension), the locoregional relapse-free rate was 79% at 4 years after EBRT. The most convincing report was from Essen (Germany) because all patients were at high risk of local recurrence, in that they had extrathyroid extension, were >40 years old, and all were treated with standard therapy of surgery, RAI and thyroid stimulating hormone suppression. In that study, the addition of EBRT was a predictive factor for improvement in time to locoregional recurrence (*P*_0.004) and time to distant failure (*P*_ 0.0003). The lack of prospective studies showing a benefit from external radiotherapy resulted in attempts in North America and Europe to start a randomized controlled study. Unfortunately, these attempts were unsuccessful. The European study, which closed early because of poor accrual, had many problems. To be entered, patients had to be older than 18 years with extrathyroid extension (T3 or T4); therefore, they were not necessarily in the high-risk group who would benefit from EBRT as defined by the ATA guidelines. Although started as a randomized study, it was changed to a cohort study because of a potential 311 patients only 47 patients consented to randomization. Of the 47 randomized patients, 26 had radiation, and of these, the mean age was only 47, and the majority (n =15) had tumors =1 cm. None of the irradiated patients had a recurrence, but there was only a 3% recurrence rate in the control arm; the difference was not statistically significant. The low recurrence rate in the control arm is probably a reflection of the lack of high-risk patients being randomized. The problems associated with this study mean that it cannot be interpreted as showing no benefit to adjuvant therapy in suitably selected high-risk patients. Similarly, in a study from Memorial Sloan-Kettering Cancer Center, of 64 patients with highrisk DTC the 4-year locoregional control rate was 75%, with more local failures in the tall-cell variant than other histologies. All these studies concluded that in patients with DTC and high risk for locoregional failure where no further surgery is possible, EBRT resulted in high regional control rates. On the other hand in a report of 28 patients with gross residual disease after surgery, after EBRT, the local relapse-free rate at 10 years was 90%, but the cause-specific survival was only 48%. This shows that although EBRT can result in control of local disease in the neck, these patients are also at high risk of distant disease that is not controlled by RAI or other systemic therapy and often results in the patient's death.

ADJUVANT EXTERNAL BEAM RADIOTHERAPY IN THE TREATMENT OF HIGH RISK THYROID CANCER: CONS

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Introduction: The therapeutic approach to differentiated thyroid cancer is usually surgery as initial treatment, which is, often, followed by radioactive iodine therapy. There are not high levels of scientific evidence regarding the use of external beam radiotherapy in these tumors. In fact, the current knowledge is based on a retrospective analysis of case studies of large institutions or database of patients treated according to established protocols. However, the data of a multicenter study has recently been published, this was planned as a prospective multicenter trial on the benefit of adjuvant external beam radiotherapy (EBRT) in locally invasive thyroid carcinoma (M.Biermann – 2009). Unfortunately the study was closed early because of poor accrual and although started as a randomized study, it was changed to a cohort study. This report nonetheless concluded there was no benefit in adjuvant EBRT. (M.Biermann – 2009 / Brierly -2012).

Radioactive iodine therapy: As already stated, the standard therapy for differentiated thyroid cancer is surgery. In patients with a higher risk of recurrence the radioactive iodine therapy after thyroidectomy can reduce this risk to a minimum. This treatment allows the destruction of residual thyroid tissue, almost always present after total thyroidectomy (Mazzaferri – 2001) and it is carried out with three objectives: 1) Follow-Up: during follow-up, the destroying of residual after surgery makes early detection of recurrence easier through the Tg measurements and/or total body scintigraphy with radioiodine; 2) Staging: The after-therapy scintigraphy may help in the staging of disease thus highlighting the previously unidentified cancer, especially in the lateral cervical regions; 3) Treatment: To reduce the risk of disease recurrence and the risk of disease-related mortality for the potential tumoricidal effect of the remaining cancer cells after appropriate surgical resection or metastatic disease (Cooper - 2009). Regarding this last point there are a large number of retrospective studies that show a significant reduction in rates of disease recurrence and cause-specific mortality (DeGroot LJ – 1990, Samaan NA 1992, Mazzaferri 1994)

External beam Radiotherapy: In the past there was some disaffection with the use of EBRT in thyroid cancer. This was mainly for two reasons. The first, a conception (now questionable) that thyroid cancer is radioresistant. The second, the proximity of organs at risk (e.g. the spinal cord) when technology did not allow accuracy in dose conformation, in particular for the irradiation of the drainage lymph node. (Basi scientifiche per la definizione di line guida – 2006). Many authors have suggested a role for external beam radiotherapy in cases where there is an increased risk of locoregional recurrence after radioiodine therapy. It is known that the risk of recurrence and death increases with age (Coburn - 1995) and that radioactive iodine therapy is less effective in controlling the disease when it is extrathyroid (Vassilopolou - 2006). The lack of effectiveness of radioactive iodine therapy in

these patients depends on the fact that radioactive iodine may not be distributed well in areas with a local invasion and in the surgical bed where the surgery may have destroyed the normal vasculature. In addition, in elderly patients the uptake of iodine may be lower for a lower tumor differentiation (Brierley – 2012). For this reason, some authors have suggested a role for EBRT in elderly patients with extrathyroidal extension. Many retrospective studies conclude that adjuvant radiotherapy should be considered in patients at high risk of local recurrence, but only where no further surgery is possible (Brierley – 2012). In the therapeutic choice however, we must consider that the treatment with EBRT for tumors of the thyroid are not toxicity free. In fact, cases of III and IV grade acute and chronic toxicity have been reported in the literature. The experience of MSKCC reported acute mucositis grade 3 in 18% and dysphagia in 32% of patients. Moreover, in this experience 29% of patients were subjected to a short-term percutaneus endoscopic gastrotomy tube and 5% required enteral feeding for long-term support. (Terezakis SA – 2009). In the randomized German trial 1 patient was subjected to tracheostomy for chronic laryngeal edema (Biermann – 2009) In another experience, the MD Anderson group describes that in patients treated before IMRT, 12% had late toxicity and 9% required dilatation for esophageal stricture while with IMRT treatment 2% of patients had significant late morbidity of equivalent severity (Schwartz DL – 2008). This means that new technologies may play a decisive role in the definition of therapies for this type of tumor. Finally, some societies are considering the EBRT as a possible choice of therapy but only in certain selected cases. The American Thyroid Association recommends the use of EBRT in patients older than 45 years with extrathyroidal extension evident at the time of surgery and with a high likelihood of microscopic residual disease, and patients with macroscopic residual tumor in whom treatment surgery or radioactive iodine would probably be ineffective.

Conclusions: The role of external beam radiotherapy in high risk thyroid cancers is an issue of debate. On one hand we have a number of retrospective studies that suggest a benefit in selected cases of patients, while the randomized German trial, though containing a series of bias, does not recommend the use of EBRT. Furthermore, the external beam radiotherapy is not free from toxicity. For these reasons, this treatment should only be reserved for certain cases at high risk of locoregional disease in whom the potential benefits will outweigh the toxicity of the therapy and in whom no further surgery is possible (Brierley – 2012). In all likelihood new technologies will play an important role in helping to conform the dose accurately. It is hoped that either a multicenter randomized trial will be started, or an international large-database will be created to definitively clarify the role of this therapy.

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VOLUMES, TECHNIQUES AND TIMING

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Introduction: Thyroid cancer management involves a combination of surgery, thyroid stimulating hormone suppression, radioactive iodine (RAI) and external beam radiotherapy (EBRT). For the subset of patients with medullary carcinoma and carefully selected patients with anaplastic carcinoma of the thyroid, in whom there is no role for RAI, EBRT often forms an important part of the management of the primary or recurrent disease. However, in the management of differentiated thyroid cancer (DTC), the role of EBRT remains controversial because the lack of prospective randomized clinical trials renders it nearly impossible to provide definitive recommendations. Most published studies are retrospective analyses of small groups of patients with wide selection bias with regard to patient selection, EBRT technique, EBRT dosing, and irradiated volume. Furthermore, EBRT is usually used in combination with surgical resection and RAI therapy, making it difficult to define the specific benefit of EBRT alone. Most authors agree that EBRT is

not required in young patients (under 45 years of age) with microscopic residual disease that is likely to be RAI-avid, but it probably improves locoregional control in the setting of non–RAI-avid, unresectable gross residual disease in patients of any age. However, considerable controversy exists regarding the role of EBRT in the management of microscopic residual disease remaining after appropriate surgical intervention in older patients. It is also important to balance the potential for significant EBRT- and RAI-associated morbidities (such as mucositis, pharyngitis, xerostomia, thick saliva, skin fibrosis, tracheal stenosis, and esophageal stricture) with the potential benefit in terms of local control often without an overall survival benefit.

Rationale for External Beam Radiotherapy: EBRT can eradicate thyroid cancer cells not sterilised by RAI and this may relate to the radiobiological benefits of fractionated treatment. Patients with the papillary histological subtype of DTC seem to benefit most from EBRT and this may be a reflection of the natural history of this disease. Papillary thyroid cancer is often multifocal and tends to metastasise in a locoregional pattern to cervical lymph nodes. In contrast, follicular thyroid cancer has a higher tendency to spread through the haematogenous rather than lymphoid route with the appearance of distant metastases often not influenced by the lymph node status.

External Beam Radiotherapy Technique: Maximizing locoregional control is paramount in patients in whom EBRT is offered. Therefore, it is important to deliver the highest dose of radiation possible without causing injury to the surrounding normal tissues, spinal cord. Typically, when radiation is delivered in the postoperative setting, the target volume should include the preoperative tumor volume and the postoperative bed, paying attention to ensure coverage not only of the trachea-esophageal groove and neck to the level of the carina, but also of the anterior mediastinum. The doses typically range from 60 to 66 Gy. When resection is incomplete, the target volume is the same except that in regions of gross disease, the dose of radiation is increased to 70 Gy. PET scan obtained at the time of radiation planning can guide the appropriate dose levels to the target volume. There are two major problems with conventional planning technique: 1- the postoperative dose the lymph node regions receive in the neck is typically only about 40–44 Gy, which may not be sufficient for the eradication of microscopic disease; 2- the maximum doses received by the thyroid bed are typically 55–60 Gy due to the limitations of spinal cord radiation tolerance, which may be inadequate. Targeted radiation techniques such as IMRT has opened up new possibilities in the delivery of radiation in thyroid cancer. Furthermore, image-guided IMRT (commonly known as IGRT), can improve the precision of radiation delivery by capturing real-time positional films of the treatment volume during radiation delivery.

Timing: The timing of radiotherapy in relation to ablative and treatment doses of RAI is also variable. One strategy is to exhaust the use of RAI completely before using EBRT. Alternatively, EBRT can be used after initial ablation, an option particularly attractive in patients with macroscopic residual disease postoperatively. However, there are some concerns that a so-called stunning effect of radiation on thyroid cells may influence the efficacy of subsequent RAI. Locoregionally recurrent disease typically is managed similarly to locally advanced disease at initial presentation and it is possible to expect local disease control, especially for isolated cervical nodal recurrences. In some series, patients with recurrent disease did not appear to fare worse relative to patients treated at initial presentation as long as all gross disease could be resected. This suggests that deferring EBRT in favor of RAI and TSH suppression alone at the time of initial disease presentation may not sacrifice ultimate local disease control or survival. However, subsequent recurrence necessitates reoperation, with significant attendant morbidity and costs. In addition, not all recurrences can be salvaged successfully. The recurrences located in the thyroid bed and/or with soft tissue infiltration are less likely to be iodine avid and are controlled less frequently. Nonavid centrally located recurrences should be carefully considered for adjuvant EBRT. As for earlier treatment, EBRT provides a potential local control benefit at the time of initial presentation of high-risk disease.

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CLINICAL TARGET DEFINITION IN NON-SMALL CELL LUNG CANCER

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Radiotherapy is a key treatment modality in the curative therapy of patients with non-small cell lung cancer (NSCLC). Careful staging and patient selection is important to achieve the maximal chance of long-term survival with acceptable side effects. Similarly, accurate delineation of target volumes is crucial for preventing geographic misses. An incorrect definition of the gross tumor volume (GTV) or clinical target volume (CTV) is a common source of error, which can lead to under-treatment and a reduced probability of tumor control. The focus of the present article is to deal with issues that will surely affect the clinical target definition.

Diagnostic pitfalls in thorax anatomy: First of all, the extent of the parenchymal disease is defined on the lung window settings. The exact setting chosen will seem to increase or decrease the size of the abnormal area. One study has found that W = 1600 and L = –600 gives the best correlation between measured and actual volumes for parenchymal disease, and W = 400 and L = 20 for mediastinal disease [1].
Moreover, normal mediastinal structures could be misinterpreted as enlarged lymph nodes and this could influences counturing. A good knowledge of the position of the intrathoracic vasculature, the thymus and the pericardium, and the ability to track them over several sections, is essential to avoid confusion between lymph nodes and normal structures. Aberrant vessels or normal vessels with delayed enhancement are likely to cause some confusion. For instance, in Figure 1a the azygous vein is unopacified and gives the impression of bulky mediastinal lymph nodes. The same is true in Figure 1b where the right brachiocephalic is unopacified. Lymph nodes in the aortopulmonary window clearly show enhancement in Figure 2a and the physician may mistake these for vessels and not include them in the treatment volume. The pericardiac recess can easily be mistaken for an enlarged node (Figure 2b).

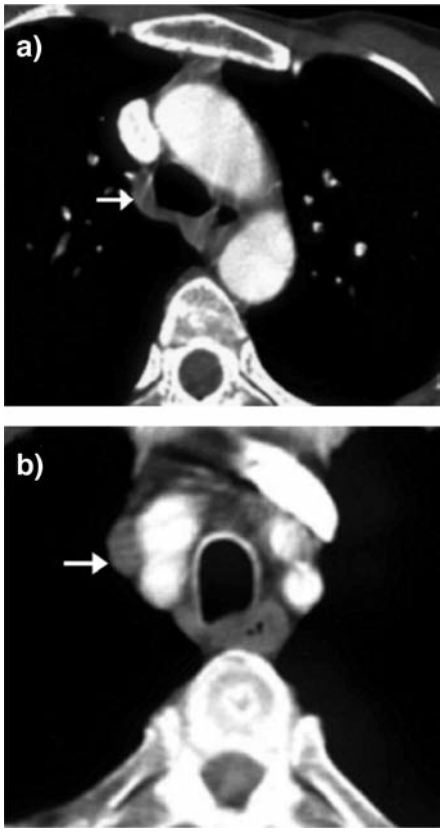

Figure 1a. The azygous vein is unopacified and gives the impression of bulky mediastinal lymph nodes; the same is true in Figure 1b where the right brachiocephalic is unopacified.

Natural History of NSCLC: The natural history of non-small cell lung cancer involves contiguous invasion of lymph nodes by metastatic tumor cells [2]. The thoracic lymph node chain is actually a functional unit, which drains lymph into the systemic circulation either into neck veins or into the thoracic duct of the mediastinum. This is one of the major pathways of metastatic spread to other organs of the human body [3-5]. In the majority of cases, tumor progression occurs contiguously without skip zones [6-9]. In both lungs, invasion starts with the hila. In the right lung, invasion continues toward mediastinal lymph nodes, in which the most frequently affected sites are inferior paratracheal lymph nodes (level 4) followed by subcarinal lymph nodes (level 7).

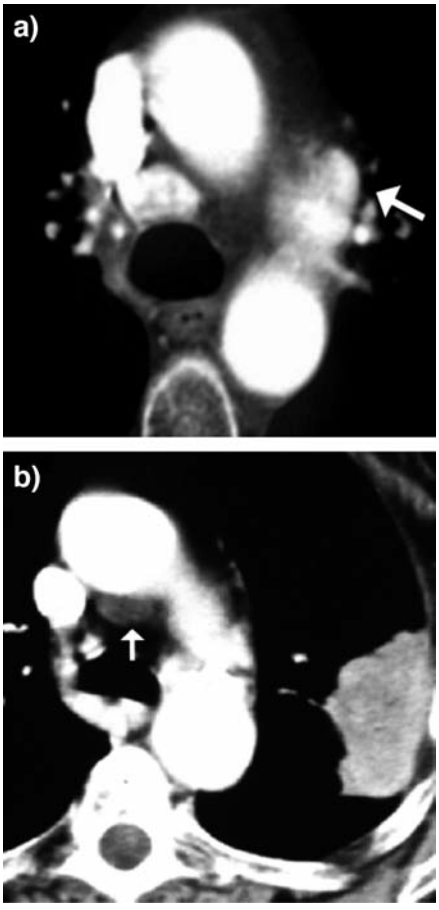

Figure 2a. Lymph nodes in the aortopulmonary window clearly show enhancement; the physician may mistake these for vessels and not include them in the treatment volume. Figure 2b. The pericardiac recess can easily be mistaken for an enlarged node.

According to Borrie et al. [10], when the primary tumor arises in the right upper lobe, tumor cells preferentially drain to lymph nodes situated around the right upper lobe bronchus and in the angle between upper lobe and middle lobe bronchi. There is no dissemination below the level of the middle lobe bronchus. Nohl-Oser et al. [11] con-

firmed these findings: the upper lobe essentially drains to the homolateral mediastinum and rarely to the subcarinal lymph nodes (1%) or the contralateral mediastinum (3%). The preferential pathways of drainage for right or left lower lobe tumors are the inferior pulmonary ligament lymph nodes and subcarinal lymph nodes. Metastatic spread rarely involves contralateral mediastinal and supraclavicular lymph nodes. The lymph nodes most frequently involved in left lung tumors are subaortic, or aortopulmonary nodes (level 5), followed by subcarinal nodes. Several authors have reported a higher frequency of subcarinal node invasion when the primary tumor arises in the left lung [12,13]. According to Borrie et al. [10], the left upper lobe drains to lymph nodes situated around the upper lobe bronchus and around the apical and basilar segmental branch of the left lower lobe. Although supraclavicular lymph nodes are conventionally included in large irradiation fields, their risk of metastatic invasion is very low, except in the case of tumors situated very high in the upper lobe. In our series, it is interesting to note that the probability of mediastinal involvement was higher when the primary tumor was located in the left lung, particularly in the upper lobe. This could be explained by the characteristics of our population comprising a large number of patients with an upper lobe tumor, but also by the lymphatic drainage of the lungs. The knowledge of the right drainage pathways plays a key role in clinical target definition for adjuvant treatment.

Volume definition in locally advanced disease: Three-dimensional conformal radiotherapy is designed to limit, as far as possible, the high-dose region to the target volume, thereby sparing the neighboring healthy tissues. However, smaller margins tend to be used to increase the therapeutic range. This reduction of safety margins increases the risk of unsuitable dosage because of missed nodal and primary microscopic tumor extension, setup errors, and organ motion. In particular, the quality of the results of 3D-CRT for NSCLC depends, among other things, on a very precise definition of mediastinal nodal volumes to be treated [14]. The Italian Survey by AIRO Lung Cancer Group [15] clearly showed that irradiation of all mediastinal nodal stations (ENI) is excluded from routine application in most institutions (87.7%). This report confirms modern literature results [16,17]. Recently, Emami et al. [17] analyzed data of 1705 patients from four RTOG protocols, and in their conclusions the authors stated that elective comprehensive irradiation of nodal regions in NSCLC does not appear to benefit patients treated with current standard therapy for the disease. Several studies have been published in which ENI has been omitted systematically. The conclusion was that studies of concurrent chemotherapy and radiotherapy for stage III NSCLC should use involved-field radiotherapy, which may result in increased local control because of the possibility to deliver higher doses with low toxicity.

PET-assisted GTV: An increasing body of evidence supports the use of PET-based imaging for selection of patients for both surgery and definitive RT. Similarly, the use of PET/CT images for accurate target volume definition in lung cancer is a dynamic area of research. In the few prospective studies where PET was used for staging and patient selection in NSCLC candidates for definitive RT, 25%-30% of patients were denied definitive RT, generally because PET detected unsuspected advanced locoregional or distant metastatic disease. PET/CT and CT findings are often discordant in NSCLC but studies with clinical-pathological correlation always show that PET-assisted staging is more accurate than conventional assessment with CT [18]. In all studies in which "PET-defined" and "non-PET-defined" RT target volumes were compared, there were major differences between PET and non-PET volumes. For mediastinal lymph node staging, the role of FDG PET scan is very well established. In the review of the literature published by Helwig and colleagues [19] it was concluded that while the average sensitivity of CT was 56%, for FDG PET, sensitivity was 83% for all stages, 91% when the CT scan showed enlarged lymph nodes and 70% for normal-sized lymph nodes. The specificity for CT was 81%, for FDG PET for all stages, 89%, with enlarged nodes 70% and with normal-appearing lymph nodes on CT it was 94%. These results should be viewed in perspective with mediastinoscopy, for which the specificity is 100%, but the sensitivity is 78% for all stages, 82% when the CT scan shows enlarged lymph nodes and 42% for normal-sized lymph nodes. Unlike PET-scans, mediastinoscopy does not survey all potentially involved nodes. It should be noted that these favorable results for PET only hold true if no chemotherapy has been administered, because chemotherapy can markedly reduce the accuracy of PET-CT imaging [20]. These results indicate that FDG PET is especially useful in NSCLC is due to its very high negative predictive value (>90%) for the detection of mediastinal lymph nodes. Therefore, in cases where PET-assisted and non-PET staging are different and biopsy confirmation is unavailable, it is rational to use the most accurate modality (namely PET/CT) to define the target volume. The use of PET/CT in patient selection and target volume definition is likely to lead to improvements in outcome for patients with NSCLC [21].

Clinical results: The PET-derived GTVs were usually smaller than those delineated with CT, thus leading to a decreased radiation exposure of the lungs and the esophagus sufficient to facilitate radiation dose-escalation [22,23]. Furthermore PET may prevent geographical misses by showing tumor in lymph nodes that appear uninvolved by CT criteria. A prospective clinical trial using this approach described isolated nodal failures in only 1 of 44 patients [24]. These results were subsequently confirmed in another, similar prospective study from the Netherlands Cancer Institute [25]. Moreover, recently has been published another trial by Fleckenstein et al. [26] on FDG-PET-confined target volume definition which confirm a low out-of-field isolated nodal recurrences on patients treated with chemoradiation. In these patients, dose escalation above 66.6 Gy was achieved and it might provide improved tumor control.

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LA NUOVA "TARGETED THERAPY" IN RADIOONCOLOGIA

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Over the last thirty years, translational research in tumor biology has led to the establishment of targeted therapy in cancer. The identification of specific molecules known to play a key role in cancer cell growth and survival has been subsequently accompanied by the development of molecularly targeted drugs. In line of principle, these substances are hypothesized to be more effective than other types of treatment, including chemotherapy and radiotherapy, and less harmful to normal cells, being able to selectively target and disrupt pathways specific to malignant cells. These biology-based advancements have profoundly expanded the potential repertoire of antineoplastic strategies and targeted agents represent integral components of today's clinical practice in several neoplasms, either alone or in combination with other treatment modalities. As such, the expression "targeted therapy" has traditionally been referred only to cellular and molecular level-oriented systemic therapies. As a matter of fact, loco-regional therapies such as surgery, radiotherapy and radiofrequency ablation are, by definition, *spatially* targeted therapies. In its essence, radiotherapy is characterized by the complex process of precise and accurate delivery of ionizing radiation to a specific site of interest. Nowadays, among the variety of modern radiation delivery technologies, the expression "targeted (radio)therapy" has progressively gained wide acceptance in reference to stereotactic radiotherapy. The term "stereotactic" simply relates to the correlation of tumor position to reliable fiducials with readily known position, thus defining a coordinate system that can be used to precisely target the lesion to be irradiated. In many clinical situations, the tumor itself can serve as the fiducial negating the need for external markers that have classically characterized stereotactic applications. In the oncology community, the interest in such highly focused radiation treatments has grown substantially in recent years, although the first implementation of some form of "targeted (radio)therapy" dates back more than 50 years ago, when frame-based, intracranial stereotactic radiosurgery (SRS) allowed the precise delivery of high doses of focused radiation in a single session. Since then, SRS and later fractionated stereotactic radiotherapy (SRT) have become a routine treatment option for

patients with metastatic disease to the brain, more commonly through frameless systems. For a long time, the possibility to extrapolate the principles of stereotaxy to extracranial sites was unthinkable due to 2 major problems. First, organ motion caused by natural physiological processes like breathing and digestion would require the addition of large safety margins to the target, resulting in excessive collateral damage of normal tissue with the delivery of high-dose radiotherapy. Second, relevant uncertainties regarding the exact definition of target extent would greatly limit the accuracy and the confidence of treatment, both for delineation, treatment planning and delivery purposes. By the early 1990s, technological advances in both tumor motion quantification and image guidance allowed the translation of SRS and SRT towards application to extracranial sites, resulting in what is now known as stereotactic body radiation therapy (SBRT). According to the American Society for Radiation Oncology and American College of Radiology definition, SBRT is a "radiotherapy treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body." The combination of a series of features such as improved machine precision, patient immobilization, motion management and image guided delivery have yielded the potential of biologically effective dose escalation through hypofractionated regimens, while sparing surrounding normal tissue. On a treatment planning's perspective, in analogy to SRS configuration, a typical SBRT implementation requires the use of many relatively weak, non-coplanar beams converging on the target, in order to create a steep dose gradient between the target boundaries and the adjacent structures. The potential to deliver very focused, precise, and biologically potent radiation dose to tumors in the chest, abdomen, and pelvis is intrinsic to SBRT definition. In a nutshell, the most significant characteristic of SBRT is the use of ablative fractionation that is facilitated by technologic innovation, with the term SABR (stereotactic ablative radiotherapy) often used instead of SBRT to further underline it. After about 20 years since its first clinical application, SBRT is today a little about "stereotaxy" in its intrinsic meaning and a lot about dose fractionation, target definition, motion control (4-dimensional therapy) and image-guidance. In recent years, increasing interest in the use of local therapies such as SBRT for metastatic patients has likely arisen also from improvements in systemic therapy. In the past, due to the ineffectiveness of cytotoxic agents in controlling tumor dissemination, such loco-regional treatments were often considered futile, or prescribed for purely palliative intent. However, the potential to aim at ablation of residual sites of metastatic disease through the adoption of potent local therapies follows the observation of longer survival of patients after effective systemic therapies in several malignant neoplasms. Although surgical metastectomy remains the most common and first-line standard among local therapies, non-surgical alternatives, including SBRT and radiofrequency ablation, have become increasingly popular because they are generally less invasive than surgery and have demonstrated considerable promise in eradicating macroscopic tumor. The rationale to recommend SBRT in patients with established metastatic disease could be justified by several assumptions, based on low or high levels of evidence. First, in some rare instances it might be reasonable to attempt to reproduce favorable anecdotal experience as in the case of healthy patients who are poor responders to chemotherapy and experience long-term disease remission after aggressive integration of local therapies (i.e, resection of multiple metastases and multiple cycles of SBRT). Second, it is not infrequent to observe some patients affected by common cancers such as breast, prostate or colon, showing prolonged disease-free intervals or better-than-expected responses to systemic therapy with only one or few original bulky metastatic sites still present: a local consolidation might prove to be beneficial. Third, as speculated by Hellman and Weichselbaum, a subgroup of patients might truly be "oligometastatic", meaning affected by a limited burden of metastatic disease, conventionally less than 5 detectable macroscopic lesions. A curative intent might even be pursued in such cases, although it would be crucial to be able to identify these patients consistently and treat them accordingly. Fourth, an upfront "debulking" procedure might result in a remaining tumor burden with a faster tumor growth rate and a higher degree of chemosensitivity, according to the Norton-Simon hypothesis. As systemic agents become more effective at limiting metastatic progression, in such patients disease control may correspond to a sort of chronic phase of latency. From time to time, macroscopic lesions might "flare up" as a result of drug resistance or changes in the host immune function. As a minimally invasive, potent local therapy with high likelihood of local control, SBRT would be a useful tool for reestablishing control of disease and help maintain a "steady state" of chronic malignant behavior. To summarize, if improvement in disease-specific survival is the goal, a local therapy like SBRT would likely be most beneficial in patients with controlled primaries, limited metastatic disease, metachronous appearance of primary and metastatic disease, histologies including colorectal, sarcoma, and renal carcinoma, younger age and higher performance status. In current practice, clinical evidence at different levels is available to support the use of SBRT in metastatic patients. Phase 3 data underline the potential of SRS in solitary or oligometastases to the brain and warrant its administration in such cases. In cases of lung, liver and bone metastases, both retrospective and prospective evidences are rapidly accumulating on the efficacy and general tolerability of SBRT. Although data for SBRT in these organs have been available for about only ten years, excellent rates of local control have been reported and prospective trials have already been developed. Interesting insights on the combination of targeted drugs and SBRT in the metastatic patient have recently been the matter of research and early publications. In this view, the expression "targeted (radio)therapy" could bring together the concepts of biologically targeting of specific pathways in cancer cells and the ablative intent of potent, highly focused SBRT. Phase I-II data are required to establish the toxicity of both sequential and concurrent administration of molecularly targeted agents

and high dose RT in metastatic disease. Apart from combination strategies and future research, SBRT has been more and more implemented in oncology practice in the last decade and its convenience, effectiveness, and favorable toxicity profile have clearly been recognized. To fully exploit its potential and integrate its role in modern treatment algorithms, several aspects will have to be clarified in the near future. From a radiobiological perspective, endothelial cell apoptosis and changes in vasculature have been reported to play a role in SBRT-mediated cytotoxicity; much remains to be explored to further understand how cells are killed and what is the impact of different dose-fractionation schedules, considering that the linear quadratic model has limitations in the application to hypofractionated regimens with more than 6 Gy per fraction. Currently, the lack of well defined biological and partly clinical predictive factors hamper the interpretation of the real impact of SBRT and to whom should it be strongly recommended. In other words, much work is needed to identify who might benefit most from intensified management strategies in the metastatic setting. SBRT should be evaluated in prospective, multi-institutional, phase II trials aimed at assessing its efficacy with measurable endpoints in well defined categories of metastatic patients, with stringent inclusion criteria. How to appropriately design such studies and integrate SBRT with systemic therapy are ongoing challenges. At present, the available data justify the prudent utilization of SBRT as an ablative therapy for treating selected patients with metastatic disease in the context of a multidisciplinary approach.

TRATTAMENTO DELLA PATOLOGIA NON ONCOLOGICA

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Cavernous angiomas him (or cavernomas) are vascular abnormalities that may occur in any part of the central nervous system. A cavernoma is an aggregate of abnormal blood vessels, dilated, in which the blood flows slowly and at low pressure. The lesion has a round shape, and a variable magnitude from a few millimeters to a few centimeters.

The cavernomas are present in 0.5% of people and equally relevant in the two sexes. It is believed that the basis of their development there is a congenital predisposition. In about half the cases can be recognized a real familiar and familial forms are often found multiple cavernomas. Recent studies have linked the predisposition to the development of cavernomas with the mutation of a specific gene located on chromosome 7.

The cavernous angiomas tend to run into repeated minor bleeding. Unlike what happens in the case of the MAV, the bleeding is most often of modest entity, since the pressure of the blood inside the cavernomas is minimal. These repeated micro-bleeding determine a progressive increase in size of the lesion, which in turn can cause neurological disorders.

Most bleeding from cavernoma is asymptomatic. The risk of bleeding is symptomatic of about 0.5% per year. This risk is increased in the case in which the lesion has already given rise to clinically significant bleeding, as well as in familial forms and in pregnancy.

The test of choice for diagnosis is magnetic resonance imaging (MRI). MR images in the cavernoma has a characteristic appearance, due to the presence in its context of degradation products of blood in different stages of development, witnessing the many micro-bleeding which the lesion has undergone

The treatment consists of total removal of the lesion and is designed to avoid the risk of bleeding, to prevent the development or worsening of neurological deficits and, in cases of epilepsy, to gain control of the crisis.

If feasible, surgical excision of the cavernoma is so plainly indicated in patients with neurological deficits and those with drug-resistant epilepsy. Given the relatively low risk of massive bleeding, in patients with asymptomatic or lesions located in critical areas can be taken into account initially a conservative approach.

The MAV (or arteriovenous malformations) are congenital lesions (but usually not inherited) of the brain and / or spinal cord are made up of a tangle of abnormal arteries and veins together without the presence of the small blood vessels of the brain , the capillaries. Inside the tangle of blood vessels there is usually parenchyma functioning. Can be found in any part of the brain or spinal cord, and it is unusual that are multiples.

It is estimated that 0.1% of the individuals is a carrier of a cerebral AVM and that these lesions become symptomatic during life in only 12% of cases. Often asymptomatic malformations are occasionally diagnosed during neuroradiological (CT and MRI) performed for other reasons. The MAV equally relevant in both sexes and usually occur in young adults (20-40 years). Some patients with cerebral AVMs develop a neurological deficit of motor (loss of strength) or sensitive (dysesthesia, paresthesia, anesthesia). These symptoms are due to changes in blood flow induced by MAV. The malformation represents the blood a preferential low-resistance: the arterial blood is diverted to the malformation and subtracted from the surrounding brain areas that undergo ischemia (mechanism of "theft").

An individual with cerebral AVMs is exposed every year to a risk of bleeding by about 4%. It follows that the overall risk of experiencing, during life, a bleeding depends on the life expectancy and is therefore significantly greater in the young than the elderly.

The risk of bleeding is higher if the MAV has already bled and this risk is particularly high during the first five years of the bleeding.

The bleeding tendency of a malformation also depends on the vascular architecture. Some structural features of the MAV, detectable by angiography, are associated with an increased risk of bleeding.

The microsurgical treatment can be recommended as the gold standard of management.

The goal of surgery is the complete removal of the MAV.

A number of considerations must be made in order to assess the risk of surgery: location, size, venous drainage.

You can use a classification system, which allows a rough estimate of the risk of treatment. This classification system (Spetzler-Martin grading) assigns 1 point to MAV less than 3 cm of diameter greater, 2 points to the MAV between 3 and 6 cm of diameter greater, and 3 points for the MAV larger than 6 cm. In addition, you add a point if the AVM is in eloquent area, and one point if it has a deep venous drainage.

Therefore, a MAV can be classified from 1 (surgical condition favorable) to Grade 5 (surgically intractable MAV).

RADIOSURGERY IN NON ONCOLOGICAL DISEASE

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Trigeminal neuralgia: TN is a severe and frequently disabling facial pain syndrome. Pain may be confined to a small area or spread throughout the distribution of one or more divisions of the trigeminal nerve. The features of the pain that characterize TN, other than its location, are its severity and lancinating or electric shock–like quality. Many procedures, including surgery and radiosurgery have been used in an attempt to alleviate TN in patients in whom pharmaceutical treatment failed to control the pain or induced side effects. Surgical treatment is successful in 90% of patients with low rate of side effects and recurrences (1,2,3). Surgical options include microvascular decompression (MVD) performed by suboccipital retrosigmoid craniotomy, and the percutaneous procedures of the nerve at the level of foramen ovale (balloon compression, glycerol rhizotomy or thermal radiofrequency rhizotomy) (4,5,6,7) In 1949, Leksell performed the first radiosurgical treatment of TN and reported positive long-term results). Following the Leksell experience, it has been possible to define the efficacy and safety of Gamma Knife stereotactic radiosurgery and an increasing number of institutions have started to adopt this procedure to treat TN . Literature data on TN treatment by SRS showed a complete pain control in 35-76% of patients and recurrence rates of 6-34% 30 days after the procedure. Hypoesthesia and numbness were the most common complications (in 10% to 50% of patients), and were related to the dose, to the length of nerve treated and to the distance from brain stem.The target definition in radiosurgery of TN is still controversial and has to take into account the pathophysiology of the disease, side effects related to the midbrain irradiation, and the length of the treated trigeminal nerve Many radiosurgery groups targeted the trigeminal segment close to the root entry zone; the rationale of this choice was based both on the concept of compression of the trigeminal nerve by a vascular structure at the root entry zone, and the higher radiosensivity of this portion of the nerve (8). Percutaneous surgical procedures targeted the Gasserian ganglion that is situated 3-4 mm anterior to the root entry zone; the good results obtained using this procedure suggested that the root entry zone was not always involved and the whole retrogasserian portion could be considered in the CyberKnife treatment of TN is still recent. In the Stanford series, pain relief was achieved within 24-72 hours in 70-93% of patients treated with CyberKnife radiosurgery. Furthermore, these results appeared to be stable after one year of follow-up. Lim et al. reported a series of 41 patients affected by TN with different aetiologies, treated by a dose ranging between 60 to 79.5 Gy to the 80% isodose line. The authors observed an onset of numbness in 51% of patients and a dose dependent increase in this side effect Fariselli et al treated 33 patients with the frameless CyberKnife system as a monotherapy All but two patients (94%) achieved a successful treatment outcome. The follow-up was 9-37 months (mean 23months). Historically, radiosurgery has been indicated for patients who failed previous treatments or were not suitable to undergo anaesthesia Currently, MVD remains the gold-standard treatment, however, the minimally invasive nature of radiosurgery seems more and more attractive for an increasing number of patients of all ages seeking surgical relief from pain. Different authors show that patients receiving radiosurgery as the first ablative intervention achieve good pain relief. Some other authors have also reported better pain relief after stereotactic radiosurgery as the first approach compared with those who received previous surgical procedures. These results could be explained by a higher efficacy of radiosurgery on an intact nerve.

Radiosurgery in invalidating tremor: Stereotactic lesioning of thalamus and basal ganglia for treatment of tremor is a well-known procedure which, prior to the introduction of deep brain stimulation, or DBS, was usually achieved using stereotactic surgical procedures. Considerable positive experience in functional radiosurgery using the Gamma Knife or linear accelerators has been reported since first Leksell's first report in 1951 Radiosurgery of invisible targets to treat movement disorders and intractable pain are still the domain of frame-based procedures, due to the need of a solid reference system registered to the anterior commissure-posterior commissure (AC-PC) line, which allows the use of stereotactic atlases. (9,10)

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RADIOSURGERY IN EXTRA-AXIAL BENIGN BRAIN TUMORS

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Extra-axial tumors are the extracerebral located central nervous system tumors. They are usually benign, and the location affects treatment planning and predicts their prognosis. The multiplanar capability of magnetic resonance imaging makes it the best technique in the evaluation of extra axial brain tumors. Extra-axial tumors that affect the brain include meningiomas, vestibular schwannomas, pituitary adenomas, and neurofibromas, as well as mesenchymal tumors of the skull and dura mater[1]. Even if surgical resection is the first line treatment of these neoplasms, some cannot be resected and others may recur despite resection. Furthermore, several of these tumors remain quiescent and do not require intervention, whereas others may grow and become refractory to standard therapy. Stereotactic radiosurgery (SRS) treats brain disorders with a precise delivery of a single high dose of radiation in a one-day session. Focused radiation beams are delivered to a specific area of the brain to treat abnormalities, tumors or functional disorders. So, SRS can create a desired radiobiologic response within the intracranial target with minimal effects to surrounding structures or tissues. Nevertheless, SRS might be suboptimal when a large volume of tumor must be covered and/or when dose prescription is limited by the tolerance of critical structures (e.g., pituitary gland and optical pathways). Fractionated stereotactic radiotherapy (FSRT) combines precision of the stereotactic approach with the radiobiological advantage of fractionation, and is an actual treatment alternative. Fractionated stereotactic radiotherapy is administered with the assistance of removable masks that achieve a lesser degree of immobilization with respect to SRS invasive frames. In clinical practice, both SRS and FSRT are used in patients with benign extra-axial tumors. However, because all forms of radiation treatments work over time, they may be inappropriate if symptoms are severe or life-threatening. Relief of acute symptoms may drive the first treatment choice to open skull surgery or medication. For instance, if the symptoms at the time of diagnosis are so severe that quality of life is affected, the appropriate choice for the first treatment may be surgery to relieve those symptoms and, the secondary treatment could then be SRS or FSRT.

Meningiomas: Surgical resection of meningiomas is generally considered the treatment of choice. However, complete tumor removal is not always possible with acceptable risk, and the tumor recurrence rate at 10-years ranges from 18% to 25%[3]. To reduce the chance of meningiomas recurrence or progression, SRS has emerged as an alternative or as an adjuvant treatment to surgical resection for an increasing number of meningiomas patients with surgically high-risk or recurrent tumors. Several studies have documented high tumor control rates after meningioma SRS[4,5]. Radiosurgery induces changes within the tumor's cells such that cellular reproduction is interfered and produces alterations within the walls of blood vessels supplying the tumor, and therefore the tumor's blood supply may be decreased over time. Comparison of the results of surgical resection and SRS for meningiomas is difficult due to selection bias. Local control rates following SRS of benign meningiomas range from 86 to 100% at 5 years and 83–95% at 10 years and are equivalent compared to total resection at 3 and 7 years[6]. Moreover, for subtotal resections SRS provides better progression free survival at 3 and 7 years than surgery[3,6]. In addition, SRS has been shown to be a highly effective adjuvant treatment for residual and recurrent meningiomas after surgery. Overall, the data suggest that subtotal resection with adjuvant SRS is as effective for tumor control as primary SRS or gross tumor resection[3]. Although SRS is an attractive alternative to surgical resection, the risk of radiation-related complications for patients with supratentorial meningiomas should lead to carefully evaluate the management decisions for these benign tumors, especially when they are surgically accessible. Indications for treatment of meningiomas with SRS continue to evolve. Most experts agree that smaller tumors (≤3 cm diameter) respond best to SRS. So, SRS is the treatment of choice for small tumors involving the skull base (including those within the cavernous sinus) and those closely associated with the venous sinuses. Larger tumors and those that can be resected easily, completely and with low morbidity (such as convexity meningioma) are generally considered for microsurgical resection. Generally, SRS doses range from 11 to 16Gy, and potential iatrogenic toxicity, such as oedema or neurologic dysfunction, is limited and minimized with the smaller treatment volumes encompassed. In order to minimize the potential for radiation-induced optic neuritis, the dose to the optic nerves and chiasm would be ≤ 8Gy. In clinical practice, FSRT is an actual treatment alternative for large tumors (>3cm) or lesions located near organs at risk. In our experience, the hypofractionated FSRT regimen (14-15 x 3Gy) adopted resulted safe and effective for patients with recurrent or inoperable intracranial meningiomas [7].

Vestibular schwannomas: The best management of patients with small- to medium sized vestibular schwannomas is one of the most controversial topics in neurological surgery. Several retrospective case-control series have been performed comparing surgical resection with SRS and, SRS had improved facial nerve outcomes and hearing preservation rates[8]. Patients returned to work faster after SRS, and the costs associated were less than open surgery[9]. In addition, patients having surgical resection have a significant decline in their daily living activities. Consequently, the best evidence supports SRS as

having better cranial nerve and functional outcomes compared to surgical resection for patients with small- to moderated sized vestibular schwannomas. Moreover, it remains to be proven that the low SRS doses (12–13Gy) provides the same high rate of tumor control respect to higher doses (14–16Gy)[10-12]. Recently, many centres are using fractionated radiation techniques to treat patients with bigger (≥3cm) lesions. This approach joins theoretical benefits of fractionation to spare the function of adjacent normal tissues. Unfortunately, because the dose and fractionation schemes adopted vary widely in published studies (e.g., 3 x 7Gy, 5 x 5Gy, 25 x 2Gy), it is impossible to identify the more effective dose fractionation schedule. Our experience with stereotactic radiotherapy in patients with vestibular schwannomas was recently reviewed. High rates of tumor control and preservation of hearing capacity were achieved with SRS (median dose 17Gy) and FSRT (27-28 x 2Gy). Toxicity resulted very limited with a low rates of damage to V° and VII° cranial nerves[13].

Pituitary adenomas: Although pituitary adenomas are generally benign and slow growing, sometimes can invade adjacent structures such as cavernous sinus. SRS is usually reserved for pituitary tumors that cannot be cured surgically and are not controlled with medical drug therapy. One of the main drawbacks of SRS is that it leads to delayed pituitary failure. This typically occurs several years after treatment, necessitating complete hormone replacement. SRS is increasingly utilized to manage patients with residual or recurrent pituitary adenomas after surgical resection. Proper patient selection is critical when considering SRS for patients with pituitary adenomas, and is generally based on the size and location of the tumor, as well as its relationship to the optic nerves and chiasm. Moreover, patients with new or progressive visual field deficits in the setting of an enlarging tumor are referred for surgical resection to reduce mass effect and improve neurologic function. Dose prescription is based on several factors including histology, tumor size, the distance from the optic apparatus, and the history of prior radiotherapy. Generally, for patients with hormone secreting tumors SRS dose ranged from 20 to 25Gy, while for nonfunctioning adenomas lower doses (14-16Gy) are adequate[14]. Particularly, SRS has also emerged as a safe and effective treatment for patients with hormone secreting pituitary adenomas. However, direct comparison of these studies is difficult because of varying criteria for defining biochemical remission. Despite the conflicting results, most recommend that patients be off pituitary suppressive medications for several months to maximize the chance of biochemical remission after SRS. Another advantage of SRS compared to standard radiotherapy for these group of patients is the fast time required to achieve biochemical remission. So, SRS is the preferred radiation management strategy for patients with either acromegaly or Cushing's disease to minimize the metabolic consequences of these conditions. Dimension of the lesion (< 3cm) and distance from the optic pathways (< 3mm) should be considered critical in the choice of stereotactic techniques (SRS *versus* FSRT) which must be adopted[15]. In our recent retrospective analysis SRS doses ranged from 12 to 20Gy, whereas FSRT schedules varied from standard (25 x 2Gy) fractionation to hypofractionation 14-15 x 3Gy (the equivalent dose in 2-Gy fraction, calculated with an a/b ratio of 3Gy, is 50Gy and 54Gy, respectively)[16]. We confirmed that SRS and FSRT are safe and effective in the management of functioning or nonfunctioning pituitary adenomas.

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THE MANAGEMENT OF CLINICAL RISK IN RADIATION ONCOLOGY

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Introduction: The risk of errors is inherent to virtually all human activities. In the field of clinical radiation oncology, the relevance of this issue is amplified by several factors: 1) the final aim of involved procedures, i.e. the cure of potentially fatal diseases (or the adequate palliation of uncurable disease); 2) the potential for significant

damages to the treated patient inherent to the treatment modality; and 3) the complexity of resources and of organizational mechanisms involved, leading on one side to the significant risk of errors in daily practice and on the other side to the potential capability of any clinical unit to limit the risk of significant errors to a minimum. Unfortunately, uniform definitions and terminology are still lacking (Fraass 2008, Royal College of Radiologists, 2008). A possible definition for "error" in radiation oncology may be as follows: "an unwanted or unexpected change (or deviation) from a normal system behaviour that causes (or has the potential to cause) an adverse effect to persons (or equipment)" (Clark 2010).The key concepts here are *the error* itself, consisting essentially in a deviation from a prescribed (or expected, or desired) sequence of events (e.g., a standardized clinical procedure), and its actual or potential outcome, the adverse event (more commonly reffered to as an *incident*).

A third important definition is *near miss*, referring to an error that is timely discovered (before treatment is actually delivered) preventing the production of any harm to the patient (i.e., the occurrence of an incident). Going back to the above mentioned factors of relevance, any error in RO has therefore the potential for directly causing, through the occurence of an incident, one or both the following adverse events: 1) a decrease in the probability of reaching the final aim of the procedure (cure or adequate palliation); 2) a direct damage to the patient of varying clinical significance but including death.

As a consequence of the relevance of these issues, and in consideration of factor 3, increasing efforts are being made by the RO community at large to develope a culture of safety and to promote the awareness of the relevance of risk management in daily clinical practice.

Magnitude of the problem: A few studies and initiatives have attempted to estimate the frequency of occurrence of errors in RO. A common preliminary observation in all reports is that the actual frequency of errors in any RO Unit is not known, as all statistics are obviously based on reported events, whereas a possibly much larger and significant proportion of actual errors goes unnoticed. Another issue in this kind of estimates is that reported errors have to be separated into subgroups according to their clinical significance and to other important features. For instance, in the report from the Ottawa Hospital Cancer Center (Clark 2010), "errors [in the report confusingly termed "incidents"] discovered during routine quality control within the work domain in which they occurred" were not considered. On the contrary, in the report by the Health Protection Agency (2012) covering a large experience in England & Wales, "non-compliance with some aspects of a documented procedure but not directly affecting RT delivery" are included in Level 5 RT errors (i.e., those with the least clinical relevance). As a matter of example, the report from Princess Margaret Hospital in Canada (Huang 2005) estimated the risk of any error at 1.97% per treatment delivered, or 1.28% per volume treated. However, if only "non-minor" errors are considered, the risk declines at 0.02% according to the Ottawa experience (Clark 2010). In the large, multicenter experience in England & Wales (HPA 2012), "Patient Safety Incidents" represented 2.4% of the total number of errors (N=3411). Interesting observations are that the progressive implementation of a "reporting and learning system" within the clinical unit is uniformly associated with increasing rates of "minor" (or clinically non significant) errors, and with decreasing rates of "major" (or clinically significant) incidents.

Operative strategies: Strategies to deal with the issue of clinical risk in RO are essentially based on two approach: proactive and reactive. The reactive approach is easier and more intuitive, as it is based on the reporting, on the recording and on the careful analysis of actual errors (for instance with the Root Cause Analysis). Its drawback is that it is based on actual errors rather than on preventive measures. However, even a brief review of reported single-instituition experiences, and of existing databases and classifications may give an exaustive picture of errors in RO. The proactive approach is essentially based on a detailed and critical analysis of the workflow within a clinical unit, aiming at quantifying the expected potentiality for error occurrence in each step. A representative methodology for this approach is the Failure Mode Effects and Criticality Analysis (FMECA) (Scorsetti 2010).

Conclusions: The risk of errors in RO is now well documented, and its clinical relevance cannot be underestimated. Operative procedures should be implemented, both at the individual RO unit level and at the community level (i.e., scientific and professional societies, health providers etc.) to minimize the occurrence of errors and of clinically significant incidents. Finally, due to the rapidly evolving nature of RO and to the frequent introduction in clinical practice of newer technologies and procedures, risk management activities in this field should be regularly updated.

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PROCEDURAL RISK ANALYSIS MODELS

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A safe and effective radiotherapy treatment necessarily consists of treating the correct tissue in the correct patient with the correct dose. This is to be accomplished in one of the most complex settings in healthcare-one that is steadily growing more complex. Radiotherapy (RT) might expose patients to unwanted risks due to many factors. First of all, patients that undergo a RT treatment are generally affected by cancer and for this reason, they are often in critical physical and psychological conditions. Furthermore, the RT process is characterised by a deep interaction between completely automated functions,

delivered by advanced hardware and software technologies, and human decisions and activities, as many health professionals are involved and many interactions between the patient and the professionals take place [1]. All these peculiarities make the RT process potentially at risk for the patient. Reported error rates have ranged from 0.06% to 4.66%, depending on how errors are quantified [14-15]. Although most of these errors are minor and treatment can be adjusted to allow effective therapy, there is a strong incentive to reduce these rates even further, given the potentially catastrophic nature of an error. In fact, despite the adoption of quality assurance programs and a tight monitoring of the process, literature reports an increasing concern for adverse events in radiation oncology [2–6], the consequences of which are sometimes fatal or strongly disabling for the patient. These evidences clearly reveal that quality and safety in radiation oncology strongly depend on a correct management of risks, which should be mapped and evaluated systematically [5]. The analysis and control of adverse events (AEs) can be done by means of different approaches either retrospective or prospective. Any time, an AE occurs, retrospective analysis is applied to investigate and correct all the criticalities that paved the way to the event, and to prevent it from happening again. Among these methodologies, the most widely used is the root cause analysis (RCA), aimed at identifying the root causes of near misses or AEs [5]. The practice of RCA is based on the belief that problems are best solved by attempting to correct or eliminate root causes, as opposed to merely addressing the immediately obvious direct causes. Other approaches to manage AEs are represented by audit techniques, data collection and statistical processing of incident reports. Indeed, voluntary reported AEs are often classified and collected into databases aimed at establishing standard taxonomies of the most frequent errors in the RT process [2–4, 6–8]. Another retrospective analysis is the Radiation Oncology Safety Information System (ROSIS) established in 2001. The aim of ROSIS is to collate and share information on incidents and near-incidents in radiotherapy, and to learn from these incidents in the context of departmental infrastructure and procedures [16].
Proactive analysis is another method to analyse the risk of a clinical process. A proactive approach allows to study the whole process or part of it, independently from the occurrence of an AE, to identify and evaluate the prevalence of all the ways in which the process may fail, impairing the achievement of the expected results. It also enables to prioritise and assess the expected benefits of corrective actions. This approach, when involving professionals of good experience, can be considered as more complete if compared to a retrospective analysis, as it allows identifying criticalities that could never be underlined if an AE did not occur or was not reported. Proactive analysis is the one that best suits to a complex process like RT [9,10]. Various proactive approaches are available in literature, among them, process mapping, value stream mapping, fault tree analysis (FTA) and failure mode effects and criticality analysis (FMECA). FMECA analysis consists of the following tasks: (1) create a visual map of the process [Figure 1], (2) identify possible failure modes; assign risk probability numbers (RPN) to each failure mode based on tabulated scores for the severity, frequency of occurrence, and detectability, each on a scale of 1 to 10; and (3) identify improvements that are both feasible and effective. The RPN scores can span a range of 1 to 1000, with higher scores indicating the relative importance of a given failure mode. [10]
In our RT and radiosurgery department we applied a proactive analysis using the systematic application of the FMECA method [11]. A quantitative analysis was made by means of the IDEFØ (Integrated Definition Function). IDEFØ is a flexible modelling technique that clearly describes the process activities by their inputs, outputs, controls, and mechanisms. The description of each activity can be refined into greater and greater detail according to the requirements and main objectives of the analysis.
The RT process was completely mapped using IDEF Ø. Organizational and procedural corrective measures were implemented. A set of safety indexes for the process was integrated within the traditional quality assurance indicators measured by the unit. A strong commitment of all the professionals involved was observed and the study revealed to be a powerful "tool" for dissemination of patient safety culture. The feasibility of FMECA in fostering radiotherapy safety was proven and it appears as a powerful and simple tool for prospective, multidisciplinary evaluation of patient safety in a radiotherapy department. Nevertheless, some lessons learned as well as weaknesses of current practices in risk management open to future research for the integration of retrospective methods (e.g. incident reporting or root cause analysis) and risk assessment. In summary, quality and safety in radiation oncology significantly depend on a correct management of risks [1,5, 11-13]. In the last few years, some RT departments began to monitor and collect errors in the RT process [11]. The introduction of efficient and objective procedures is strongly suggested for monitoring and preventing the risks.

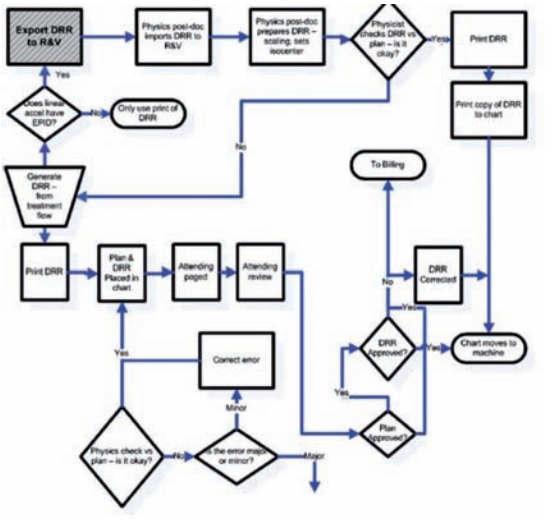

Figure 1. Example of process map highlighting the production and handling of digitally reconstructed radiographs (DRR) in the radiation treatment planning process.

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RISK CONTAINMENT PLAN

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Backgrounds: Modern radiation therapy is complex and rapidly evolving and involves understanding of the principles of medical physics, radiobiology, radiation safety, dosimetry, radiotherapy planning, simulation and interaction of radiation therapy with other treatment modalities. Typical steps of radiotherapy treatment include: 1) assessment of patient; 2) decision to treat; 3) prescribing treatment protocol; 4) patient positioning and immobilization; 5) simulation, imaging and volume determination; 6) planning (equipment and software commissioning); 7) treatment information transfer; 8) patient setup; 9) treatment delivery; 10) treatment verification and monitoring [1].

The literature in the area of radiation safety is limited, however, it shows that in the years 1976 to 2007, 3125 patients were reported to be affected by radiotherapy incidents that led to adverse events. About 1% (N=38) of the affected patients died due to radiation overdose toxicity. Only two reports estimated the number of deaths from under-dosage. A summary of injurious and non-injurious reported incidents (near misses) for the last 30 years (N=7741) reveals that the highest number of injurious incidents (N=1702, 22% of all incidents) were reported in the "planning step", and the highest number of near misses were related to the "information transfer" step (N=1732, 22% of all incidents). [1]. The attention to the risk management by radiotherapists and the increasingly widespread culture about QA has improved the effectiveness of the treatments and nowadays it can be stated that: "Radiotherapy is widely known to be one of the safest areas of modern medicine, yet, for some, this essential treatment can bring harm, personal tragedy and even death" (*Sir Liam Donaldson Chair, World Alliance for Patient Safety*). Quality assurance (QA) in radiotherapy is: "*all procedures that ensure consistency of the medical prescription, and safe fulfillment of that prescription, as regards to the dose to the target volume, together with minimal dose to normal tissue, minimal exposure of personnel and adequate patient monitoring aimed at determining the end result of the treatment*". [2]

Risk containment plan: Modern radiotherapy departments are multisystem dependent environments where the interaction of many health-care workers collaborating on diagnosis and treatment procedures with highly complex technical measurements and calculations can be a source of risk and error. One of the most crucial activities in a QA-certified radiation oncology department is the organized review and monitoring of all aspects of safety, errors and quality. The first step is to create a "culture of safety". Safety protocols should be adhered to for all stages of radiation treatment namely: patient evaluation, tumor localization, patient immobilization, field placement, daily patient setup, dose calibration, calculation, treatment delivery and verification, as well as for equipment commissioning and maintenance. The recent "blue book" of the ASTRO [3] reports some instructions to control and contain the risk such as: *QA Committee* - A dedicated formal multidisciplinary team (e.g., physicians, medical physicists, medical dosimetrists, nurses, radiation therapists and information technology support). QA committee should meet regularly to develop initiatives related to patient safety which are feasible and work best for the individual institution. This committee should establish a mechanism for reporting and monitoring quality problems, near-misses and errors in treatment, diagnosis, patient care or other procedural problems that might lead to errors. Employees should be encouraged to report both errors and near-misses (errors that almost happen). The study of near-misses is powerful in identifying problems with work processes that can lead to an error. The reporting of near-misses should be met

positively, and not with fear of punitive action. *Minimizing Time Pressures* - In order to avoid safety problems or quality lapses caused by rushing to meet unrealistic scheduling expectations, each institution should determine the appropriate process time allocated for each step in the process. It is the responsibility of each institution to develop its own guidelines for the amount of time allocated to each step in order to avoid inappropriate time pressures. Schedules should be realistic to avoid/minimize hurrying through a given task and risking error. An excessive workload can lead to errors. Conversely, light workloads can also be a problem since a certain level is needed to maintain "situational awareness". *Incorporating QA Tools/Functionality Into Software* - Some embedded automatic QA functions would be useful, such as: For a new plan, the system searches its directory archive for patients with the same name to identify inadvertent retreatment. For common diagnoses, the planning system compares the proposed target volumes and associated dose parameters to a library of user-specified "expected parameters and issues predefined alerts". Normal tissue dose-volume parameters are compared to user-specified constraints. Common nomenclature of target volumes, organs at risk and plans to facilitate review of plans and identification of outliers. *Peer and Interdisciplinary Review* - Peer review is an essential part of the safe delivery of radiation. Physician to-physician peer review is useful (review target delineation and chart round process). Peer review is important for all team members as well. As an example, medical dosimetrists can check each other's work (e.g., choice of beam selection/weighting). There is additional utility to prospective multidisciplinary interactions (e.g., between physician, medical physicist, medical dosimetrist, nurse and radiation therapist). A dosimetrist might note inconsistencies in the segmentations and directives, and anticipate dosimetric challenges prior to initiating planning. Such a preplanning/treatment meeting facilitates a healthy interdisciplinary dialogue that can make the subsequent planning/treatment processes smoother, but may also require more time between CT-simulation and treatment. *Daily Morning Meetings* - Having all members of the team meet daily to review the upcoming clinical activities can be a useful exercise to prevent potential problems. For example, the CT-Simulation therapists can review the day's schedule, noting patients whose records lack clear directives. Patients presenting unique challenges or learning opportunities can also be identified and discussed. The morning meeting serves the practical function of trying to anticipate the upcoming challenges and avoid chaos in the clinic. It also serves a social and cultural function to bring the department together daily, fostering an environment of easy communication among all team members. Issues relating to safety/quality/efficiency should be routinely included in all departmental activities. For example, the morning meeting is a good opportunity for leadership to make announcements about ongoing initiatives. *Monitoring* - Regular reports summarizing the outcomes of safety meetings can be provided to all department members and posted in prominent locations throughout the department.

Our proposal: At our institution we have implemented some of the principles already mentioned, e.g. multidisciplinary approach to cases, peer review, double check, daily morning discussion, using video-conference calls connecting the center of Modena (hub) with that of Carpi (spoke) also. Nevertheless we are constantly looking for methods that can increase the safety of our work in cooperation with Medical Physic Unit. Classically risk management in health care is based on a retrospective approach (when the event has already happened) or prospective approach (preventing the possible occurrence). Without neglecting the crucial role of a retrospective approach, in recent years, the prospective approach has taken an increasingly important role for the risk management in radiotherapy, in particular that provided by the FMEA (Failure Mode and Effect Analysis) or FMECA (Failure Mode, Effects, and Criticality Analysis). This forecasting methodology, used for many years in the management of complex organizations (aerospace, nuclear, military), allows you to obtain high reliability. It consists of several steps: 1) identification of critical process to analyze, 2) study of the process, 3) risk analysis, 4) definition and implementation of containment plans of the risk and 5) monitoring of results. Experiences with FMEA/FMECA analysis has been implemented and reported by some Italian institutions [4] pointing out that incident reporting and analysis are not sufficient for assuring patient safety and proactive risk assessment should also be implemented. One of the most important issues that may limit the practical use of FMEA/FMECA is the difficulty of identifying the critical process: it can be difficult to judge in advance which process can be more "risky" in the context of clinical radiotherapy and deserves a containment plan. We present our proposal to combine the retrospective approach to that perspective to plan programs by direct detection, of adverse events or near misses within our division as proposed by WHO [1] during all steps of our full radiation oncology QA program. Starting from the step proposed by the WHO for the subdivision of the clinical context of radiotherapy (see above) we use paper lists of the risks for each individual step checking continuously every treatment. These lists are utilized by operators involved in every step asking them to write down any error found.
Based on the collected data we identify critical processes in all stages in order to modify our containment risk plans and optimize the QA efficacy.

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THE MANAGEMENT OF NEW TECHNOLOGIES

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Advanced technologies intended to improve the accuracy of radiations delivery, such as intensity modulated

(IMRT) and image guided radiation therapy (IGRT), have revolutionized radiation therapy over the past 10–15 years and their use is rapidly increasing worldwide. These technology are very complex due to the need for simultaneous implementation of supplementary technology, such as imaging modalities and computer softwares. Also in the areas of diagnosis, treatment simulation, tumor and tissue contouring, we are witnessing an increasing use of complex, software driven multi-modality imaging technology. Combinations of computed tomography (CT), magnetic resonance (MR), magnetic resonance spectroscopic imaging (MRSI), single photon emission CT, and positron emission tomography (PET) image fusion are fast becoming common place for many types of radiation therapy treatment planning, providing enhanced information on targeting and on sub-targets. IMRT can deliver multi-targeted dose-sculpted irradiation to these defined volumes. IGRT, using various in-room imaging techniques, provides precise real-time monitoring of target position, enabling treatment verification and correction and also the basis for responsive adaptive techniques. Imaging information supports decisions on geometric uncertainties, margins and correction strategies. 4D techniques underpin strategies for dealing with organ motion. Last but not least, the increased use of radiosurgery and hypofractionation and the pressures to treat more patients in less time results in the treatments becoming increasingly automated, complex and critically software reliant. The synergistic exploitation of all these multiple advances can reduce the probability of many types of medical events and provides an on-going revolution in the clinical strategies of radiation oncology. However, each of these advances introduces its own potential for problems and new types of errors are now being seen. Therefore, to ensure safety and high quality, each advance brings the necessity for careful systematic acceptance, evaluation, commissioning, clinical implementation and comprehensive quality assurance (QA), appropriate staff resource and on-going training. The challenges are numerous and include (a) the prescriptive methodology of QA used may not be appropriate for currently implemented new technologies, (b) resources are becoming scarce, (c) advanced radiation therapy technologies have been introduced too rapidly, (d) advances in radiation therapy technologies have become too sophisticated and specialized with each therapy modality having its own separate set of equipment, for example its own dose planning software, computer system and dose delivery systems requiring individualized QA procedures. Many of the errors we are seeing with new technologies are more often the result of software errors and corrupted data files, coupled with improper staff training in the use of new technologies. A sound understanding of the (minor) role of human errors of operators and the (major) role of process design is a pre-requisite for appropriate management. What has to be considered is that systems have become more complex, more automated (the human is relegated to a pure supervisory function) and less transparent. Many errors and faults made by the staff do not directly reveal themselves and can remain dormant in the system, sometimes during very long periods. One danger of any paradigm that requires humans to check computers, that are nearly always correct, is the natural tendency to become lax in the QA process. A false sense of security can lead to weakening checks of computers and software, or to clicking "override" without thinking or investigating the true nature of a potential problem. IGRT also requires that users check or oversee complex computer systems and hardware. In short, the increasing complexity of radiation therapy technology and the quantity of data required to define a treatment plan and patient treatment needs additions to the traditional QA paradigm and further knowledge and expertise. For example, QA for the imaging modalities (as MR and PET) is beyond the skill of most radiation therapy physicists resulting in reliance on manufacturer supplied image transfer, fusion, and picture archiving and communication systems (PACS), often with little understanding of how they work or even how to perform acceptance and commissioning tests for them. Increasing reliance on technology in treatment planning for tumor definition, contouring, and real time corrections of radiation delivery poses challenges and dangers of a different nature than have historically taken in consideration. Further, the tendency to use such technology to decrease treatment field margins and to escalate doses leaves less margin for error than when treating with conventional technologies. Another aspect to consider is the change of tasks and responsibilities often associated with the adoption of these advanced techniques. The increased use of computers, computer controlled systems, and IGRT has transferred more of the responsibility for treatment verification and image registration onto radiation therapists rather than radiation oncologists. Further, the increased reliance on RV systems and computer controlled linacs has transferred more responsibility for the accuracy of treatment delivery on the physicists performing system QA rather than on the radiation therapists actually delivering the treatments. Similarly, conformal and inverse treatment requires more contouring than conventional planning and part of this responsibility has been delegated by radiation oncologists to treatment planners. Thus, the proliferation of high technology is changing, in a significant way, the job responsibilities of virtually everyone on the radiation therapy treatment team.

In conclusion, the introduction of new techniques needs to be carefully planned with thorough risk assessment, review of staffing levels and skills required, and documentation updated. All staff involved in the process should undergo specific training in the new treatment. The training and expertise factors differ around evolving and complex technologies, not only because they require the acquisition of new skills by an entire team but also because these skills are not easily acquired through didactic training. Training improvements are an important part of complex system management. Although it has a ''cost'' in terms of working hours spent away from the production line, it is a valuable long-term investment likely to reduce the break- down times (better maintenance and better reaction in case of problem) technique or process prior to clinical use. A good QA program is an ongoing process that must continually adapt to new technologies and treatment techniques. The proliferation of computerized and complex highly automated modalities of radiation therapy have changed the nature of the

process, but the last line of defense in any QA system is still a well trained and attentive professional staff. One other significant task made more immediate by new technology is the education and information to the public and to healthcare policy-makers and decision-makers. The benefits of modern radiotherapy are not well reflected in general impressions still held about the modality, which rest on concepts of side-effects from older techniques. In addition, new technology potentially has the two-fold negative perception of being expensive and being associated with some dangers. The multi-disciplinary radiation oncology community must increase awareness and public confidence that radiotherapy is the most cost-effective cancer treatment, of course in optimal synergy with other cancer treatment modalities, and also that it is one of the safest medical specialties. Thanks to the long history and detailed attention to QA, the incident rate in radiotherapy is very low. A rate of around 2% of treatment courses has incidents discovered after treatment has begun, but between 0.1% and 1% may have significant clinical consequence, and the risk of incidents leading to serious clinical consequences is less than this by factors of at least 10. The rates are significantly lower than those reported for other medical procedures. Irrespective of this, any incident causing harm is catastrophic to the patient/s involved and a zero-tolerance towards significant incidents should be pursued. New technology that is optimally implemented, appropriately applied and robustly assured will support this goal.

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TOSSICITÀ TARDIVA IN RADIOTERAPIA: IPOFRAZIONAMENTO *VERSUS* FRAZIONAMENTO CONVENZIONALE. L'ESPERIENZA CLINICA NEL POLMONE

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Radiation therapy represents, in combination with chemotherapy, the most important treatment option for patients with inoperable locally advanced Non-Small Cell Lung Cancer (NSCLC). Despite progression in radiation therapy delivery and the introduction of new pharmacologic molecules, local control rates in this subgroup of patients remain unsatisfactory, with a loco-regional control probability of approximately 40% with a standard combination of concurrent chemo-radiotherapy in stage IIIA-B (1). There is an indirect evidence on the impact of local control on overall and progression-free survival, as shown by previous experiences (2,3) and confirmed by a recent analysis of RTOG studies (4). Given the biological background of a steep dose-response relationship in lung cancer, in the past years a lot of clinical trials were designed with the aim of improving local control by either escalating radiation dose with conventional/altered fractionation or by reducing overall treatment time or both, even in the context of combined chemo-radiotherapy. Hypofractionated radiation therapy means delivering fewer fractions of radiation with higher doses per fraction compared with conventional 2 Gy fractions. The theoretic advantage of hypofractionation is related to dose escalation-treatment acceleration with logistics and patient convenience; on the other hand late reacting tissue such as the lungs are more sensitive to increments in fraction size as their responses have a relatively larger quadratic component. However a renewed enthusiasm in hypofractionation derived from the important technological advances in radiotherapy planning and delivery of these recent years (the incorporation of functional imaging in target volume definition, 4D CT, IMRT, IGRT) providing an increased level of accuracy, and as a consequence, a better sparing of normal structures such as normal lungs. Few studies have been published testing moderate hypofractionated radiotherapy in NSCLC (apart from the great experience in stereotactic radiation therapy in early stage disease) and most of them are retrospective or small prospective phase I-II, designed with the aim of investigating feasibility and toxicity of this strategy. To our knowledge, currently there are no reports on phase II-III randomised trials designed with local control and/or survival rates as primary endpoints testing hypofractionated radiotherapy compared with a standard fractionated radiotherapy. The study by Vogelius et al. (5), shows that hypofractionated radiotherapy with highly conformal techniques, gives rise to dose distributions for which the relative disadvantage, for normal tissue endpoints, of moderate hypofractionation is estimated to be minimal compared to 3D conformal techniques (3D-CRT) with standard fractionation; this result is in agreement with the study by Jin et al. (6). A phase I/II trial by the Netherlands Cancer Institute, including inoperable patients with stage I-III disease, started in 1998, with the primary endpoint of finding the highest possible tumour dose that could be delivered with acceptable complication rates (7). Locally advanced disease accounted for approximately 50%. Overall treatment time was restricted to 6 weeks, with dose fraction size at 2.25 Gy. Patients were stratified in 5 groups, with different risks to develop radiation pneumonitis, and dose was escalated in absence of dose-limiting toxicity. Final results showed that dose escalation is safe up to 94.5 Gy in 42 fractions in 6 weeks, with a MLD of 13.6 Gy or less. The involved field approach was used, with a benefit for local control and failure-free interval for higher doses. In a study by Kepka and collaborators (8), 173 patients with stage III NSCLC were treated using

accelerated 3D-CRT and the simultaneous boost technique. Initially, the total dose of 56.7 Gy (including 39.9 Gy to the elective area) was delivered over 4 weeks in fractions of 2.7 Gy (1.9 Gy to the elective area), then the dose per fraction was increased from 2.7 through 2.8 Gy (level 1 escalation) to 2.9 Gy (level 2 escalation); the total dose increased, respectively, from 56.7 Gy through 58.8 Gy to 60.9 Gy. Fit patients received two to three courses of chemotherapy before radiotherapy. Two of the nine patients who received the level 2 escalation (60.9 Gy) died of pulmonary toxicity, while 58.8 Gy in 2.8 fractions was an acceptable schedule. Data on local control and overall survival were promising but the study was not designed with these endpoints. A phase I/II study by Brussels University Hospital was designed to determine the maximum tolerated dose (MTD) of radiotherapy in patients with locally advanced NSCLC treated with concurrent RT-CT (9). A dose per fraction escalation was applied starting at 2 Gy, with an increase of 6% per dose cohort (DC). Dose escalation was performed in 34 patients over 5 DCs to a dose per fraction of 2.48 Gy. No differences were observed in acute toxicity between the different DCs, but a significant increase in late lung toxicity was recorded in DC IV (fraction size of 2.36 Gy). The overall incidence of acute grade > or =3 oesophageal and pulmonary toxicity was 24% and 3%, respectively. The overall incidence of late lung toxicity was 21%, but the incidence was an acceptable 13% in DCs I, II, and III. In a recent phase II study by Zhu et al (10), a total of 34 patients with stage III NSCLC received a combination of conventional and hypofractionated radiotherapy (initially 50 Gy/20 fractions, then a dose per fraction of 3 Gy up to 65 or 68 Gy) using 3D-CRT, without elective nodal irradiation (ENI). All patients received 2 cycles of induction chemotherapy, and 1-2 cycles of consolidation chemotherapy were given to 31 patients. Radiation toxicity was minimal. The median and 3-year OS and PFS were 19 months, 32.1% and 10 months, 29.8%, respectively. The 1-, 2-, and 3-year LR-PFS was 69.6%, 60.9% and 60.9%, respectively. MAASTRO Clinic group (11) developed a clinical concepts represented by the INDividualized iso-toxic Accelerated Radiotherapy (INDAR), which combines the advantages of high dose with an individualization of the therapeutic program, minimizing the incidence of grade 3-5 toxic effects and opening to the possibility of an adaptive combination of high dose RT and chemotherapy. Results obtained with this approach are very promising and further advancements could be hypothesized. With these approaches, the possibility to explore new combinations of slightly hypofractionated/accelerated isotoxic radiotherapy schedules with chemotherapy is concrete, and further clinical research through well-designed prospective trials is needed. Due to technical progresses (Image-Guided Radiotherapy and Intensity Modulated Radiotherapy), probably hypofractionated-accelerated schedules, guided by response during radiotherapy and planned by using predictive factors of radiation induced lung injury, will play a major role in improving results in next years. The combination between these adaptive radiotherapy protocols and chemotherapy and/or targeted agents remains to be explored in phase I-II studies.

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THE CLINICAL EXPERIENCE IN BREAST CANCER

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In women with breast cancer who undergo breast-conserving surgery, radiotherapy reduces the risk of local recurrence and can prevent the need for mastectomy (1-4). Historically, conventional fractionated whole breast irradiation (CF-WBI) (50 Gy in 25 fractions of 2.0 Gy over 5 weeks) has been recommended on the basis of the theory that small daily fraction sizes lower the risk of late normal tissue toxicity without compromising cancer control. The duration of postoperative radiotherapy may generate discomfort in some women eligible for conservative treatment because it requires multiple access to the radiotherapy center. A shorter course of irradiation would result in

improved quality of life for patients, in potentially better integration with systemic treatments and it would also contribute to a far more judicious use of resources in some busy Radiation Oncology department. Based on these promising considerations hypofractionated whole breast irradiation (HF-WBI) has been increasingly used in recent years. Several experiences and results of randomized trials have been reported offering encouraging outcomes but it remains controversial whether these results apply to all subgroups of patients. A task force authorized by the American Society for Radiation Oncology developed an evidence-based guideline to provide direction for clinical practice. In particular they identified and analyzed six randomized clinical trials that compared HF-WBI with CF-WBI (Hopital Necker, Queen Elizabeth, Canadian, Royal Marsden Hospital/Gloucester Oncology Center and Standardization of Breast Radiotherapy - START A- B). They evaluated the results of two randomized clinical trials that compared HF-WBI with partial breast irradiation (PBI), two randomized clinical trials that compared HF-WBI with no irradiation and one randomized trial that compared HF-WBI alone with HF-WBI followed by a boost to the tumor bed. The majority of patients in the analyzed randomized trials were aged 50 years or older, had disease Stage pT1-2 pN0, did not receive chemotherapy, and were treated with a radiation dose homogeneity within ±7% in the central axis plane. The obtained results have demonstrated that HF-WBI and CF-WBI are equally effective for in-breast tumor control and comparable in long-term side effects for patients with the characteristics given above. As the data were insufficient the task force was unable to reach agreement for the equivalence of the two schedule for patients who do not satisfy all these criteria, and thus, they could not make a recommendation either for or against the use of HF-WBI in such patients. Moreover, they have stressed that this should not be interpreted as a contraindication to its use. The scarcity of available data makes it difficult giving considerations on any volumes that can be treated with hypofractionated regimens. Most of the patients included in the trial had undergone conservative surgery, so there are few data to determine the appropriateness of HF-WBI for mastectomy patients. Similarly a minority of women received hypofractionated regional nodal irradiation and although brachial plexopathy has not been seen in the RMH/GOC, START A, and START B trials, for ASTRO task force the follow-up in these studies may not be considered sufficient to exclude such late toxicity. Conversely for other authors the length of FU and radiobiological considerations seem to allow the exclusion of the onset of a late toxicity (6). There are limited data taken from randomized trials on the impact of chemotherapy on toxicity in patients treated with HF-WBI, but receipt of chemotherapy was not associated with increased risk of toxicity.
According to some authors (6), "results of clinical trials need to be applied to the population from which patients were recruited, but there is no clinical rationale for excluding underrepresented subgroups without very good cause". In this view, hypofractionation trials analyzing patients operated conservatively, provide data that could be extrapolated to patients mastectomy. Different hypofractionated schemes have been programmed on radiobiological considerations and applied in and outside trials, but it is unclear whether one is superior to the others or if they can be considered equivalent. Despite the persistence of some uncertainties the avilable data justify the routine use of modest hypofractionation for adjuvant whole-breast radiotherapy in women with early breast cancer.
Administer 40 Gy in 15 fractions or 42.5 Gy in 16 fractions , or radiobiological equivalent schedules, seems to be gentler on normal tissues than 50 Gy in 25 fractions, without evidence of inferior local tumor control. So these schemes can be recommended as safe and effective alternatives to standard fractionation for whole-breast or post-mastectomy chest wall radiotherapy(6).

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HYPOFRACTIONATED RADIOTHERAPY: CLINICAL DATA IN PROSTATE CANCER

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Recent *in vivo* and clinical data suggest that prostate cancer may benefit from hypofractionation (higher dose/fraction, the total dose is usually given within the shorter overall treatment time) due to the lower a/b ratio than that of the rectum and other pelvic organs (for example, the α/β ratio for prostate cancer is in the range of 1.0 to 3.0 Gy and for the rectum between 3.0 and 5.4 Gy) (reviewed in 1). Indeed, a recent review of four reports including 21 studies estimated a 1.3 Gy a/b ratio for the prostate. The a/b ratio describes the sensibility of the tissue to the fraction size. The low a/b ratio indicates high sensibility to the fraction size. In consequence, increasing the fraction size above conventional 2 Gy (a method used in the hypofractionated schedules or high dose rate, high dose rate HDR brachytherapy) should potentially carry therapeutic gain. Numerous studies showed the feasibility of external beam hypofractionated radiotherapy in the prostate cancer (rewiewed in 1). Actually, in some Canadian and UK centers the fractions of >3 Gy/day (up to 36 Gy in 6 fractions) were traditionally prescribed without significant toxicity, however total doses were usually low (2, 3). Up till now, 5

randomized trials using hypofractionation schedules were published (4, 5, 6, 7, 8). In the Canadian study PR5, T1 or T2 prostate cancer patients were assigned to 66 Gy in 33 fractions over 45 days (long arm) or 52.5 Gy in 20 fractions over 28 days (short arm) (4). At 5 years, the biochemical or clinical failure probability in the long and short arms was 53% and 60%, respectively. A possibility that the hypofractionated arm may even be inferior cannot be therefore excluded (lower effective dose in this arm for a/b of 1.5 Gy, could explain these findings). Acute toxicity was slightly higher, but late injury remains similar between arms. Acute toxicity was slightly higher, but late injury remains similar between arms. An Australian study showed better biochemical control in hypofractionated arm and no difference in terms late toxicity between 55 Gy/20 fractions/4 weeks and 64 Gy/32 fractions/6.5 weeks (5). As these trials used relatively low total dose, their results are not applicable to the modern radiotherapy practice (the higher doses have been proposed for the new ongoing Canadian study) (9). The third study compared 76 Gy in 38 fractions to 70.2 Gy in 26 fractions of 2.6 Gy (equivalent to 84.4 Gy in 2 Gy fractions for a/b of 1.5 Gy), using image-guided IMRT in both arms (6). The preliminary analysis showed no differences in the efficacy and in acute gastrointestinal or genitourinary toxicity (6). A prospective phase III randomized clinical trial by Arcangeli et al. (7), compared hypofractionation *versus* conventional fractionation in patients with high-risk prostate cancer. The purpose of this study was to compare the toxicity and efficacy of hypofractionated (62Gy/20 fractions/5 weeks, 4 fractions per week) *versus* conventional fractionation radiotherapy (80Gy/40 fractions/8 weeks). From January 2003 to December 2007, 168 patients were randomized to receive either hypofractionated or conventional fractionated schedules of three-dimensional conformal radiotherapy to the prostate and seminal vesicles. No difference was found for late toxicity between the two treatment groups, with 3-year grade 2 rates of 17% and 16% for gastrointestinal and 14% and 11% for genitourinary in the hypofractionation and conventional fractionation groups, respectively. However, the 3-year freedom from biochemical failure rates were 87% and 79% in the hypofractionation and conventional fractionation groups, respectively (P =.035). Fifth study is a multicentre, randomised trial that recruited 153 men with localised prostate cancer between Oct 18, 2002, and Aug 12, 2006, at 11 UK centres (CHHIP) (8). The conventional schedule was 37 fractions of 2 Gy to a total of 74 Gy. The two hypofractionated schedules involved 3 Gy treatments given in either 20 fractions to a total of 60 Gy, or 19 fractions to a total of 57 Gy. Hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years. More recently, stereotactic body radiation therapy (SBRT) delivering a very high dose of radiation to the tumor target with high precision using single or a small number of fractions (extreme fractionation) has been applied to the prostate cancer. Several pilot and phase I/II studies have been published using recently introduced high-precision modalities (eg. CyberKnife, Tomotherapy, Vero, Novalis, Varian Trilogy and TrueBeam) (10). Promising results in terms of toxicity and tumor outcome have been reported, although some schemes have been demonstrated too toxic (10 Gy x 5 fractions) (10). Interestingly, HDR brachytherapy with single or double applications is also under investigation (11).

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TOSSICITÀ TARDIVA IN RADIOTERAPIA: IPOFRAZIONAMENTO *VERSUS* FRAZIONAMENTO CONVENZIONALE. L'ESPERIENZA CLINICA NEL RETTO

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Preoperative radiotherapy +/- concomitant chemotherapy has increased long term results in locally advanced rectal cancer: at least 65 % of patients are long survivors. Combined modality treatments are also responsible of cumulative toxicity on pelvic organs leading to alterations of stoma and anorectal function, bowel function, urinary and sexual function and it is somewhat difficult to incriminate the treatment responsible for the specific tox-

icity. Although continence, sexuality and urinary functions may be impaired by surgery, is however well known that radiotherapy may increase the probability of their appearance. Data on the contribution of radiotherapy on late toxicity mainly come from studies comparing preoperative short course radiotherapy *versus* surgery alone, rather than conventional preoperative radiotherapy treatments. These studies demonstrated a worsening of intestinal and sexual functions when short course radiotherapy is delivered. Although data comparing long course radio+/-chemotherapy are lacking, some conclusions may be derived from long term results of randomized trial comparing preoperative long course radiotherapy *versus* chemoradiation in uresectable patients. Better anal function was found in patients treated with preoperative radiotherapy alone compared to chemoradiation (30 *vs* 11%, p = 0.046), although not significant there was and higher rate of bowel obstruction in patients treated with preoperative chemoradiation, in general one quarter of patients reported urinary disfunction. Direct comparison of short course preoperative radiotherapy with long course chemoradiation didn't show any significant difference in terms of late toxicity. Continence, bowel, urinary and rectal function are directly related to the dose received during radiotherapy treatment. To prevent and decrease late toxicity several strategy may be adopted, such as the modulation of tumor border according to tumor presentation (stage and location) and the introduction of new radiotherapy techniques such as IMRT/IGRT, in those cases in which organ at risk, due to their vicinity to the CTV, may be not or may be barely avoided.

ACTIVE SURVEILLANCE (AS): PRO

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In recent decades the widespread introduction of new diagnostic methods and screening programs such as mammography, PSA, colonoscopy or other imaging techniques has significantly changed the epidemiology of cancer. The observed improvement in survival of many cancers is the result of the combined action of early diagnosis and treatment as the main tool to fight cancer. For example, prostate cancer mortality in the USA has fallen by about 33% since 1993, from 38.6 to 24.6 per 100 000. and a similar trend has been seen in breast cancer. These two types of cancers are those that have most benefited in mortality reduction from the improved possibilities for diagnosis and early intervention, but a similar behavior can be observed also for thyroid tumors and melanoma. Early diagnosis has also allowed less invasive treatments contributing, in turn, to the reduction of mortality. Thus, despite a significant increase in the incidence and a longer life, mortality from some cancers is falling down. Since 1982 it is well known from autoptic studies the high frequency of latent cancers (ie, about 30% of men aged > 50 years has histologic evidence of prostate cancer) with up to 80% of these tumors measuring less than 0.5 cm in size and low in grade, suggesting that the majority are clinically insignificant. However, in these times of PSA-screening, approximately 70% of patients with prostate cancer have low-risk disease (ie, Gleason score, ≤6; pretreatment PSA, ≤10 ng/mL; clinical stage, T1c or T2a). The natural history of these cancers is very favourable, even when clinically detected. The overdiagnosis begins to be estimated accurately and it is impressive: according to the aggressiveness diagnostic varies from 50 to 250%, which equates to say, in other words, that it goes from a latent cancer every two diagnosed, 5 latent diagnosed every 7. Despite this, current trends in practice patterns suggest that approximately 91% to 95% of low risk patients receive a definitive therapy. In a survey from US of urologists and radiation oncologists in which several hypothetical prostate cancer scenarios were generated and questions regarding the recommended management were posed, both type of specialist commonly recommended the therapy that they were capable of offering and also tended to overestimate the therapeutic benefit of definitive therapy. But all currently available radical treatments, no matter how well delivered, have considerable side-effects and may be associated with potential decrement in quality of life in multiple domains (eg. urinary, sexual and bowel functions.). Reducing overtreatment in patients diagnosed with indolent disease is critical to the success of the screening itself. Active surveillance (AS) is rapidly gaining favour as a viable treatment option for managing early, slow growing prostate cancer. AS involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses. According to the 2011 NCCN guidelines update AS should include PSA measured at least as often as every 6 months, digital rectal exam performed at least as often as every 12 months, and a needle biopsy repeated as often as every 12 months. Several different criteria for patient's inclusion in AS protocols have been described but a general consensus does not exist. Who are the best candidates for AS? The most common clinical data used to define low-risk prostate cancer include a Gleason score ≤6 (no pattern 4 or 5 disease), PSA level ≤10 ng/mL, and clinical stage T1 to T2a disease. Other characteristics to consider include PSA density (PSAD < 0.15), percent positive cores at biopsy (<33%), the extent of cancer in any core (<50%), and PSA kinetics (stable) before diagnosis.

Small indolent cancers do not receive unnecessary treatment: The one successful randomized trial that compared surgery with AS demonstrated a statistically significant survival benefit to men undergoing surgery. The absolute benefit at 10 years was modest, although the men enrolled had intermediate- to high-risk disease, and only 5% of patients were diagnosed on the basis of PSA testing. The median PSA at diagnosis in this group was 12.8 ng/mL. With regard to studies of AS alone, given the often prolonged natural history of prostate cancer, the median follow-up is relatively short and the results have yet to be evaluated with caution. There are seven published AS series that take in account almost exclusively favorable-risk patients. These vary in size and duration of follow-up. The cohort constitutes approximately 3000 patients in total. The median age is 68. Median follow-up is 43 months. Approximately, 150 patients in the six series have been followed for more than 10 years. The overall survival in the cohort is 90%, and the disease spe-

cific survival is 99.7%. About one-third of patients have been treated definitively. Nonetheless, the ratio of non-prostate cancer to prostate cancer mortality is about 30 : 1, an impressive figure. (A 30 : 1 risk of other cause to prostate cancer mortality also approximates the lifetime risk of dying of prostate cancer in undiagnosed men). In one of the largest published series to date with nearly 450 patients and 7 years of median follow-up, overall survival was 78.6%, with a 10-year actuarial cancer-specific survival rate of 97%. All prostate cancer mortalities (5) occurred in men who had been reclassified as higher risk and were offered radical treatment.

Avoiding the side effects of definitive therapy & Quality of life and normal activities are retained: The most important reason for patients to accept AS is the delay of potential side effects, reasons to reject include fear of cancer progression to incurable stages. Men who have selected AS score better on physical domains than those on radical therapy and do not seem to show high anxiety or distress levels on short-term after diagnosis. For example, Hayes et al. used a decision analysis simulation model on hypothetical cohorts of men with low-risk prostate cancer to examine the QoL benefits and risks of AS. AS was associated with the highest quality-adjusted life expectancy when compared to radiation therapy, brachytherapy, or radical prostatectomy. This difference remained even so if the relative risk of disease specific death of initial treatment *versus* AS was as low as 0.6. The comparative effectiveness and value of several management options for low-risk prostate cancer has been evaluated from the Institute for Clinical and Economic Review including AS, open and robotic/ laparoscopic radical prostatectomy, brachytherapy, intensity-modulated radiation therapy (IMRT), and proton beam therapy. The main message of this research was that all modalities of surgery and radiotherapy have comparable rates of disease recurrence and overall and cancer-specific mortality. Moreover, AS translated into 1 year or more of increased quality-adjusted survival over immediate therapy. Only a few stop AS due to uncertainty or nonmedical issues. Longer term effects are unknown and may show different results. However, it's important to note that observations from randomized studies could give different conclusions.

Decreased initial costs: Economic analysis of AS in low-risk prostate cancer patients is difficult due to prolonged natural history of the disease. Estimated direct cost of AS over 5 years is the lowest as compared with immediate therapies including radical prostatectomy, external beam radiation therapy with or without androgen deprivation therapy (ADT), ADT or brachytherapy. Prostate biopsy is the highest expenditure for men on AS, frequency of which is the key determinant of cost difference between AS and other therapies.

Conclusions: As the costs of health care rise, through the utilization of progressively more expensive technologies, the relative clinical and economic benefits of an AS paradigm for the treatment of low-risk prostate cancer will likely become increasingly attractive.

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ACTIVE SURVEILLANCE: CONS

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The treatment of localized prostate cancer continues to be a major challenge for urologic oncologists. Screening with PSA has resulted in increased numbers of low risk prostate cancer being detected. Aggressive whole-gland therapy is associated with potentially life-altering treatment-related side effects such as urinary incontinence , bowel toxicity and erectile disfunction.

Active Surveillance (AS) may be a reasonable treatment option for many patients with low risk and some men with intermediate risk prostate cancer.Several large surveillance cohort studies have been reported recently, showing excellent medium-term outcomes in well selected patients, with approximately a third of patients going on to have deferred treatment. AS does not delay therapy until a man is symptomatic a nd no longer curable; the goal of AS is to

closely monitor men for changes in the aggressiveness of their disease via several biopsies and PSA measurements and, if an unfavorable change is detected, to offer definitive local therapy with curative intent.

Debate continues on the most appropriate elegibility criteria, what triggers for intervention should be used ,how routinely to perform biopsies and how to incorporate imaging into the monitoring programs. This issues are not currently being addressed by randomized trials but AS strategies have been provided from epidemiological studies and prospective case series. Selection criteria, patient and tumor characteristics are different among the published studies ; definitive monitoring during AS to identify the subset of patients with biologically aggressive cancer and triggers for interventions are under investigations :PSA levels, PSA kinetics, MRI imaging, biopsy template and informations on the volume of disease and Gleason score need to be carefully considered. A patient remains suitable for ongoing surveillance as long as he continues to regard the risk of radical treatment to outweight the benefits.

Elegibility criteria and triggers for treatments are different sides of the same coin. It's not possible to define a single modality of evidence-based criteria to define elegibility for surveillance or to serve as a triggers for intervenction (there is not "one size fits all" set of criteria). PSA kinetics as a sole trigger for intervention are of limited value because there is no velocity threshold above wich adverse histology is certain, or below wich adverse histology may be excluded and PSADT is less significantly associated with subsequent adverse biopsy findings. Repeat biopsies gives information on tumour size and grade but how big does a cancer has to be or how high does the Gleason score need to be , in order to merit treatment? Related to this issue a consensus of the most appropriate cut-off points to use is lacking. Prostate biopsy carries risk of bleeding and infection can be serious but occasionally life-threatening so we need for a non invasive method of monitoring disease progression during AS in order to identify appropriate triggers for intervention. Biopsy sampling error is a significant limitation of surveillance. This has been addressed in part by serial biopsies with particular attention to the antero-lateral horn, a common site for disease missed on routine biopsies. There remains a very real need for better biomarkers of untreated prostate cancer behaviour that could be used to identify who does or does not, need treatment. Lastly, the psychological effects of living for many years with untreated cancer are a potential concern and anxiety about PSA recurrence may be common if patient is not educated to appreciate the very indolent natural history of poor risk prostate cancer.

CONTROVERSIES ABOUT LOW RISK PROSTATE CARCINOMA. BRACHYTHERAPY

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Prostate cancer is the most common male cancer in the United States and the second leading cause of male cancer death. Initial suspicion of prostate cancer is based on an abnormal digital rectal examination (DRE) or an elevated PSA level. A PSA value of 4.0 ng/mL or less is considered normal; however, 15% of men with this "normal" PSA will have prostate cancer and 2% will have high-grade cancer. In fact, there is no PSA level below which cancer has not been detected; a few men with PSA values of 0.5 ng/mL or less have had high-grade prostate cancer on diagnostic biopsies [1]. Definitive diagnosis requires biopsies of the prostate, usually performed by the urologist using needle under transrectal ultrasound guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Patients are stratified ad diagnosis for initial treatment recommendations based on anticipated life expectancy of the individual patient and on whether they are symptomatic from the cancer. For patients with a life expectancy of less than 5 years and without clinical symptoms, further workup or treatment may be delayed until symptoms develop. Patients with low risk for biochemical recurrence include those with tumours stage T1 to T2a, low Gleason Score (<=6), and serum PSA level below 10 ng/mL. Although 40% of men older then 50 years of age harbour prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of a prostate cancer-specific death. Therefore, active surveillance is recommended for men with low-risk prostate cancer and life expectancy less than 10 years. Evidence for this approach is supported by data showing that the 5 to 10-year cancer specific mortality is very low for most prostate cancers except those that are poorly differentiated [2,3,4]. If the patient's life expectancy is 10 years or more, the treatment recommendations also include radical prostatectomy with or without a pelvic lymph node dissection if the predicted probability of pelvic lymph node involvement is 2% or greater. A study by Johansson and colleagues assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up [5]. They found that most prostate cancers diagnosed at an early stage have an indolent course; however, local tumour progression and aggressive metastatic disease may develop in the long term. The mortality rate was significantly higher after 15 years of follow-up when compared with the first 5 years. Their findings support early radical prostatectomy, especially among patients with an estimated life expectancy exceeding 15 years. Radiation therapy using either 3DCRT/IMRT with daily IGRT or brachytherapy is another option. Surgery, EBRT and Brachytherapy carry different side effects profile that will likely influence decision making. An analysis of 475 men treated for localized disease revealed that urinary incontinence was more common after prostatectomy (n = 307) than after brachytherapy (n = 90) or external beam radiation therapy (n = 78) (both P <.001), whereas voiding and storage urinary symptoms were more prevalent after brachytherapy than after prostatectomy (both P <.001), with substantial time-dependent recovery to baseline levels. Sexual dysfunction profoundly affected all three treatment groups, with a lower likelihood of regaining baseline function after prostatectomy than after external beam radiation therapy or brachytherapy (P <.001). Bowel dysfunction was more common after either form of radiation therapy than after prostatectomy. [6]. ADT as primary treatment for localized prostate can-

cer does not improve survival and is not recommended. Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that achieves damages to tumor tissue through local freezing. Based on different definitions of biochemical failure, the reported 5-year biochemical disease-free rate following cryotherapy ranged from 65% to 92% in low-risk patients [7]. However, this technique is not recommended as primary therapy due to lack of data from long-term studies for comparison with radiation and radical prostatectomy [16]. Brachytherapy has been increasingly utilized for the treatment of early-stage prostate cancer. Technological advances, including improvements in imaging, planning, and post implant quality assessment by dosimetry have led to widespread use of brachytherapy. Outcomes for prostate brachytherapy have been shown to be equivalent, in selected patients, to those of other treatment modalities for prostate cancer, including radical prostatectomy and external beam radiation therapy. Further, prostate brachytherapy has quality-of-life benefits in comparison to these other treatment modalities, particularly in the domain of sexual function. Radical Prostatectomy and ultrasound-guided transperineal brachytherapy are both commonly used for the treatment of localized prostate cancer. No randomized trials are available to compare these modalities. Therefore, the physician must rely on institutional reports of results to determine which therapy is most effective. While some investigators have concluded that both therapies are effective, others have concluded that radical prostatectomy should remain the gold standard for the treatment of this disease. The data indicate that for low-risk disease both treatments are effective, controlling disease in over 80% of the cases, with no evidence to support the use of one treatment over the other. [8]

GI and GU toxicities: Grant et al. [9] reviewed the records of 525 patients with low risk prostate cancer treated in 1999 to examine gastrointestinal (GI) and genitourinary (GU) late toxicity profiles. The patients were treated with external beam radiotherapy (RT), prostate interstitial brachytherapy (PI) or radical prostatectomy (RP). Overall, all three modalities were associated with relatively low late GI and GU toxicity rates. The frequency of late GU toxicity (grade 2 or higher) was 6.8% for all patients and was 4.3% for PI patients, 5.1% for RP patients, and 10.5% for RT patients. The presence of DM (Diabetes Mellitus) was associated with higher rates of GU toxicity. The major causes o GU toxicity were increased frequency/irritation and varying degrees of incontinence. The vast majority of toxicities resolved with further follow-up or intervention. There were no late GI toxicities (grade 2 or higher) observed for patients who underwent RP. The frequency of late GI toxicity (grade 2 or higher) was 3.3% for all other patients. For patients treated with PI the frequency was 1.7% and was 8.1 for patients treated with RT. DM was significantly associated with late GI toxicity. The major causes of GI toxicity were rectal bleeding and proctitis. The vast majority of toxicities resolved with further follow-up or intervention. The relative increase in GI toxicity seen in patients who underwent RT compared to RP and PI could potentially be attributed to the hypofractionated dose of IMRT (the standard was 2.5 Gy per fraction).

Cost-effectiveness: Brachytherapy *vs*. IMRT: Brachytherapy provides comparable outcomes and improved cost-effectiveness in the treatment of low/intermediate prostate cancer. Shah et al. reported that they evaluated 1328 patients with low or intermediate risk of prostate cancer. They were treated with LDR (207), HDR with four fractions (252) or IMRT (869). Overall, no differences in 5-year biochemical control (BC) or cause-specific survival were noted among treatment modalities. The calculated reimbursement for LDR brachytherapy, HDR brachytherapy with four fractions, and IMRT was $9,938; $17,514; and $29,356, respectively. HDR and LDR brachytherapy were statistically less costly to Medicare and the institution than IMRT ($p<0.001$), and LDR brachytherapy was less costly than HDR brachytherapy ($p=0.01$ and $p<0.001$). Incremental cost-effectiveness ratios for cost to Medicare for BC with IMRT were $4045 and $2754 per percent of BC for LDR and HDR brachytherapy, respectively. Incremental cost-effectiveness ratio using institutional cost comparing IMRT with LDR and HDR brachytherapy was $4962 and $4824 per 1% improvement in BC. [10]

Knife or Needles? Fisher et al. retrospectively analyzed data from 371 men with clinical T1a-T2c disease with PSA level < 20ng/ml and GS 6-7 who were treated with Radical Prostatectomy (n=279) or Brachytherapy (n=92). After RP, 5-year BRFS rates were 96.1% and 90.6% for low- and intermediate-risk disease, respectively. After BT, 5-year BRFS rates were 92.5% and 95.8% for low- and intermediate-risk disease, respectively. The Author concluded that excellent disease control outcomes can be achieved after either RP or BT as monotherapy for men with early stage prostate cancer. Five-year prostate cancer-specific survival rates were 100% for both RP and BT. [11]

Gleason scores of 3+4 and 4+3: There appears to be a clear difference in cancer control outcomes for patients with Gleason scores of 3+4 and those with scores 4+3 after radical prostatectomy. It has been documented that patients with Gleason 4+3 prostate cancer have higher incidences of non-organ-confined disease than those with primary pattern 3. Higher rates of extra-capsular extension, seminal vesicle invasion and positive margins have been found to be associated with primary pattern 4 over 3. Stock et al. provided information on the prognostic significance of primary Gleason pattern in the brachytherapy management of prostate cancer. A total of 560 patients with Gleason 7 prostate cancer were treated between 1990 and 2008 with brachytherapy, alone or in combination with hormonal therapy and/or external beam radiation therapy. There were 352 patients with Gleason pattern 3+4 and 208 with Gleason pattern 4+3. The mean (range) presenting PSA level was 11.2 (1-300) ng/mL, and the median was 7.8 ng/mL. The presenting clinical stages were T1b in 1%, T1c in 33%, T2a in 16%, T2b in 32%, T2c in 16% and T3 in 2%. The actuarial freedom from biochemical failure rate at 10 years was 82%. There was no significant difference between 10-year freedom from biochemical failure rates for patients with Gleason scores of 3+4 (79%) and those with scores of 4+3 (82%). Biological effective dose and presenting PSA level were both significant predictors of biochemical failure in multivariate analysis. The primary Gleason pattern in

Gleason 7 prostate cancer shows no significant effect on biochemical failure when treated with brachytherapy. These results are different from those found after radical prostatectomy and are probably attributable to the enhanced local control afforded by a brachytherapy approach to this disease subset. [12]

Learning curve: A learning curve in prostate brachytherapy programs affect not only the outcome but also the toxicity from the treatment. Taussky et al reported that a total of 22.8% of patients lost at least one seed. The highest percentage of patients losing any number of seeds was in the first 100 (38%). This number decreased gradually and was only 9% in patients 400-499. The seed loss rate to the thorax changed significantly over time (p=0.009). It rose after an initial rate of 0.25-0.42% in patients 200-299 and 300-399 and declined later to a rate of 0.21% in the last 100 patients. Keyes et al. evaluated the incidence of acute urinary retention that in the first 200 patients was 17% *vs* 6.3% in the most recently treated 200 patients (p=0.002). [13,14]

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LOW-RISK PROSTATE CANCER. EXTERNAL RADIATION THERAPY

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Prostate cancer is the most common malignancy in men with more than 42.000 diagnoses per year in Italy (*AIRTUM*). Radiation therapy is as efficacy as surgery in the treatment of low-risk prostate cancers and it is frequently used to treat this kind of disease especially in older men. An important issue in this scenario regards the choice to treat or observe localized low-risk prostate cancer men because up-to-date many men are receiving curative therapy for prostate cancer who would be better served by observational treatment. While many men will benefit from immediate surgery or radiation, many also would benefit from delaying treatment and adopting a "watchful waiting" approach, according to numerous international guidelines. There is now an emerging consensus on a definition for low-risk prostate cancer: a prostate-specific antigen (PSA) level less than 10 ng/mL and a Gleason score of 6 or less. Using this definition, it is estimated that more than 100,000 men of the 240,000 diagnosed with prostate cancer in the United States each year would be candidates for active monitoring, rather than immediate treatment.

Over the past decade, newer and more expensive alternatives have been introduced for the treatment of prostate cancer. For men who choose radiation Intensity-Modulated Radiation Therapy (IMRT), Stereotactic Body Radiotherapy (SBRT), and Proton therapy are a more expensive alternative to traditional three-dimensional conformal radiotherapy (3DCRT) due to more intense physics planning and quality assurance time, as well as treatment delivery time and soft-ware and hard-ware costs. Despite interest from patients and providers in these newer technologies there was only limited comparative effectiveness data when they were introduced, and to date there have been no randomized trials testing their clinical efficacy compared to traditional, less expensive counterparts.

In a recent observational study Sheets et al (*JAMA. 2012;307(15):1611-1620*) demonstrated that the use of IMRT compared with both 3DCRT and Proton therapy, was associated with less gastrointestinal morbidity, but more erectile dysfunction using IMRT compared with 3DCRT.

In another paper from Jacobs et al (*Eur Urol 2012 In Press*) on comparative effectiveness of external beam irradiation in prostate cancer (IMRT vs 3DCRT), Authors conclude that IMRT appears to show a benefit in terms of reduced salvage therapy without an increase in complications only in a subset of higher risk patients; for other both risks and complications are comparable between the two modalities.

Finally, in addition to the improvement made in tech-

niques of delivering irradiation, other radiotherapy techniques have also been developed that allow a reduction in the high-dose volume by use of a tighter margins. Image-guided radiotherapy (IGRT), motion-adapted radiotherapy (gating or tracking), or a combination of both can decrease the incidence of toxicities or allow dose escalation . When used in combination with IMRT or 3DCRT, these techniques can contribute to, or even be the main reason, for improved clinical outcome.

CONTROVERSIES IN HORMONE THERAPY FOR PROSTATE CANCER

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Prostatic adenocarcinoma is one of the most common malignancies for which screening is performed ad for which treatment is ultimately administered (6). Because of the dependence of prostate cancer on testosterone, hormone therapy is used throughout a wide range of disease presentation (7). After success in the setting of disseminated disease, subsequent efforts involved the use of hormones with local treatment, predominantly radiotherapy for locally advanced disease (10). Use of androgen deprivation therapy (ADT) for the treatment of prostate cancer began in 1941, when it was shown that reduction in testosterone levels by surgical castration or oestrogen treatment led to improvements in levels of phosphatases and relief of symptoms. Long-acting synthetic GnRH agonists were introduced in the 1980s and improved the treatment of prostate cancer by allowing effective reduction of testosterone levels without the psychological consequences of orchidectomy. For the past 30 years androgen deprivation as a means of treatment of locally advanced and advanced prostate cancer has been based on similar-acting GnRH agonists. They work by providing constant overstimulation of the pituitary gland which ultimately down-regulates the production of testosterone. GnRH agonists overstimulation of the pituitary results in increased testosterone levels producing a testosterone surge at initiation of therapy. Increases in testosterone have a negative impact on progression free survival and may result in stimulation of the tumour. In advanced disease anti-androgen therapy has to be taken in conjunction with GnRH therapy in order to reduce the symptoms associated with testosterone surge. Although many investigators have examined the role of hormones with radiotherapy (RT) in early-stage prostate cancer, there is a very paucity of data examining the benefit of endocrine therapy in this particular prostate cancer population. Viceversa, ADT has often been added to RT for intermediate-risk prostate cancer (IPPC), based on multiple randomized trials of mostly high-risk patients that show a clear improvement in biochemical failure-free survival, overall survival and/or non-specific survival (2,4,13). In the Harvard trial, the 5-year BFFS rate was 79% *vs* 55%, with an 8-year OS rate of 74% *vs* 61% (12). In the RTOG 94-08 trial, for IRPC, the rate of biochemical failure at 10 years was 45% *vs* 28% for ADT group *vs* no-ADT group, and the corresponding 10-year OS rate was 61% *vs* 54% (9). Again, ADT was not associated with additional RT-related genitourinary or gastrointestinal toxicity and high-dose external bean radiotherapy (5). A very original method to quantify the benefit of short-term (≤6 months) hormone therapy adjuvant to radiotherapy in the group of patients with early (clinical stage T1-T2c) prostate cancer is represented by the number needed to treat (NNT) methodology. In a retrospective study on 3652 patients, after adjustment for hormone-induced functional loss, the advantage of hormones remained considerable in the high- and intermediate risk groups, with the utility compromised from complications in the low-risk group (8).
The GnRH receptor blockers, of which degarelix (FIRMAGON©) is an example, are a new class of hormonal treatments for prostate cancer. A number of GnRH antagonists have been used previously in infertility treatment regimens. The mode of action of GnRH receptor blockers differs from that of GnRH agonists. GnRH receptor blockers act by preventing the action of GnRH on the pituitary gland. This in turn prevents the release of LH and FSH, removing the stimulus to the testes to produce testosterone. The direct action of GnRH receptor blockers on the pituitary means that reduction in testosterone levels starts immediately. A 1-year, phase III, open-label, multicentre comparative study evaluated the efficacy and safety of degarelix in 1-month dosing regimen in 610 patients with prostate cancer requiring ADT (Klotz et al, 2008). Degarelix was administered subcutaneously at a starter dose of 240 mg (40 mg/mL), followed by monthly maintenance doses of either 80 mg (20 mg/mL) (n = 207) or 160 mg (40 mg/mL) (n = 202) *versus* monthly leuprolide 7.5 mg (n = 201) administered intramuscularly (11). In this study, suppression of testosterone to 'castration' levels (≤0.5 ng/mL) occurred more rapidly in patients receiving degarelix than in those receiving leuprolide. At day 3, testosterone levels ≤0.5 ng/mL were achieved by 97% and 96% of degarelix-treated patients (240/160 mg and 240/80 mg groups, respectively), compared with 0% in the leuprolide group; corresponding values at day 14 were 100%, 99.5%, and 18.2%. This difference between the degarelix groups and the leuprolide group in the proportion of patients with median testosterone levels ≤0.5 ng/mL at day 3 was statistically significant (P <0.0001). Degarelix was also associated with a significantly faster reduction in PSA levels compared with leuprolide. After 14 days of treatment, median PSA levels had declined by 64% in patients receiving degarelix 240/80 mg and 18% in patients receiving leuprolide; corresponding values at day 28 were 83%, and 68%. The differences in the reduction in PSA from baseline between degarelix and leuprolide patients at days 14 and 28 were statistically significant (P <0.0001) (11). Results from a pre-defined secondary endpoint showed that compared to leuprolide, degarelix reduced the risk of PSA progression or death by 34% (HR =0.664 – 95%CI, 0.385-1.146). In a subset of patients with more advanced disease (PSA>20 ng/ml at diagnosis), analysis of the time taken for the first 25% to experience PSA progression showed that FIRMAGON can delay PSA progression by 7 months compared to leuprolide (p=0,01). (17). A further analysis of secondary endpoints suggests that degarelix offers a greater

reduction of serum alkaline phosphatase (S-ALP) than leuprolide, in patients with metastatic disease (p=0,014) (14). In prostate cancer, elevated S-ALP levels are associated with progression of skeletal metastases as well as being significant predictors of early death. Data from the ongoing degarelix extension study (CS21a) demonstrated the long-term efficacy and tolerability of degarelix and support its use as first-line androgen deprivation therapy (16). Recent data from two Phase III trials comparing degarelix with a combination of GnRH agonist goserelin plus bicalutamide in men with advanced hormone-dependent prostate cancer, showed that degarelix was non inferior to the agonist GnRH at reducing total prostate volume and offered better relief from lower urinary tract symptoms (LUTS). LUTS can have a major negative impact on quality of life for men with prostate cancer (1). In the long-term, open-label extension study, the incidence of adverse events, and of musculoskeletal events in particular, was measured. The overall incidence of adverse events was similar in those who had received continuous degarelix and those who switched from leuprolide after 1 year, and decreased throughout the 4 years of follow up. After a median follow up of 27.5 months, the lower probability of occurrence of musculoskeletal or connective tissue adverse events that was observed with degarelix 240/80 mg after 1 year persisted during subsequent treatment (3). Finally a recently published meta-analysis, showed that cardiovascular event rates were similar before and after degarelix treatment in the general population of patients with prostate cancer (15).

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IMPOSTAZIONE BIOLOGICA E CLINICO-TERAPEUTICA

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Radiobiological modeling of tumor control or radiation side effects development is a process that deeply involves clinicians. The definition of accurate models first of all requires the correct clinical definition of outcomes that have to be analyzed and the correct classification of the outcome is a needful requirement both for the evaluation of tumor control probability (TCP) and normal tissue complication probability (NTCP). In case of TCP, an adequate definition of 'control' is required: usually it can be assessed by using a time cutoff where the control of the tumor has to be checked. A snapshot of an observed patients population at 5 years after the first observation of the complete response or the arrest of cancer growth at site of origin (local control LC) have been primarily used in radiobiology to define the 'control'. On the other hand, the use of the n-years disease free survival (DFS) or the n-years overall survival (OS) can be affected by other variables that can hide the direct radiation on primary tumor site effect: indeed the DFS can be influenced by the rising of metastases, the use of further anti-cancer treatments (chemotherapy, surgery or both) while the OS can be shortened by not tumor caused death of the patient. In case of NTCP the definition of the complications is a complex process due to the need to exploit several elements that can influence the same NTCP definition:

1. Clinical definition of the 'complication'
    1. Toxicity scoring system
    2. Observation time (usually at a given moment in the follow up history of the patient)
    3. Homogeneity of evaluation criteria (intra- or inter-observer evaluation variability)
        1. Subjective – a score given by the observer or using patients addressed specific questions
        2. Objective – a score obtained by laboratory measures or specific diagnostic procedures

2. Reliability of the model
    1. Sample size
    2. Modeling mathematical procedure
        1. Confidence intervals
        2. Consistence and practical application of parameters to be used in clinical setting

It seems clear that the complexity of the factors that influence the modeling procedures, by the different variables included in the same process, can independently modify and affect the reliability of the outcome calculation. Clinicians can be often tempted to use models to predict the outcome during treatment planning sessions or just for discussing the therapy course with the patients. But the consistence of the results, often cut down by the width of confidence intervals, leads the clinicians to be wary about the daily use of radiobiological evaluation, together with the intrinsic difficulties in routinely applying the outcome calculation, because of the mathematical complexity of same models. Many dose–volume outcome models have been proposed in the literature. The Lyman–Kutcher–Burman model was one of the earliest proposed and uses a simple power law, with an exponent that controls the volume effect. The often-used generalized equivalent uniform dose equation (also called the generalized mean dose) is the same as the dose–volume reduction model used by Lyman–Kutcher–Burman, with a slight change of parameter definition. Other models have been proposed that attempt to explicitly model tissue architecture. All of these models use information only about the dose distribution and fractionation. However, it is well known that the probability of a complication may be affected also by multiple clinical prognostic factors, such as surgery, diabetes, smoking, age, anemia, gender, etc. Highly simplified models applied to the data, although useful, have the fundamental limitation that they cannot follow the presumably complicated shape of the outcome probability surface as a function of dose and other correlated factors. It seems unlikely that any single mathematical function (calculated over mean dose, maximum dose, equivalent uniform dose, etc.) will alone provide the best approximation for the true NTCP or TCP response curve. So it seems likely that in all end points of interest for NTCP and TCP modeling, there is no "*perfect model*". There is only an outcome probability surface that, as a result of highly complicated radiobiologic and physiologic effects, is a very complicated, nonlinear function of treatment-, patient-, and disease-related factors. The high complexity of these models rises the need to get and analyze a large amount of clinical data, in addition to the dosimetric ones, in order to achieve the most reliable predictive model as possible. But the approach to the analysis of large amount of clinical data together with dosimetric ones is highly complex and needs to use automated computer procedures and complex analysis tools in order to screen the useful data and get their impact on final outcome together with the confidence intervals that estimate the model accuracy. The last years trend in the medical research is moving from the relatively low complexity level of the randomized controlled trials, which allow to minimize differences among patients groups recruited, giving the possibility to analyze few variables in order to determine which one of them is the more effective in determine the outcome, to the level of large complex database retrospective analysis. In this condition the great bias of the retrospective studies, always considered of low power in terms of level of evidence definition, can be overcome by using automated or semi-automated data analysis procedures, that get over the concern about the influence on data collection due to the clinician observer involved in the study work. The machine learning workstations can be tuned in order to definitely acquire every kind of clinical, dosimetric, biological, genetic and therapeutic data and so finally setting a consistent *ontological framework* where the software analysis has to be performed. The most time-spending step in the machine learning process is indeed the realization of this platform which every further step in the modeling process depends from. The variable analysis strictly depends from the amount of data and from the entirety of the available data as well. There are specific techniques that allow to correct errors or missing data using interpolation methods ensuring at the same time the consistency of the data provided for the analysis. Nowadays every radiotherapy center has at disposal a variable quantity of data that could be used for in-house analysis or shared, after anonymizing the privacy tags of the patients, with other centers in order to provide large amount of data to be used and managed for very complex and robust analysis.

MATHEMATICAL MODELLING TO ESTIMATE THE RADIOBIOLOGICAL PARAMETERS AND THE FACTORS PREDICTIVE TO THE RADIOTHERAPY RESPONSE

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Introduction: In recent years, several treatment schemes of the prostate, lung, breast or head and neck cancer have been proposed and tested. Those schedules could indirectly allow the determination of radiobiological parameters. Unfortunately, some of these methods have led to solutions difficult to interpret or wide confidence inte vals with a loss of informative features. In particular for prostate cancer, some radiobiological parameters, such as intrinsic radiosensitivity, fractionation sensitivity, repopulation doubling time and number of clonogens, have been extracted using the clinical outcome after radiotherapy also differentiating for low-, intermediate- or high-risk group of patients. Based on these studies, the value of the α/β ratio, for example, has been normally considered as very low by the radiotherapy community, who are just coming to terms with utilizing hypo-fractionation. However, it still remains unclear whether hypo-fractionation provides any significant therapeutic benefit in the treatment of prostate cancer and also, whether there are different radio-sensitivities for really no different disease risk groups. Moreover, the repopulation of prostate tumor cells has often been neglected in some published studies even though the biologic effectiveness of the treatment can be reduced by tumour repopulation, if it is significant. The above reasons reopened the discussion about the values of the α/β ratio and the other radiobiological prostate parameters whereby several investigators in joining this debate. These kind of

studies have been often focused on the effects of accelerated production of clonogenic cells during radiotherapy, for which an amount of a given dose of radiation may be used to sterilize cells produced during the treatment. Therefore, by maintaining the same total dose, a reduction of the overall treatment time (OTT) results in increased T-site control. The benefit of reduced OTT was tested in several studies comparing conventional treatment with accelerated fractionation schedules showing an improved 5-year probability of avoiding local regional (LCR). However, the response was heterogeneous with respect to the different expressions of molecular factors, such as epidermal growth factor recptor (EGFr), in the patient population. EGFr is overexpressed in the majority of tumors and activation of the receptor leads to phosphorylation of the tyrosine kinase domains on the intracellular part of the receptor, activating downstream cascades which result in altered gene activation and modulation of the cell products. This has been related to increased cell proliferation, decreased apoptotic activity, increased angiogenesis, increased invasive and metastatic potential and hence increased resistance to anti tumor therapy. Several studies have been shown that tumors with high expression of EGFr have a better LCR when treated with accelerated radiotherapy, while there is no benefit of acceleration in tumors with low EGFr. Consequently, high EGFr has been suggested as a negative prognostic factor when OTT is prolonged, and as a positive predictive factor when treatment time is reduced.
Overall, to determine a self consistent set of radiobiological parameters and also to investigate the correlation between molecular factors and radiotherapy response for any pathology treatable by radiotherapy, a new analytical/graphical method based on the linear quadratic model (LQ), has been developed. In order to provide a self consistent set of LQ parameters the model has been employed to fit clinical data for prostate cancer and to investigate the correlation between the membrane expression of EGFr and the reduction of the effective doubling time during the radiotherapy of head and neck squamous cell carcinoma (HNSCC). The parameters analyzed were intrinsic radiosensitivity (α), fractionation sensitivity (α/β), repopulation doubling time (T_d), number of clonogens (N) and kick-off time for accelerated repopulation (T_k).

Materials and Methods: Based on the generalized LQ model and without assuming the iso-effective hypothesis, the potential applications of the method have been investigated using the clinical outcome of the biochemical relapse free survival (*bRFS*) recently reviewed in literature for prostate cancer. On the other hand, a survey of the published papers comparing 3-years LCR of patients treated with conventional and accelerated radiotherapy and with a pretreatment assessment of EGFr expression, was made for HNSCC. In the latter, different values of T_d were obtained incorporating in the model the overall time corrected *BED* and a 3-year clinical LCR for high and low EGFr groups of patients (H_{EGFr} and L_{EGFr}), respectively. By obtaining T_d from the above analysis and the subsites' potential doubling time (T_{pot}) from flow cytometry and immunohistochemical methods, the model were able to estimate the average T_d for each sub-site included in the analysis. Moreover, the dose that would be required to offset the modified proliferation occurring in one day (D_{prolif}), was estimated. The strength and limitation of the method, regarding the fitted parameters and 95% confidence intervals ($CI_{95\%}$) were also evaluated.

Results: In prostate cancer analysis, the best estimates of α/β were 1.69-Gy- $(1.29\text{-}2.14)_{95\%}$, 1.74-Gy- $(1.06\text{-}2.39)_{95\%}$ and 1.88-Gy $(1.21\text{-}2.83)_{95\%}$, for to low-, intermediate- and high-risk patient groups, respectively. The correspondent α values were 0.11-Gy^{-1} $(0.09\text{-}0.13)_{95\%}$, 0.12-$Gy^{-1}$ $(0.08\text{-}0.16)_{95\%}$ and 0.15-Gy^{-1} $(0.09\text{-}0.21)_{95\%}$. These values are compatible with a realistic number of clonogens ($1.8\bullet0^6$, $1.2\bullet0^7$, $5.8\bullet0^8$). The cell doubling time T_d estimated for each risk group were very low, compared to those reported in literature: 8.2 days $(5.6\text{-}17.1)_{95\%}$; 6.4 days $(4.8\text{-}16.2)_{95\%}$; 4.5 days $(3.2\text{-}15.1)_{95\%}$. This corresponds to high doses equivalent to 2-Gy that would be required to offset the repopulation occurring in one day (D_{prolif}): 0.35-Gy $(0.28\text{-}0.43)_{95\%}$, 0.42-Gy $(0.33\text{-}0.55)_{95\%}$, 0.50-Gy $(0.32\text{-}0.76)_{95\%}$; with a long start-up time T_k of 34-$(28\text{-}48)_{95\%}$, 37-$(31\text{-}52)_{95\%}$, 42-$(36\text{-}56)_{95\%}$ days from the start of radiotherapy.
In the HNSCC analysis, assuming an onset of accelerated proliferation T_K at day 21, the averages of T_d were 77 $(27\text{-}90)_{95\%}$ days in L_{EGFr} and 8.8 $(7.3\text{-}11)_{95\%}$ days in H_{EGFr}, while a reduction of about 7 $(6.6\text{-}8.3)_{95\%}$ times on average was found with respect to other T_K. The correspondent H_{EGFr} sub-sites' T_d were 5.9 (6.6), 5.9 (6.6), 4.6 (6.1), 14.3 (12.9) days with respect to immunohistochemical (flow cytometry) T_{pot} for Oral-Cavity, Oro-pharynx, Hypo-pharynx, and Larynx, respectively. The D_{prolif} for the H_{EGFr} groups were 0.33 (0.29), 0.33 (0.29), 0.42 (0.31), 0.14 (0.15) Gy/day if α=0.3Gy^{-1} and α/β=10Gy were assumed.

Conclusions: The method we have introduced to analyze data including differences in terms of effectiveness of radiotherapy schedules, allows to avoid the iso-effective hypothesis and then to reduce the systematic errors when comparing different radiotherapy Centers.
By the above analysis we confirm a very low value for α/β of prostate cancer with a correspondingly high value of intrinsic radiosensitivity, a realistic average number of clonogens, a long kick-off time for accelerated repopulation and a surprisingly fast repopulation that suggests the involvement of subpopulations of specifically tumorigenic stem cells during the continuing radiotherapy.
Moreover, because of the increased expression of the EGFr lead to enhanced proliferation which can be countervailed by reducing the time available for tumour cell proliferation, the correlation between EGFr expression and reduced repopulation doubling time for HNSCC, has been quantified.
Therefore, the methodology we have introduced would be useful to plan new schedules, analyze clinical data and set clinical radiotherapy studies for any pathology treatable by radiotherapy.

RUOLO DEGLI INIBITORI FARMACOLOGICI DELLA VIARHO/ROCK E LORO AZIONE FIBROLITICA IN DIVERSI MODELLI DI FIBROSI ANIMALE RADIOINDOTTA

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Radiation oncology is a cornerstone of modern multidis-

ciplinary cancer treatment. It has a place in the management of most common types of cancer, either as a single modality and organ-preserving alternative to surgery, for example, in organ-confined prostate cancer, or as an element in a sequence of treatment steps, such as in adjuvant radiotherapy after breast-conserving surgery for breast cancer. Strategies to improve the outcome of radiotherapy have aimed to improve tumor control rates, thereby increasing the chances of cure in radical or adjuvant therapy and the rates of symptom response in palliative situations. Thanks to technological advances like Image Guided Radiotherapy (IGRT) and Intensity Modulation Radiation Therapy (IMRT), reduction of toxicity and late effects on healthy tissue was also partially gained. At the same time, evolution of the standard of care toward combination therapies (radiotherapy + chemotherapy + targeted drugs) does enhance the rate and severity of both acute and delayed complications at the normal tissue level.

The physiopathology of normal tissue injury has been extensively studied by radiation oncologist and radiation biologist. Today, normal tissue toxicity is known to be the result of treatment modalities, tumor type and patient's characteristics that include biological heterogeneity, genetic factors, co-morbidities. Tissue response to radiotherapy depends upon the total dose delivered and the volume irradiated. In addition, radiation therapy is delivered fractionated and thus causes multiple and iterated cellular injuries. Radiation produces free radicals, damages to the vasculature, induces a cascade of local and systemic cytokine and chemokine expression, elicits inflammatory response, and causes death of cells. The tumor itself also leads to architectural destruction of the organ affected, releases cytokines, affects the immune system, and alters vascular permeability. Patients may have underlying medical conditions predisposing to injury (e.g., diabetes, poor underlying pulmonary function, or certain collagen vascular diseases) or have genetic susceptibility. All these factors may contribute to individual radiation sensitivity and their relative importance is difficult to assess. Nonetheless, it is becoming clear that abnormal microenvironmental conditions exist that are sustained long after the beam is turned off, the drugs are discontinued, and the tumor is eradicated, which appear to be responsible for the perpetuation of the tissue atrophy or hypertrophy, loss of epithelial/vascular/parenchymal cells, and excessive fibrosis characteristic of late normal tissue injury after cancer therapy. The main feature of tissue fibrosis is excessive accumulation of abnormal and cross-linked collagen mainly composed of fibrillar and immature extracellular matrix (ECM) components. The organs that can be affected by this phenomenon are liver, skin, intestine, kidneys and lungs. Research over the past 15 years has led to a better understanding of the underlying molecular events responsible for the development of normal tissue injury after cancer therapy. Characterization of the signalling pathways involved in radiation-induced fibrogenesis has mostly focused on one potent fibrogenic growth factor: the transforming growth factor β1 (TGF-β1) and today, inhibitors of TGF-b1 such as Pirfenidone are used in the clinic to halt progression of Idiopathic Pulmonary Fibrosis (IPF). More particularly, in the context of radiation-induced fibrosis several strategies have also been used in experimental models and in the clinic. Strategy conducted in our lab and others, was to characterize the molecular signals involved in fibrogenesis to provide new therapeutic targets. Using molecular profiling approaches, we have shown that the activation of Rho/ROCK/CTGF pathway was controlling the fibrogenic differentiation in several organs: the gut (human radiation-induced enteropathy), the heart and lungs (experimental models in C57Bl6 mice). Then we showed that it was possible to target it to prevent and reverse radiation fibrosis in the organs mentioned above using statins. Inhibitors of Rho/ROCK/CTGF pathway such as statins that inhibits Rho isoprenylation; Y-27632 an allosteric inhibitor of ROCK and monoclonal antibody against CTGF have shown anti-fibrotic properties. The pleiotropic actions of statins are mediated by inhibition of the production of isoprenoid residues and subsequent modulation of post-translational protein prenylation, including that of Rho. Pre-clinical studies showed that Pravastatin inhibited the Rho/ROCK/CTGF cascade in human samples *ex vivo* and reversed intestinal radiation-induced fibrosis *in vivo*. In addition, Pravastatin protected normal intestine and cutaneous from radiation damage without interfering with the anticancer action of irradiation in experimental models, both *in vitro* and *in vivo*. Other studies using Simvastatin confirmed these results. Additional mechanism may also be involved, such as preservation of endothelial barrier function, anti-inflammatory action, modulation of platelet activation and anti-thrombotic action, antioxidant properties and may certainly contribute to the anti-fibrotic action of Pravastatin. Our main hypothesis was that persistent alteration of the cell phenotype induced by irradiation depended, at least in part, upon the Rho/ROCK/CCN2 pathway in various organs. First, we showed that the pathological activation of Rho/ROCK pathway was not specific of radiation-induced intestinal fibrosis but could be considered as a general mechanism as it was also observed in lungs (and heart). We showed activation of the two important fibrogenic pathways: TGF-b/Smad and Rho/ROCK, in response to radiation-exposure *in vivo* in lungs of mice, 15 and 30 weeks post-irradiation. This fibrogenic molecular imprint was associated with long-term remodelling of pulmonary histological structures was successfully modulated using Rho/ROCK inhibitors (statins and Y-27632) that induces a normalization of fibrogenic markers. Secondly, our work focused on ECM remodelling and fibrolysis induced by Pravastatin *in vivo* and *in vitro*. To investigate this question, we used the two long-term experimental models of radiation-induced (RI) fibrosis available in our laboratory that model fibrosis in two majors dose limiting organs: the intestine and the lung. Then, we studied gelatinase and TIMP regulations and showed that Pravastatin administered as a mitigator induces a persistent activation of the MMP2-TIMP2 axis in the mucosal and muscular compartment of the gut. When Pravastatin was administered with curative intent the mechanism seemed different since no significant modulation of MMP2-TIMP2 was observed in the gut whereas local fibrolytic process was observed in lungs. Our results suggest that Pravastatin anti-fibrotic action is mediated by

Rho/ROCK pathway inhibition and gelatinase-mediated fibrolytic induction. Finally, *in vitro*, we investigate by zymography the expression of gelatinases (MMP2 and MMP9) in primary lung fibroblasts cultures exposure at the different radiation and Pravastatin doses.

In conclusion, our findings extend the biological rational for using Pravastatin to treat radiation-induced fibrosis in the patients. Pravastatin offers a safe and efficient therapeutic opportunity potentially usable either before or after radiation exposure. This approach is especially attractive in (1) the radiation oncology setting, as it does not interfere with prior anti-cancer treatment and in (2) radioprotection, as applicable to the treatment of established radiation injury, for example in the case of radiation accidents or acts of terrorism.

L'IMAGING MOLECOLARE ED I MODIFICATORI EPIGENETICI DI RADIORESISTENZA

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Prostate cancer (PCa) is the most commonly diagnosed cancer in men in the US and is a heterogeneous disease, the aetiology of which appears to be related to a complex range of risk factors, including lifestyle patterns, genetic factors and epigenetic modifications. In addition to genetic alterations, epigenetic mechanisms have recently been described as important factors contributing to the carcinogenesis and progression of Pca. Epigenetic mechanisms, defined as heritable changes in gene expression that occur without changes in DNA sequence, not only play a central role as modifiers of hormonal sensitivity but also seem to have some role in the mechanisms underlying radioresistance. Post-translational epigenetic modifications include (i) lysine sumoylation, (ii) serine phosphorylation, (iii) methylation and ubiquination and lysine acetylation and deacetylation (iv). These post-translational modifications affect chromatin conformation and play a major role in modifying the DNA accessibility to transcription factors. These post-translational events control multiple key cellular processes such as (i) DNA damage repair; (ii) tumour cell invasion and metastasis, (iii) hormonal response, (iv) cell cycle control and (v) neuroendocrine differentiation. So, inappropriate silencing of genes involved in these biological processes contribute to tumour initiation, progression ,metastasis and resistance to treatments. So, advances in translational research have to represent the next required step in improving the oncological outcome of men who remain at high risk for failure. This aim may be achieved by improving the diagnostic performances of conventional imaging modalities better predicting tumor response to conventional treatments.

Although radiotherapy and hormone manipulation are effective in reducing cancer growth, many Pca will recur or progress despite these treatments. We now have a greater understanding of the mechanisms sustaining castration- resistant prostate cancer (CRPC) upon hormonal manipulation. Interestingly has been suggested that long term hormonal manipulation appears to result in more radioresistant phenotype than the androgen-sensitive 22RV1 cells. Although 22RV1 cells, like the LNCaP, have androgen-responsive AR and p53 expression, they expressed a truncated AR and exhibited a partial androgen-insensitive type. The same group examined the cellular growth and radiosensitivity in LNCaP-HR founding that the more rapid growth and radioresistance were noted in LNCaP-HR when compared with LNCaP cells. Other recent evidence indicates that CRPC cells may acquire radioresistance by androgen receptor (AR) signalling modulation. TNK2, also known as Ack1 tyrosine kinase, mediates AR-tyrosine 267 phosphorylation and is emerging as an important modulator of radioresistance.

There are well-known limitations and inaccuracies with the current approaches for monitoring biological changes governing tumor progression and radioresistant phenotype by imaging in prostate cancer. The growing number of alternative treatments and the need for an early identification of non-responders has considerable stimulated the interest in developing new functional and molecular imaging techniques. So, the close integration of molecular biology and clinical imaging could make easier the development of new molecular imaging agents providing novel tools to monitor a number of biological events that, until a few years ago, were studied by conventional molecular assays. With regard to prostate cancer, progress in quantification, characterization and timing of biological processes could create novel opportunities to characterize more fully many biological events and to monitor the performances of well-established as well as novel treatment modalities. However, there are theoretical and practical challenges in attempting to translate these imaging strategies to clinical applications. Some of these challenges include the need to overcome problems related to the amplification of low level in vivo signals of biological events, and the development of integrated imaging platforms with sufficiently high spatial and temporal resolution. Another practical hurdle faced in translating imaging of Pca from bench to bedside is the need to reach the target in vivo to achieve satisfactory specificity.

Historically, most radiology research has been primarily focused on the attempt to improve technological quality, and undoubtedly it has served to this specialty well. Today's imaging technology is much improved in terms of resolution and speed reaching a stage where cell trafficking can be efficiently imaged. Among the many putative biological targets for imaging cancer, angiogenesis, apoptosis, signal transduction, and metabolic imaging have been the subject of intense research. In prostate cancer, many targets have been the subject of imaging inquiry such as gene delivery and expression and multidrug resistance. The most promising receptor-based targets are (i) steroid receptor proteins including the androgen receptor, (ii) the prostate specific membrane antigen (PSMA) and the free PSA (fPSA), (iii) and bombesin. Differently MRI is interesting in monitor tumor hypoxic changes, a well known phenomenon linked to radioresistance and that is governed by epigenetic phenomena. Steroid receptors can be modified by many different post-translational modifications such as phosphorylation, acetylation, ubiquitinylation and sumoylation. These

changes have the potential to affect many key biological processes such as the subcellular localization, interaction with other proteins within the transcription machinery complex or receptor stability.

The dehydrotestosterone analogue 16b-[18F]fluoro-5a-dihydrotestosterone (FDHT) has been developed as a tissue specific agent to imaging Pca and its uptake has been shown to be proportional to the AR concentration in primary Pca. A correlation between positive FDHT PET and increased PSA levels has been documented in clinical settings. Hence, it has been proposed that (18)-FDHT-PET may be used as a non invasive technique for predicting response to hormone therapy in Pca since the uptake of FDHT is AR receptor-mediated and seems to be proportional to the number of occupied receptor sites. Preliminary clinical experience suggests that (18)F-FDHT PET is a simple way to estimate free AR concentration in men suffering from androgen independent metastatic Pca. In fact, the engagement of AR with competitive androgen-receptor antagonists such as flutamide results in a significant decrease in FDHT uptake. The group led by Larson S., from the Memorial Sloan-Kettering Cancer Centre, found that 18F-FDHT may be a promising radiotracer for the study and imaging of AR biology in the progression to a castration resistant phenotype. In their study a total of 59 lesions, identified using conventional imaging procedures, were also positive to 18F-FDHT-PET [58 (98.9%)] suggesting that, by this radiotracer, we have the possibility to look inside the PCa tumor cells to see when it switch from androgen-dependent to androgen-independent phenotype. At the Washington University the team led by Dehdashti found that 10 of the 15 patients with advanced Pca and studied with 18F-FDHT-PET, computer tomography (CT), and bone scintigraphy, had tumors that took up FDHT. In these 10 patients with positive FDHT-PET the tumor FDHT uptake after one single dose of flutamide was significantly decreased with a mean drop in intensity around 60%. If this early response to antiandrogens predicts the long-term therapy response to hormonal manipulation remains unclear, but the evidence that after flutamide treatment tumors that disappear on FDHT-PET are still visible on conventional imaging (FDG-PET or CT scan) suggests that this radiotracer may used as a early marker that something's really going on in the biology of these cancers. PSA expression reflects AR transcriptional activity in normal and cancerous prostatic epithelia, although additional factors regulating the PSA promoter have been identified. Although no direct evidence exists regarding the PSA epigenetic control, sound preclinical findings suggest that androgen deprivation therapies select for a series of epigenetic and genetic changes in AR transcriptional co-activator proteins, contributing to the persistent PSA expression in androgen-independent PCa despite castrate androgen levels. So, PSA-targeted molecular imaging may configure as a surrogate of AR-mediated epigenetic changes improving in the evaluation of CRPC patients. So, apart from a few clinical contexts, changes in PSA levels are hard to interpret and over the last few years new PSA fractions have increasingly been used to improve the diagnostic PSA performance. Serum PSA exists as a free-floating PSA. Clinical and biological data suggests that a tumor tissue produces greater amount of free-PSA (fPSA) than normal tissue and this seems improve the predictive value of this marker in detecting PCa. In a recent report a team led from Charles L Sawyers reported the use of a monoclonal antibody (5A10) conjugated with ^{89}ZR that specifically binds fPSA and features the AR-driven prostate tumor activity These authors show that changes in the expression of fPSA can be monitored by this novel radiotracer ^{89}Zr-5A10. The most interesting evidence is that ^{89}Zr-5A10 is suitable for quantifying AR transcriptional activity in castration-resistant preclinical models of Pca. Additionally, ^{89}Zr-5A10 co-localizes in PSA- and AR-positive Pca models and quantitatively predicts response to antiandrogen therapy in human xenograft models of CRPC. Interestingly, since this radiotracer seems preferentially targets tumor cells it can individuate more accurately cancers induced than non-malignant induced skeletal changes. Another AR target gene epigenetically controlled is the Prostate-specific membrane antigen (PSMA). Although PSMA is no longer considered as prostate specific, literature indicates that this glycoprotein may be used in nuclear medicine to imaging benign and malignant prostate tissue. In Pca PSMA seems to work as epigenetically controlled oncosuppressor which activity and expression parallels androgen independence. This clearly indicates that exist a link among PSMA, epigenetic mechanisms and androgen independence. A well known FDA approved agent targeting PSMA in Pca is capromab pendetide (ProstaScint®). The relatively disappointing results of these studies with ProstaScint® are partially due to the fact that the murine monoclonal antibody mAb 7E11 needed to be internalized into cells prior to binding because the antibody recognized an internal epitope of PSMA. Thus, only apoptotic or necrotic cells, which had damaged cell membranes, bound mAB 7E11, greatly decreasing the overall performance of this imaging modality . More recently, several novel radiolabelled mAbs targeting PSMA has been developed for molecular imaging (3/F11, 3/A12, 3C6 and 3/E7) which have a strong affinity for three different extracellular PSMA epitopes. However, their use in clinical practice has disadvantage mainly due to their slow uptake and clearance rate resulting in delayed imaging. Low-molecular-weight radiopharmaceutical agents have more performing pharmacokinetics properties than radiolabelled mABs. These low-molecular-weight molecules have induced the onset of a new generation of PSMA targeting molecules for SPECT/CT and PET/CT imaging.

Emerging evidence is now demonstrating as androgen ablation therapy may contribute to induce tumour hypoxia. Rothermund et al 2005 examined gene expression profile of LNcap cells after prolonged androgen ablation treatment with bicalutamide. He found a significant over-expression of many hypoxia target genes concluding that hormone manipulation may favour hypoxia. These data are in line with an earlier report that observed that the LNCaP subline (LNCaP-H1) growth in androgen depleted medium was fast growing, was able to result in growth of endothelia cells and was resistant to both radiotherapy and chemotherapy. At the same time available data indicates that tumor cell lines growth under chronic hypoxic condition, not only, more easily developed androgen independence, but

are much more radioresistant with an high tendency to genetic instability. The prognostic implications of hypoxia have also been studied in men with Pca. Vaupel 2008 recently showed that men with laboratory evidence of hypoxia had a poor overall survival than patients with normoxia. However the mechanisms linking the resistance to radiotherapy and hormone manipulation with hypoxia are still largely unknown. To adapt to hypoxia, tumor cells may switch from oxidative phosphorylation to anaerobic glycolysis, which terminates with the formation of lactate which is recognized as a marker of response to treatment So, the non-invasive detection of lactate may be used for monitoring the changes of tumor hypoxia in response to treatment. MRSI enables the detection of lactate and the estimation of its concentration, and dynamic contrast-enhanced (DCE) MRI allows the visualization and quantification of tumor perfusion and permeability. However, the measurement of lactate in vivo remains a challenge due to an overlap between the spectra of lipids and lactate with a relatively low lactate concentration. In Pca preclinical models, high uptake of fluorodeoxyglucose has been shown to correlate positively with histologically measured tumor hypoxia and to correlate negatively with blood flow in the central regions of the tumor. Other evidence in the established and well-characterized Dunning prostate tumor model suggests that lactate is detected in a heterogeneous pattern in fast-growing, but not in slow-growing tumors, suggesting that the presence of lactate may be a feature of aggressive tumors. This observation was supported by the perfusion/permeability measures performed by DCE MRI, which are significantly lower in the core than in the rim of experimental tumor.

Finally, non invasive measurements of hypoxia by imaging have been performed using PET with 1-α-D-(5-deoxy-5-[18F]-fluoroarabinofuranosyl)-2-nitroimidazole (18F-FAZA). Clinical experiences with this radiotracer have been performed in several human cancers with good tumor-to-background ratio. Nitroimidazole radiotracer uptake has been linked to treatment resistance of several cancers in preclinical and clinical studies. Interestingly, this radiotracer has shown its potential for detection of hypoxic prostate tumors in patients treated by radiotherapy. Some authors have tried to correlate imaging findings with biological markers merging histological findings with PET/CT or MRI. For example the 18F-FAZA PET/CT measurements were made possible by a sophisticated fusion technique involving MRI. Previous experiences demonstrated that the registration errors for fusion of in-vivo imaging with histology involving specimen MRI were in the range of 2–4 mm. So, there is sufficient evidence in support of the necessary accuracy for spatial comparisons of volumetric imaging modalities with pathological findings.

There is limited knowledge on the influence of epigenetic mechanisms on the development of resistance to conventional treatments. New imaging modalities allowing the investigation of molecular events in terms of the spatio-temporal dimension, are needed to follow the intracellular signalling pathways both in the tumour itself and in the surrounding normal tissue. Molecular imaging comprises a cluster of technologies allowing the measurement of biological events that are relevant for the understanding and the monitoring of prostate cancer especially when it becomes resistant to treatments. Each different imaging modality presents its unique set of advantages and disadvantages in terms of sensitivity, resolution and type of information provided. To overcome these drawbacks, innovative and new technologies allowing the integration of different imaging modalities have been developed which integrate biological with morphological information with improved penetration through body tissues. Further advances are also expected in the way tracers are conceived to widen the number of biological events that can be studied and monitored by molecular imaging. Among them, PET-based technologies are promising modalities which have opened up new avenues for visualizing and understanding the biological changes occurring during epigenetic processes. Although these imaging modalities have not been fully explored for the study of epigenetic signaling, we expect that they, when combined with tracers targeting specific biological targets, will significantly improve the spatial resolution of epigenetic domain from a single cell level to a whole body. Obviously, the information obtained by molecular imaging cannot be sufficient to unravel the molecular pathways that governs the epigenetic mechanisms involved in the resistance to treatments but may represent a powerful tool to identify subjects who are at risk to hormonal- and radio-resistance. Hopefully, the knowledge of critical molecular events involved in these biological processes will allows us to identify unique epigenetic signatures useful to inspire new therapeutic strategies for overcoming the problem of resistance to conventional treatments.

PHARMACOLOGICAL MODULATION OF THE NORMAL TISSUE RESPONSE TO RADIATION

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Radiotherapy (RT) constitutes nowadays a primary anticancer treatment approach. Despite improvements in the development of radiotherapy treatment planning and treatment technologies, there remains a significant toxicity of radiotherapy to normal tissues and organs. Improved local control and overall survival by radiotherapy dose escalation in cancer patients is associated with significant toxicity and normal tissue damage; often more theoretical effective dose cannot be used in reason of acute toxicities occurring during radiotherapy. In order to allow for increased radiotherapy doses, pharmacological approaches to radioprotection of normal tissues must be developed. Two characteristics are necessary for these approaches: selectivity for healthy tissues to avoid tumor cells protection and safety of the administrated pharmacological compounds. The molecular pathways utilized for radiation protection are based on current knowledge regarding the molecular biological mechanisms of ionizing irradiation induced cell killing at the level of single cells, tissues and organs. The killing of cells by radiation is mediated by the ionization of irradiated matter; in particular ionizing irradiation, hits intracellular oxygen and water molecules causing the production of radical oxygen species (ROS) that deplete cellular antioxidant stores.

The most well known principle of radioprotection involves using antioxidants, which act as scavengers of ROS. Amifostine, a scavenger of ROS , is currently the only drug approved for clinical use to protect against radiotherapy-induced toxicity. It reduces DNA strands breaks inducing upregulation of DNA repairs proteins and inhibition of proinflammation cytokines. The protective activity on normal tissue is demonstrated for the endothelium, salivar glands and connective tissue. However, clinical use of Amifostine is complicated by its own toxicity, the most common adverse events are hypotension, nausea, and hypocalcemia. Amifostine is an inactive prodrug that cannot protect until dephosphorylated to the active metabolite WR-1065. The hypovascularity and low pH of the tumor tissue respect to the normal tissue guarantee the cytoprotective selectivity of Amifostine. The U.S. Food and Drug Administration has approved the use of Amifostine to reduce the renal toxicity associated with cisplatin administration in patients with advanced ovarian cancer and to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer. Several studies are interested in the radioprotective properties of a new class of agents: the Heparan Mimetic Biopolymers. Heparan Mimetic biopolymers mimic the protective properties of heparan sulfates toward heparin binding growth factor (HBGF) against proteolitic degradation. The activity of Heparan Mimetic Biopolymers results in a modification of inflammation kinetic inhibiting activities of plasmin, cathepsinG, and neutrophil elastase and stimulation of tissue repair enhancing the bioavailability of FGF-2 and TGF-β1. ReGeneraTing Agents (RGTAs) are engineered biopolymers that mimic the protecting and potentiating properties of heparin sulfates toward heparin binding growth factors (HBGF). University of Florence in collaboration with the Institut Gustave Roussy of Paris investigated the role of a RGTAs called RGTA-OTR4131 for the treatment of oral mucositis in head and neck cancer patients undergoing radiotherapy. It was used a preclinical model of radiation-induced oral mucositis using mice and large single fraction (16.5 Gy) and RGTA-OTR4131 was administrated 3 or 24 hours after irradiation. Amifostine was used as a reference to be compared with RGTA-OTR4131. A significant reduction of oral mucositis was demonstrated ($p = 0.0009$) when OTR4131 was administered 24 h after irradiation. The most interesting results was that the combined administration of Amifostine 10 min before irradiation with OTR4131 24 h after irradiation yielded a striking protective effect and almost completely abrogated macroscopic damages induced by 16.5-Gy irradiation on the lip mucosa ($p = 0.0003$). In the same study no protection on tumor cells by Amifostine- OTR4131 administration was found. A recent study published by Spiegelberg focused on the potential of RGTA-OTR4120 to treat radiation-induced damage of salivary glands. In this study RGTA-OTR4120 administration showed a positive effect on salivary flow rates in irradiated mice on the short term. The effect was absent 10 weeks after radiotherapy, while at that time point mucin producing-activity of acinar cells was elevated by RGTA-OTR4120 administration. Given these results and the advantages of RGTA use in irradiated patients, further investigation on the potential of this drug to treat radiation-induced salivary gland damage, alone or in combination with other drugs, such as amifostine, is necessary. Several studies are actually investigating the radioprotective role of peroxisome proliferator-activated receptor γ ligands (PPARγ). PPARγ is a member of nuclear receptor superfamily and is expressed in several cells in the body, including cells of the gastrointestinal tract, liver, kidney, heart, adipose tissue, central nervous system, lung, skeletal muscle, endothelium, neutrophils, macrophages, dendritic cells, T cells, mast cells. PPARs are nuclear receptors expressed by a wide variety of cell types both within and outside the immune system. PPARs dimerize with the retinoid X receptor (RXR), and the binding of PPAR-RXR heterodimers to PPAR response elements regulates the transcription of target genes. Four PPAR isotypes have thus far been reported to regulate adipocyte differentiation and metabolism. Several models have been suggested to describe transrepression by PPAR-γ interacting with the transcription factor nuclear factor $\varkappa$B (NF-$\varkappa$B). NF-$\varkappa$B plays an important role in the regulation of immune and inflammatory responses, for it induces the expression of multiple target genes that promote cell proliferation, regulate apoptosis, facilitate angiogenesis and, in carcinogenesis, stimulate invasion and metastasis. PPAR-γ was originally described as a differentiation transcription factor for adipose tissue; thiazolidinedione drugs are used for the treatment of type II diabetes and specifically target PPAR-γ.A large volume of studies show efficacy of PPAR treatment on cell lines and animal models. It is well established that the activation of each subclass of receptors can result in antiproliferative, proapoptotic, prodifferentiation, and antiangiogenic effects in cell lines or animal models. Zhao et al. considering the putative role of inflammation in radiation-induced brain injury thought that the administration of the anti-inflammatory peroxisomal proliferator-activated receptor agonist pioglitazone (Pio) to adult male rats would inhibit radiation-induced cognitive impairment. The results showed that the administration of Pio before, during, and for 4 or 54 weeks after whole brain irradiation (WBI) prevented the radiation-induced cognitive impairment; on the other hand the administration of Pio for 54 weeks starting after completion of fractionated WBI substantially but not significantly reduced the radiation-induced cognitive impairment.The University of Florence is evaluating the radioprotective effect of Rosiglitazone (RGZ), a PPAR-γ agonist, on a murine model of pulmonary fibrosis and of acute intestinal damage. Mice were treated with bleomycin with or without RGZ(5mg/Kg/day). Mice underwent 12Gy total body irradiation(TBI) with or without RGZ. 24 or 72h after TBI ileum and colon segments were collected for histopathological and real time polymerase chain reaction (RT-PCR) analysis. Thorax CT showed irregular septal thickening, and patchy peripheral reticular abnormalities with intralobular linear opacities. RGZ markedly attenuated the radiological signs of fibrosis. Histological analysis revealed that in bleomycin-treated mice fibrosis involved 50-55% of pulmonary parenchyma; on the other hand in RGZ-treated mice fibrosis involved only 20-25% of pulmonary parenchyma without alterations of the alve-

olar structures. Analyzing the intestinal mucosa 24h after 12Gy TBI villi shortening, mucosal thickness, crypt necrotic changes, oedema and inflammatory infiltrate was found. RGZ showed an histological improvement of tissue structure. The preliminary results seems to demonstrate that RGZ displays a protective effect on pulmonary fibrosis and radiation-induced intestinal toxicity in mice. Molecular targets of new radioprotectors should concentrate on the mechanisms of action on irradiation-induced damage, focusing instead on distal steps in the cellular response, and steps in induction of the cell death pathways including autophagy, apoptosis and necrosis. New strategies to identify metabolic differences between normal tissue and tumor cells will also be critical to the design of new classes of radioprotectors for clinical use.

AUTOPHAGY MODULATION AS POTENTIAL THERAPEUTICAL TARGET IN GLIOBLASTOMA

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Backgrounds and Purpose: Several studies seem to show an emerging pivotal role of cell autophagy, adding apoptosis, in response to radiation treatment, expecially in glioblastoma (GB). We previously demonstrated, in clinical setting study, the prognostic role of autophagical markers in patients affected by GB undergone to radiation treatment. From bed-side to bench-side, we assessed a pre-clinical study aimed to understand and quantificate potential relationship between autophagy and response to radiation treatment in cells colture of GB.

Materials and Methods: Human malignant glioblastoma cell lines, T98G and U373-MG, were cultured and irradiated by a 6-Mv X-ray linear accelerator (Clinac 600) at dose-rate of 12.5cGy/min (LDR) and 244.5 cGy/min (HDR), with different dose (0.12; 0.35; 0.70; 1; 1.2; 2; 3; 4; 5 and 6Gy). Cell coltures were irradiated in different conditions of autophagy modulation (basal, inhibition and induction conditions). Rapamycin added to the cultured cells was used to autophagy induction. To inhibit autophagy, knockdown of the autophagy related gene *ATG*-7 was performed by specific siRNA transfection. We used clonogenic assay to evaluate the response to treatment. The surviving fraction (SF) was calculated, dividing counted clones by plated cells and normalizing to the corresponding control sample, deriving the survival curve. Each experiment was performed in triplicate. We performed a statistical analysis (ANOVA) to evaluate the difference in response to radiation treatment between the two different lines at different doses, dose-rates and autophagy conditions . We performed a modelling of survival curves and estimation of parameters α and β according a Linear-Quadratic model. We also implemented a new mathematical model for quantitative analysis of cell coltures with not Linear-Quadratic response to radiation treatment.

Results: T 98G cells showed a different survival response by rates, dose and autophagy condition. In basal condition this line had a Low Dose Radiation Hypersensitivity (LD-HRS) and a bifasical (not L-Q) dose - response curve. The LD-HRS was further enhanced in LDR *vs* HDR ($p<0,05$) irradiation conditions. In HDR irradiation, Autophagy-induction reduced mean T98G SFs in all doses checked (low- intermediate and high doses) respect to basal condition ($p<0,05$). Autophagy-inhibition, instead, seemed to turn off LD-HRS ($p<0,05$) and reduced radiation response at intermediate doses ($p>0,05$), but not in higher doses than 3 Gy ($p>0,05$), with a classic LQ response to radiation treatment respect to basal condition. In LDR irradiation, the survival response differences according to different autophagy modulation were confirmed ($p<0,05$), even if, with mean lower SFs than HDR ones ($p<0,05$), except for higher doses than 4 Gy ($p>0.05$).
U373 cells showed different response to radiation treatment according to different conditions of rates, dose and autophagy modulation as well. In basal condition, U373 cells showed a L-Q response to irradiation with a significative difference in SF curves between HDR and LDR ($p<0,05$) with mean lower SFs in LDR ones. In HDR irradiation, Autophagy-induction reduced U373 SFs in all doses checked ($p<0,05$) respect to basal condition. Autophagy-inhibition, to the other side, didn't seem to modify response to treatment respect basal conditions at all doses checked ($p>0,05$). In LDR, all difference found in HDR conditions according with autophagy modulation status were confirmed ($p<0,05$), but with mean lower SFs ($p<0,05$). The two cell lines showed a global different response to radiation treatment according different autophagy modulation conditions ($p<0,05$). Using a LQ model to extimate alfa and beta values from experimental SFs data, we found in U373 cells this model is very fittable and useful to compare the different condition. We found classic LQ model no fittable for T98G cell response to treatment causes their LD-HDR. We implemented a new model in which we considered a pro-death (autophagy and apoptosis) and a pro-survival response (autophagy or just a default effect) to treatment..This more complex model was able to compare mathematically T98G response to treatment in different irradiation and autophagy modulation conditions.
Conclusions: This biomolecular and modelling preclinical approach, even with their intrinsic limitations, seems to show a potential role as therapeutical target of autophagy modulation in GB. In particular, new autophagy inducers could be object of futher studies about treatment of GB.

CLINICAL VOLUMES IN THE TREATMENT OF GYNAECOLOGICAL TUMOURS

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In recent years, external beam radiotherapy techniques

have advanced considerably. An example of this is how the treatment planning for uterine cervical cancer has transitioned from a two-dimensional (2D) approach based on bony landmarks to a three-dimensional (3D) technique. The 3D treatment planning involves the direct input of target volumes and organs at risk (OAR) using cross-sectional images from computed tomography (CT) and magnetic resonance imaging (MRI). Technical advances in the radiation delivery devices as well as ancillary equipments such as radiotherapy treatment planning systems and on-board imaging devices enable the precise delivery of external beam radiotherapy. Intensity-modulated radiation therapy (IMRT) has proven to have a significant dosimetric advantage in comparison with conventional treatment planning for various malignancies including gynecologic cancers (1). Although improvements have been made in treatment equipments and techniques, determination of both target volumes and OAR has not been well standardized. In particular, contouring of the clinical target volume (CTV) of regional lymph nodes requires thorough understanding of both the distribution patterns of microscopic metastases and anatomic features on cross-sectional images. Lack of a standardized contouring protocol may result in considerable variation in contouring (2). Therefore, a global consensus is needed for the standard CTV for regional nodes in cervical cancer in order to optimize the delivery of high precision external beam radiotherapy including IMRT. In Europe, the nodal CTV was first standardized for head and neck cancers (3,4). CTV standardization has also progressed in prostate cancer (5) and anorectal cancers (6) in the USA. For uterine cancers, the Radiation Therapy Oncology Group (RTOG) (7) and UK investigators (8,9) have also recently published their guidelines. Previously published guidelines on CTV delineation (7–9), imaging studies (10–14), as well as gynecologic surgery series (15, 16,17) (reviewing the distribution of pelvic nodal metastases), and papers and textbooks of pelvic anatomy related to images (18,19) have been used. Margins are designed around blood vessels which serve as good surrogate targets for regional nodes (7,8,12,20). Chao and Lin (12) studied the pelvic node distribution in patients with uterine cervical cancer who underwent lymphangiography. They showed that 10–15 mm margins adequately covered the pelvic node regions. However, the working group felt that these margins were unnecessarily expansive. Taylor et al. (8) demonstrated using the intravenous ultra-small particles of iron oxide (USPIO) MRI that a 7 mm margin around the vessels achieved 88% nodal coverage in the assessed regions. The RTOG guideline also employed this basic definition of a 7 mm margin (7). In addition to that, Taylor et al. (8) modified the definition and achieved a coverage ratio of 99%. For the common iliac region ideally, the region should be defined based on the blood vessel anatomy at the level of common iliac arterial bifurcation. But RTOG guideline maintained a definition based on the bone anatomy (7). A second issue is the posterior margin of the CTV which involves adipose connective tissue between the iliopsoas muscles and the lateral surface of the vertebral body. This is based on the analysis of CT/MRI images In the external iliac region, the caudal margin was defined as the level of the superior border of the femoral head. According to this anatomical definition, the margin should move caudally until it reaches the level at the junction with the femoral vessels or the level at the intersection with the transverse abdominal muscles. The incidence of nodal metastases reported in surgical series is relatively low (15–17). Sakuragi et al. (16) analyzed the distribution patterns of metastatic nodes in 208 patients with Stage I/II cervical cancer treated with radical hysterectomy and pelvic node dissection. They reported that only 3.8% of the patients had pelvic nodal metastases in the external iliac region (16). The CTV definition of the internal iliac node region differs in the different guidelines A significant number of enlarged nodes mat be observed from the lateral margin of the adipose connective tissue to the medial surface of the iliopsoas muscle, or at the level of the sacral wing tips, which are not included in the RTOG guideline (7). The conventional 2D fields usually cover this area. Taylor's guideline also employed a similar definition (8,9). Therefore, the current RTOG definition on lateral expansion of the CTV for the internal iliac node may be insufficient. The parametrial lymph node region is not defined and should be included in the guideline for primary tumour CTV. T the obturator node region distribute into the anatomical level where the obturator vessels penetrate the obturator foramens. In cases of external beam radiotherapy, the conventional 2D pelvic fields also include the foramens. The upper level of the foramen should be included in the nodal CTV. The presacral node region (7–9) are sparsely distributed and CTV coverage was not required extensively (8). The conventional 2D lateral field covers extensively entire sacral surface intended to achieve adequate coverage of the parametrial tissues which is included in the CTV for primary tumour (9,22).

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STRATEGIE TERAPEUTICHE NELLE METASTASI LATEROCERVICALI DA FOCUS IGNOTO. IL RUOLO DEL CHIRURGO

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Introduction: Cervical lymph node metastasis is frequently the first clinical manifestation of a head and neck squamous cell carcinoma (SCC). An appropriate H&N examination, coupled with endoscopy and imaging, most often allows to detect the primary SCC in the head and neck mucosal districts. Very small tonsil and tongue base SCCs, radiologically and endoscopically undetectable and presenting with enlarged neck nodes, can be adequately diagnosed by base of tongue biopsies and tonsillectomy as indicated by many guidelines P P. Nevertheless in a percentage ranging from 1 to 5% of all head and neck malignancies, usually characterized by unilateral metastases at the level IIa (jugulodigastric), the primary SCC remains clinically undetectable (unknown primary tumors) after a thorough and appropriate work-up P[2-4] P. The primary tumor becomes apparent on follow-up only in a few cases. Anyway H&N SCC of unknown primary site is a highly curable disease. After appropriate treatment, most patients experience low morbidity and many will be cured.

Patients and Results: We evaluated a series of 20 consecutive cases of neck metastases from unknown primary SCCs evaluated at Università Cattolica del Sacro Cuore between January 2010 and January 2012. All the patients came to our observation with a neck mass, for which we performed a complete H&N examination, which turned out to be negative. Personal data were collected, with particular attention to environmental risk factors (smoking, alcohol consumption), and with the exclusion of antecedent history of malignancy and of prior excision, destruction, or regression of cutaneous lesions. Endoscopy of the upper airways and imaging of the head and neck region (contrast-enhanced MRI and CT) and of the chest (contrast-enhanced CT) were negative as well. A FNA was then performed with a cytology positive or suspicious for SCC. Neither the following PET CT nor multiple biopsies of the base of tongue and bilateral tonsillectomy allowed the identification of the primary. Therefore the diagnosis of unknown primary was formulated and a comprehensive monolateral neck dissection was performed which confirmed the presence of metastatic SCC in one or more neck nodes. We then evaluated, in the positive nodes, HPV DNA and mRNA, and EBV DNA. We found viral nucleic acids in 11/20 cases (55%). DISCUSSION Our clinical experience and the results of the present paper, lead us to define the diagnostic algorithm in the presence of a neck mass suspected to be a metastasis from an occult T.

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THE ROLE OF BIOMARKERS IN CHEMO-RADIOTHERAPY OF CERVICAL METASTASES FROM UNKNOWN PRIMARY

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Squamous cervical cancer of unknown primary site (SQCCUP) presents in patients as neck lymph nodes involved by squamous carcinoma in the absence of identificable primary in the head, neck or lung. This CUP subset affects prevalently male patients previously exposed to alcohol and tobacco, though a proportion of cases may be related to chronic infection of the oropharynx by human papilloma virus (HPV). A standardised diagnostic work-up consisting of panendoscopy of the upper aerodigestive tract, CT of the chest/abdomen, CT-PET scan and histology supplemented by immunohistochemistry is warranted for the diagnosis. Aggressive multimodal therapy results in longterm disease control in 50–60% of patients, though data are mainly based on retrospective cohorts. Factors predicting for superior patient outcome are radical management with surgery or radiotherapy, low stage and volume of disease, absence of extracapsular spread and good performance status. Recently introduced molecular profiling platforms may provide biological classification to a primary tissue of origin as well as insights into the pathophysiology of this clinical entity (1). The incidence of the appearance of primary site in patients with SQCCUP is around 10% (ranging between 5% and 30%) and it usually occurs within the first 2 years of follow-up. Several authors consider primary tumours arising later than 5 years after primary diagnosis as second primaries. The most common sites of the appearance of primary tumours include nasopharynx, base of the tongue, tonsil and pyriform sinus. Patients undergoing bilateral tonsillectomy have a 3-fold increased chance of discovering the primary site in the tonsils. The optimal treatment of cervical SQCCUP has not yet been defined and remains controversial because cervical SQCCUP are often excluded from major randomized clinical trials; studies reported are usually single institution retrospective series, and patients are treated with heterogeneous treatments. Recommendations for treatment vary and include surgical excision of the involved lymph node alone, neck dissection, radiotherapy, or combinations. Moreover, varying sequences of treatment modalities have been used in previously reported retrospective series. Concurrent chemoradiotherapy has now become an integral part of standard non-surgical treatment of patients with locally advanced head and neck cancer, and postoperative treatment in pathologically high-risk patients. However, the role of chemoradiotherapy for cervical SCCUP has not yet been established (2). Inadequate efforts have been invested in unravelling the molecular biology of unknown primary cancer. A major problem with any research effort is the heterogeneity of this clinical entity, which would result in multiple molecular aberrations being responsible for the distinct behaviour of the different CUP subsets. The molecular biology of SQCCUP has not been investigated, probably due to the rarity of this patient population, and any insights into its pathophysiology stem from extrapolated data from head/neck cancer of known primary. Chromosomal abnormalities commonly seen in head/neck carcinomas are 3p, 9p deletions and loss of heterozygosity at 4q, 8p, 11q, 13q, 14q and 17p. Common genetic alterations in head/neck cancer of known primary (incidence 30–60%), such as COX2 activation, EGFR overexpression and inactivation of the tumour suppressors p16, p21, p53 and pRB, have not been investigated in SQCCUP. Angiogenesis is particularly active in head/neck cancer and microvessel density and VEGF expression by immunohistochemistry or PCR have been associated with aggressive disease course and poor outcome. Some data have recently been reported on molecular aberrations in unselected populations of patients with CUP tumours. EGFR and COX2 oncoproteins were overexpressed in 12–60% of CUP tumours, although no activating EGFR gene mutations or gene amplifycation were found in 50 CUP cases examined. Active angiogenesis was evident in CUP: CD34-based assays of microvessel density and immunohistochemical VEGF-A expression disclosed increased angiogenic activity in 26-83% of examined CUP tumours in several retrospective series of moderate sample size. However, the exact incidence and biologic significance of the molecular traits described above in SQCCUP is unknown and their potential for targeting with smart drugs unproven (4,5). While traditional histochemistry has been established as a useful technique in other tumour types, it has not proven particularly helpful in the diagnostic work-up of SQCCUP. Advanced molecular techniques such as *in situ* hybridisation or polymerase chain reaction could be useful in detecting Epstein-Barr virus (EBV) or HPV, differentiating a nasopharyngeal or oropharyngeal primary cancer, respectively. Some investigators have controversially advised diagnostic tonsillectomy in the presence of HPV DNA in involved cervical lymph nodes (3). Concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck significantly improves response rate and overall survival. In addition, the combination of platinum-based chemotherapy with cetuximab increased efficacy as first-line treatment in patients with recurrent or metastatic head and neck cancer. All these studies are large well conducted randomised studies published during the last few years. Unfortunately, up to now there have been no randomised reports on the efficacy of chemo-radiotherapy in patients with SQCCUP. Practically there are only few retrospective studies with approximately 100 patients treated with various cytotoxic drugs (platinum or non-platinum). Chemotherapy was administered before, during or after radiotherapy and results in some studies were compared with historical controls. In the most recent retrospective report by Shehadeh et al. (2) patients with SQCCUP were managed with neck dissection followed by concurrent high-dose cisplatin and bilateral neck/mucosal sites irradiation. A total dose of 64 Gy was administered in the involved side of the neck and 50 Gy to uninvolved neck and mucosal sites. At a median follow-up of 42 months, 89% of patients were alive. Only two regional and four distant relapses were observed. These encouraging results were coupled to safety of therapy (incidence

of severe mucositis 46%, xerostomia 30%). Based on these encouraging preliminary results, prospective multicentric studies in a larger number of SQCCUP patients will be warranted, in order to establish the efficacy of concurrent chemoradiotherapy in a cohort of patients with bulky neck disease. High-throughput molecular profiling technologies have provided rapidly accumulating data on expression (transcription) of multiple genes in several human tumours. These oligonucleotide hybridisation microarray platforms, coupled to bioinformatic analysis tools, enable scientists to identify a 'typical' multigene expression profile for each solid tumour. Accordingly, gene expression in CUP tumours may be studied by the use of the same methods and compared to the typical genetic profiles of known cancers. Recently published data show that a primary tissue of origin can be molecularly assigned with high accuracy in 70–85% of CUP cases. Four studies reported use of multiple gene expression profiling platforms for the identifycation of tissue of origin in CUP. In these studies, three microarray genetic signatures biologically classified more than 500 CUP cases with 76–96% accuracy. A head/neck squamous primary was biologically assigned as the occult primary in less than 5–10% of cases analysed. Despite the accuracy of microarrays in identifying molecular similarities, it is unknown if a squamous head/neck CUP molecularly assigned to a head/neck primary tumour indeed behaves similarly to a typical metastatic tumour of the same primary. Head/neck CUP tumours and metastatic head/neck tumours of evident primaries may harbour some distinct genetic or epigenetic lesions. The hope that molecular classification of CUP followed by primary site-specific therapy would improve patient outcome should be validated in prospective clinical trials. In such a trial, a poor-risk CUP patient cohort should be randomised to empiric management or molecularly assigned primary site-specific management.

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RADIATION THERAPY CLINICAL VOLUMES IN METASTATIC NECK NODAL CARCINOMA OF UNKNOWN PRIMARY

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Cervical lymph node metastases from unknown primary tumours are rare, constituting only about 2% of all new head and neck cancers. The optimal management of this type of tumor is still controversial because a standard therapy has not been identified yet so the management of these patients remains a major challenge in oncology. Recommendations contain surgery alone, radiotherapy alone, or combined modalities. Surgery alone seems to be sufficient in nodal status N1 with no extracapsular extension. The majority of patients are treated by surgery followed by radiotherapy. In radiation therapy one of the most controversial topics in the management of occult head and neck primaries is the role of mucosal irradiation. In fact several authors have recommended bilateral neck and mucosal site irradiation, several others advocated treatment of the involved side of the neck alone with surgery or radiotherapy and observation of the occult primary sites and controlateral neck. There is no doubt that bilateral neck and mucosal irradiation causes significant acute toxicity and chronic morbidity, mainly xerostomia with its associated complications; it is well known from other head and neck series that radiation morbidity is highly related to the irradiated volume. On the other hand, treatment of the involved side of the neck alone may have a detrimental effect on the patient's outcome because potential sites of occult primaries in the head and neck mucosa, and any subclinical metastatic disease in the contralateral side of the neck are left untreated. The reported incidence of occult primary development has ranged from 12% to 25% after surgery alone, and from 5% to 15% after ipsilateral neck irradiation alone. The lower incidence of occult primary development reported in the ipsilateral neck irradiation series might be due to the technique used for irradiation of the ipsilateral neck. The technique most commonly used was a pair of anterior and posterior tangential portals; hence, the ipsilateral oropharynx, larynx, and hypopharynx might have received sufficient radiation for sterilization of small occult primaries in these areas. The arguments for ipsilateral treatment have been that by sparing most of the mucosa and the entire contralateral neck, patients will tolerate treatment much better and have the same survival rate in fact many authors have observed that mucosal irradiation reduced both the emergence of primary tumor and regional recurrence without impact on OS. On the other hand, the arguments for large mucosal fields have been to prevent potentially incurable loco-regional relapses. The potential mucosal primary tumor sites in the head and neck area are anatomically disparate (nasopharynx, tonsillar fossae, base of tongue, supraglottic larynx and hypopharynx), and their uniform inclusion in radiations portals entails a large volume of sensitive normal tissues with consequent appearance of large-volume mucositis acutely and cronic xerostomia. A rewiew of the tipical site of presentation of late mucosal primary disease in surgery alone series can support the elimination of specific mucosal sites from inclusion in radiation portals. Thus, depending on the nodal location, individualization of volumes should be possible limiting toxicity. To answer the question which target volume should be irradiated, a prospective randomized study has been initiated by the EORTC comparing postoperative limited (ipsilateral irradiation) radiotherapy *versus* extended (ipsilateral and contralateral irradiation including potential primary mucosal sites) radiotherapy (Intergroup Study EORTC 24001-22005, "Randomised phase III study on the

selection of the target volume in postoperative radiotherapy for cervical lymph node metastases of squamous cell carcinoma from an unknown primary [CUP]"). Hopefully, the results of this current study will solve the therapeutic dilemma between minimizing side effects and maximizing therapeutic effects.

THE MANAGEMENT OF SIDE EFFECTS IN LATERAL CERVICAL METASTASES FROM UNKNOWN FOCUS

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Cancer of unknown primary accounts for approximately 3% of all head and neck squamous cell carcinomas. The lack of randomized, controlled trials and the decreasing incidence of CUP make it difficult to draw conclusions regarding an optimal treatment plan. Options range from surgical treatment of the neck alone to radiating bilateral necks, with or without radiation to possible primary sites as well ± chemotherapy. The radiation fields have classically covered all potential mucosal disease sites. Although this treatment has been effective, it has also been associated with significant long-term side effects, such as xerostomia and dysphagia [1] The H&NM sites to be treated with RT are dependent on the level of nodal involvement [2,8] Treatment of H&NM sites is often withheld for patients with Level 1 nodal involvement because of the potential morbidity associated with RT to the oral cavity and the relative ease in detection and treatment of carcinomas developing in the oral cavity. For patients with Level 2 and Level 5 nodal involvement, RT is often delivered to the nasopharynx and oropharynx. Treatment of the nasopharynx, oropharynx, hypopharynx, and larynx is often recommended for patients with Level 3 nodal involvement. However, RT may be confined to the nasopharynx and oropharynx because of the low rates of detecting occult carcinomas in the hypopharynx and larynx, and potential complications after RT to the hypopharynx and larynx. The main complications associated with RT to H&NM sites are xerostomia and difficulty in swallowing. The rates of osteonecrosis, myelitis, and radiation-induced malignant tumors are very low. The rates of complications after RT to H&NM sites are dependent on the H&NM sites treated and total RT dose.[8]

In recent years, concurrent chemotherapy is given more frequently. The advent of intensity-modulated radiotherapy (IMRT) make feaseable to treat the nasopharynx, oropharynx and bilateral neck in association with chemotherapy. This technique could prove especially advantageous in the setting of head and neck cancer of an unknown primary, in which large regions require treatment and for which the toxicity affecting critical normal structures can have a profound impact on the patient's function and quality of life. IMRT provides the potential advantages of sparing or limiting the dose to critical normal tissue, including the major and minor salivary glands, mandible, cochlea, brainstem, cord, and optic structures.[3] In Literature [4,5,6,7] different experience with IMRT in CUP showed that most frequent acute toxicities in combined treatment are mucositis, skin toxicity, fatigue, xerostomia, and nausea (32% Grade 1-2). Grade 3 toxicities include hematologic toxicities (10%), acute skin toxicity (31.8%-5%), mucositis (52%-14%), dehydration (10%), renal toxicity (5%), pulmonary toxicity (5%), infection (5%), pain (5%), and gastrointestinal toxicity (5%). A high portion of patients (50-72%) during a combined modality approach require a PEG tube, but when a dose-volume constraint for oesophagus is defined no Grade 3 long term dysphagia is observed. Chronic toxicity include Grade 1 chronic tinnitus (5%), Grade 1 or 2 hearing loss (24%), and Grade 1 chronic neuropathy (24%), esophageal strictures (14%) in studies in which no contraint for oesophagus was used. The median Dmax for the esophagus in the region of the stricture was 60,19 Gy (range, 58,69–60,52). Management of toxicities (acute and late) should include measures that exploit the capability of IMRT technique to reduce dose to organs at risk and sensible structures and accurate choice of CTV (for example if there are no metastases in lymph nodes Level I, reducing mucosal and salivary toxicity would presumably be achieved by excluding the mucosa and the salivary glands of the oral cavity from the target). Because relapse in elective neck is rare and because nodal failure occure primarly in previously enlarged lymph nodes, dose reduction to elective nodal sites might preserve swallowing function and reduce skin fibrosis without compromising treatment effectiveness. Nutritional support and speech patologist intervention should be considered especially in this subset of patients.

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THE ROLE OF RADIOTHERAPY AND CHEMORADIATION

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Introduction: Radiotherapy (RT) and chemoradiation (CHRT) represent important clinical options in the management of pancreatic adenocarcinoma. These treatments are recommended in different stages of the disease and in different therapeutic settings. Aim of this brief review is to summarize the potential role of RT in the treatment of this disease.

Resectable disease: These patients ideally should be enrolled in clinical trials despite the poor prognosis after radical surgery. Currently an interest in the possibility to improve clinical outcome using induction treatments before surgery is growing. CHRT with fluoropirimidines (5-Fluorouracil or capecitabine) or with gemcitabine has been suggested as an option, eventually after 2-3 courses of induction chemotherapy. Recommended doses are 45-54 Gy (1.8-2 Gy/fract) or 36 Gy (2.4 Gy/fract.), followed by surgery after 6-8 weeks

Locally advanced disease: Recommended options for these patients are: 1) CHRT with 5-FU or capecitabine; 2) CHRT with gemcitabine; 3) induction chemotherapy followed by CHRT. Maintenance chemotherapy should be considered in patients treated with CHRT. Recommended doses are: 45-54 Gy (1.8-2 Gy/fract) or 36 Gy (2.4 Gy/fract). It has been suggested to start with chemotherapy in the following situations: 1) patients unlikely to be resected; 2) suspicious metastases; 3) patients not able to tolerate CHRT. On the contrary it has been suggested to start with CHRT in patients with poorly controlled pain or with local obstructive symptoms. Stereotactic body RT has also been proposed in this setting but no standard doses and fractionations are available.

Resected disease: Several different options have been suggested in these patients: 1) CHRT (5FU or capecitabine or gemcitabine) followed by adjuvant chemotherapy; 2) chemotherapy (1 cycle) followed by CHRT (5FU/capecitabine) and then by chemotherapy; 3) chemotherapy alone; 4) chemotherapy (2-6 cycles) followed by CHRT. Suggested doses are: 45 Gy + boost (5-9 Gy) or IORT boost in patients with close-involved margins.

Metastatic disease: RT can be considered in patients with metastases requiring palliation for obstruction or pain, or elderly and/or without indication for definitive therapy. Suggested doses are 30-36 Gy (2.4-3 Gy/fract.)

Conclusions: RT and CHRT represent important treatment options in the different stages of pancreatic adenocarcinoma. Further studies are needed to better define treatment sequences and the potential role of newer RT techniques.

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RADIOTHERAPY IN PANCREATIC CARCINOMA: FROM PLANNING TO DELIVERY

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Pancreatic carcinoma is one of the leading cause of cancer-related mortality in the Western World. In Italy, the incidence rates and mortality rates are respectively 12.3 and 11 per 100.000 people with a slight prevalence in Northern Italy (1). Approximately 30% of pancreatic cancer patients present with locally advanced, unresectable nonmetastatic disease (2-3). Surgery offers the only prospect of cure for these patients but resection with radical intent can be performed in only 25-30% of cases (4-5). After radical surgery, even in the absence of nodal involvement, the prognosis remains unfavorable with 5 year survival of less than 5% (6). In most of cases the disease recurs at distance, generally in the liver but also the percentage of local recurrence is high, with rates up to 50% in patients undergoing to surgery alone (7). For these patients, two therapeutic options exist: systemic chemotherapy or chemoradiotherapy. Adjuvant treatment options are represented by combination of Radio-Chemotherapy alone. Particularly, while there is a strong rationale on the use of adjuvant radiotherapy in an attempt to improve local control, its role is still cause for debate and there is no clear consensus on its use. Moreover, the only loco-regional control of disease is not sufficient since the first cause of recurrence is at distance; therefore the radiation treatment is generally administered in combination with chemotherapy regimens. Within this context, the optimal technique for pancreatic irradiation is not clearly defined. The minimal requirements for the setting and execution of the treatment planning radiotherapy with neoadjuvant, adjuvant or palliative purposes are the following: abdomen pre and post CT-scan with contrast medium (mandatory), CT-PET (optional), histology (T size, grading, tumor location, description of the lymph nodes, status of resection margins and of retroportal lamina and the surgery description. To prepare the patients to CT planning will be used specific protocols with contrast medium for the best visualization of the small intestine. Patient should be supine with arms above the head with device immobilization (e.g Vac Lock). The immobilization devices and use of respiratory gating are strongly recommended in IMRT/SBRT techniques. About the clinical volume delineations, GTV will be the previous site of the tumor in the case of adjuvant radiotherapy (pre-surgery CT based) and bulky disease in neoadjuvant/exclusive radiotherapy (pre-surgery CT based), respectively. CTV should include GTV plus anterior and posterior pancreaticoduodenal lymph nodes, superior and inferior pancreatic lymph nodes, celiac, porta haepatis, spleno-pancreatic lymph nodes, superior mesenteric and haepatoduodenal lymph nodes. Splenic hilum lymph nodes should be included in the CTV in the case of tumors body-tail of the pancreas. The margin for the expansion CTV-PTV should be preferably of 10 mm in cranio-caudal direction and 5 mm in the posterior direction although is strongly recom-

mended to define the PTV margins customized for each radiotherapy center. The craniocaudal margins can be reduced with the use of respiratory gating. The organ at risks to delineate are the following: kidneys (right, left and whole volume), liver, stomach, large bowel, small bowel and spinal cord. With regard to the dose-constraints for the conventional techniques, less than 30% of the total volume of the kidneys should receive 50% of the dose (V25 Gy < 30). The volume of the liver receiving 30 Gy must be less than 50% (V30 Gy < 50%). For the spinal cord, no point exceed 45 Gy. For the stomach and bowel the maximum dose should be 52 Gy; for both of these organs not more than 15% of the organ may receive a dose over 45 Gy (V45< 15%). The planning must include the absorbed dose at the reference point and therefore the minimum and maximum dose to the PTV following ICRU 62 rules. The variation of absorbed dose within the PTV should be contained between ± 5%. 3D-CRT technique can be considered the gold standard but IMRT technique can be preferable because advantageous in terms of limited toxicity (8). Recently, an expert panel with members of the RTOG and GERCOR cooperative groups reviewed the eligible studies about radiation treatment planning using the Medline database and Cochrane Databse (1980-2010) and prepared the guidelines evaluating five endpoints: total dose, target volume definition, radiotherapy planning technique, dose constraints to organs at risk and quality assurance (9). Moreover, more accurate descriptions of the methodology contouring for the adjuvant and neoadjuvant/exclusive treatment are shown, respectively, in the RTOG Consensus Panel 2012 and in the work of Caravatta L. et al. (10-11). Based on this analysis of the literature, we recommend either three-dimensional conformal radiation therapy or intensity-modulated radiation therapy to a total dose of 50 to 54 Gy at 1.8 to 2 Gy per fraction. Stereotactic body radiation therapy should not be used for pancreatic cancer outside of clinical trials (single fraction of 24-25 Gy or 10-12 Gy for three fraction).

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ONCOPLASTIC SURGERY

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Roma

Breast conserving surgery (BCS) combined with postoperative radiotherapy is acknowledged as the gold standard locoregional treatment for early-stage breast cancer, with equivalent survival to that of mastectomy and improved body image and quality of life scores.

In an effort to reduce the incidence of local recurrence and maintain natural breast contour, the techniques of oncoplastic breast surgery (OPS) have been introduced as an alternative pathway in the surgical treatment of breast cancer (1-2).

Today, OPS includes a wide range of modified breast-conserving surgical techniques that are tailored to ensure optimized resection of the cancer with wide tumor-free margins along with optimized cosmetic outcomes.

According to the modalities that are used to deal with the glandular defect that is generated as consequence of the cancer resection, OPS techniques can be classified in two different categories: volume displacement and volume replacement techniques (3-4).

In volume displacement techniques, the resection defect is reconstructed using some form of local glandular flap within the breast, that is mobilised and advanced into the defect. This approach leads in most cases to a reduction in breast volume, and contralateral surgery can be considered to restore symmetry. Accurate planning of the most convenient skin incision is of critical importance, as well as undermining of the skin and eventually of the nipple-areolar complex (NAC) to facilitate glandular reapproximation with optimal cosmesis. To ensure adequate cosmetic results, repositioning of the NAC may be required, particularly for larger parenchymal resections.

Mammoplasty techniques can also be used, specially in large and ptotic breasts, most often with the use of a superior pedicle or inferior pedicle approach.

The superior pedicle approach enables wide resection of tumors located in the lower quadrants of the breast, where extensive volume loss would otherwise expose to the risk of cosmetic deformities, while the inferior pedicle approach is mainly used for tumors located in the upper pole of the breast.

A range of other mammoplasty techniques have been described, which utilize adaptations of the superior and inferior pedicle approaches.

Other established and widely used OPS volume displacement techniques include the 'round block' and "batwing mastopexy" approach.

The "round block "technique has its best application in the treatment of periareolar lesions, particularly in breasts with moderate ptosis or hypertrophy. In this operation, circles of two different diameters are designed around the nipple. The skin between the two circles is resected. This incision allows comfortable access to the entire periareolar region through a wider incision when compared with traditional conservative techniques. Quadrant resection of the breast parenchyma is then performed, extending the dissection to include the pectoralis fascia and at least 2 cm of macroscopic clear margins on all sides.Reshaping of the breast is achieved by partially dissecting the residual gland off the pectoralis major muscle with the use of electrocautery. Care should be taken to avoid or limit the dissection of major vascular perforators between the pectoralis muscle and the preserved breast to minimize the risk of ischemic injury to the residual glandular tissue. The larger circle is reduced in diameter using a pursestring suture and is then sutured to the new border of the areola. If the two circles are concentric, the nipple is not elevated. If the outer circle is centered around a point superior to the existing nipple, the nipple can be slightly elevated as a consequence of the procedure. With regard to the diameter of the inner and outer circles, the latter should not exceed that of the existing areola diameter by more than 20–25 mm in order to prevent widening of the circumareolar scar or excessive flattening of the breast (1).

"Batwing mastopexy" can be considered for cancers located deep within or adjacent to the NAC, but not directly infiltrating the major ducts. Two closely similar half-circle incisions are made with angled wings to each side of the areola. Full-thickness excision is undertaken and the fibroglandular tissue is advanced to close the subsequent defect. By allowing ample removal of the skin overlying the lesion, this procedure can improve local control of cancers located superficially. Patients with pendulous breasts are particularly eligible for this procedure, which can also be applied to the contralateral breast to achieve symmetry (1).

In volume replacement techniques, the resection defect is reconstructed with the transposition of autologous tissue from an extramammary site - usually the latissimus dorsi. These techniques allow to maintain the original shape and size of the breast and achieve a balanced cosmetic result without the need for any contralateral surgery. The options include musculocutaneous flaps and perforator flaps that can be transferred on a vascularized pedicle or as a free tissue transfer. Technique selection will depend upon the clinical situation and the experience and preference of the reconstructive surgeon.

The most widely used flap for immediate reconstruction of the partial mastectomy defect has been the latissimus dorsi musculocutaneous flap. This flap has been the preferred choise for deformities of the superior, lateral and inferior aspects of the breasts. Several methods by which the latissimus dorsi flap can be harvested have been reported (4-5). The traditional technique was based on a wide posterolateral wide thoracic incision, whereas the more modern technique utilizes an endoscopic approach. With the endoscopic technique the muscle is accessed through the breast and axillary incision (4).

To ensure oncological safety as well as maximal cosmetic outcomes, stringent patient and technique selection criteria are required.

OPS techniques are indicated in those cases of breast cancer for which a standard BCS with safe margins would either result impossible or lead to a major deformity (large tumor size, extensive ductal carcinoma in situ, multifocality, and partial or poor response to neoadjuvant treatment, resection of more than 10-20% of the breast volume, tumors in central, medial and lower pole) (6-7).

Volume displacement techniques with adjacent tissue rearrangement are indicated for cases where < 20% breast volume will be excised excision and for patients with large-medium sized breasts, ptosis and dense glandular tissue. These procedures are particulary appropriate for tumor localized in lateral and superior quadrants.

Volume displacement techniques with reduction mammoplasty are indicated for resections that will reduce the breast volume of 25-50%, particularly in patients with large-medium sized and ptotic breasts. These procedures can be used for tumor localized in any site, but they are especially valuable for tumors in unfavourable locations, as such central, inner-upper and lower quadrants.

Patients with heavy, ptotic breasts and symptomatic macromastia are optimal candidates for the use of reduction mammoplasty techniques, as these patients in addition to receving better local control of their cancer, will also benefit physically from the use of a bilateral breast reduction procedure.

Volume replacement is indicated for patients with small-medium sized breasts and minimal ptosis that require a 20-50% breast volume excision and, who cannot afford to lose the volume associated with volume displacement techniques, or who wish to avoid mastecomy or contralateral surgery. The volume replacement is appropriate for tumor localized in any site.

Surgeons should take into consideration not only tumors features and cosmetic wishes but also the features of the donor site as well as secondary procedures and effects over time. The importance of proper patient counseling, with close attention to the short-term and long-term consequences, should not be dismissed.

The outcome measures reported in most studies of OPS are associated with low rates of local recurrence and good or excellent cosmetic results (8-10). Even though these studies are mostly retrospective and based on limited number of patients, the consent for OPS techniques is constantly growing.

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RADIOTHERAPY AFTER NEOADJUVANT SYSEMIC THERAPY: IRRADIATION OF LINPH NODE CHAINS? PRO

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Neoadjuvant chemotherapy has became the standard in locally advanced breast cancer (stage III-IV), but in the treatment of lower stages, it is still an option even if on the increase. Not all authors agree in considering useful, in term of local control and desease free survival, irradiation of lymph node chains after adjuvant chemotherapy; for this reason, the debate is still more intense when we talk about radiotherapy of these districts after neoadjuvant chemotherapy (NAC). The Danish 82b and 82c trials and a randomized prospective trial from Vancouver, British Columbia, all demonstrated that the addition of radiation to mastectomy and adjuvant chemotherapy resulted in an approximately 20% proportional reduction in the risk of death[1,2,3] but it is unclear if this percentage is the same after NAC. Both National and International guidelines suggest, with evidence 1, to treat this pathology according to the peculiarities at the diagnosis. Therefore, RT on lymph node chains is advised in case of 4 or more positive lymph nodes or T3-4 stage, while it is optional for cases with 1-3 positive lymph nodes. Waiting for suitable perspective studies to value radiotherapy effect after NAC, we can only base our indications on the retrospective studies published till now. M. D. Anderson Cancer Center Houston's publications are really interesting. Indeed, using a series of retrospective studies, the authors are trying to identify the role of radiotherapy after NAC and mastectomy, comparing the results with patients who are treated with radiotherapy, both as local control and survival terms; is important to note that all the patients included in these studies have been subjected to RT both on chest wall and lymph nodes. By this analysis is emerged that the rate of locaregional recurrence is doubled in patients not treated with RT (22% *vs* 11% at 10 years). According to data observed about patients subjected to adjuvant chemotherapy, even for post NAC ones, radiotherapy reduces significantly the rate of recurrence in advanced stages (T3-T4, N2-3, stages III e IV). Analysing the survival as cause-specific survival (CSS), it does not exist important differences between these two groups globally intended, but in IIIB-IV stages CSS at 10 years is 42% *vs* 20% and in N+ more than 3 is about 38% *vs* 15%[4,5,6]. Factor found to be significant for worse CSS in multivariate analysis included: lack radation therapy, clinical stage IIIB to IV, residual pathological tumor involvement after chemotherapy, four or more positive nodes, minimal or worse clinical response to NAC, fewer then 10 axillary nodes sampled, no tamoxifen and receptors-negative desease. Then, in univariate analysis the achievement of a clinical or pathological complete response was associated with lower LRR and higher CSS. However, neither clinical nor pathological complete response to NAC was independently associated with LRR or CSS in multivariate analysis. In another study of the M.D. Anderson a significantly higher proportion of irradiated patients had pathology involved in LNs and were ≤40 years old. Among them the LRR rate was lower in those who received RT (p <0.001)[7]. Breast cancer patients with clinical T3N0 disease treated with NAC and mastectomy but without RT had a significant risk of LRR, even when there was no pathologic evidence of LN involvement present after NAC. RT was effective in reducing the LRR rate. This suggest RT should be considered for patients with clinical T3N0 disease. In a Japanese study published in 2012, Takahashi and coll, demonstrate that the false negative rate in sentinel lymph node biopsy after NAC was 27.3 % in clinically node-positive patients before NAC who were clinically node-negative after NAC[8]. Nodal Ratio might be a useful tool to identify the patients at high risk of relapse after NAC. In a prospective study published on 2009, Keam & others, demonstrate how relapse free survival of the patients who had a nodal ratio > 0.25 was significantly shorter and this was also associated with a shorter overall survival[9]. A French Study published in 2010 compares the outcome of 76 patients with node-negative at axillary lymph node dissection (pN0) after neoadjuvant chemotherapy treated with or without elective regional lymph node areas irradiation. At 10 years survival without local-regional recurrence was 95% and 91% (p =.59), survival without distant metastasis was 97% and 78% (p =.018) and overall survival was 96% and 75% (p =.013) respectively[10]. As regard the management of Internal Mammary Nodes (IMN) a study of M.D. Anderson demonstrated a significant risk of radiographically detected IMN metastases in patients with N2–3 breast cancer. With multimodality therapy (NAC, surgery and radiation therapy), these patients have more than 50% DFS at 10 years with acceptable rates of local control at the IMN region. To date, recent National Comprehensive Cancer Network Clinical Practice Guidelines for breast cancer recommended radiation therapy to the IMN that are clinically involved or pathologically positive[11]. A Greek study published in 2011 demonstrates an acceptable toxicity and no treatment-related death in fifty-six women treated with NAC (EPI followed by three DOC); surgery 3-4 weeks from CT completion, followed by radiation therapy and CT according to response[12]. Another very similar French study demonstrate that acute toxicity was higher in the chemoradiotherapy group compared with the radiotherapy alone group: 37% patients *versus* 10% experienced a grade 2/3 epithelitis (P=0.002); 48% *versus* 8% experienced a grade ≥1 mucositis (P=0.00001); but late toxicity was not significantly different (51% *vs*. 49%; P=0.79)[13]. Results of MA-20 (ASCO 2011) demonstrate

that additional nodes irradiation increase pmeumonitis grade 2 or more from 0.2% to 1.3% and linphedema from from 4.1% to 7.3%, date not statistically significant. So the fear of toxicity is not a good reason to omit radiotherapy after NAC. In conclusion both the clinical and pathologic extent of disease must be considered when deciding whether to administer radiation to a patient treated with neoadjuvant chemotherapy. Patients with locally advanced disease (independent of the pathologic response) and patients with positive lymph nodes may benefit from radiation.

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RADIOTHERAPY AFTER NEOADJUVANT SYSEMIC THERAPY: IRRADIATION OF LINPH NODE CHAINS? CONS

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Neoadjuvant chemotherapy is widely used in the treatment of locally advanced, operable breast cancer and is increasingly used for treatment of women with early stage breast cancer. Randomized clinical trials have established that neoadjuvant chemotherapy given before surgical removal of breast cancer provides equivalent survival outcomes to chemotherapy after upfront surgical resection (1). Neoadjuvant chemotherapy allows physicians to observe tumor response and modify chemotherapy plans if necessary. Additionally, administration of chemo-therapy before surgery decreases tumor size, thereby increasing the proportion of women who can undergo breast-conserving surgery rather than mastectomy (2). The role of loco-regional nodal irradiation is still debated and it is not clear. The goal of Clinical Oncologist is to appropriately select women in which administration of post-mastectomy radiation therapy may lead to a reduction in terms of loco-regional recurrence and a breast-cancer survival improvement. Women enrolled in Danish and Canadian randomized trials established the benefit of post-mastectomy radiation therapy; they underwent upfront, modified radical mastectomy and received adjuvant chemotherapy or tamoxifen (3-5). The benefit of post-mastectomy radiation for patients with positive lymph nodes who received upfront surgery and adjuvant chemotherapy was confirmed in a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (6). While the role of post-mastectomy radiotherapy in high-risk >4 node-positive breast cancer patients and unfavorable biological markers is largely accepted, irradiation of patients that underwent surgery after neoadjuvant chemotherapy is really unclear. Since neoadjuvant chemotherapy modifies the pathological extent of disease, it is essential to accurately document the clinical extent of disease in the breast and lymph-node

basins before chemotherapy. Nodal response to neoadjuvant chemo therapy also has important prognostic information, including the risk of loco-regional recurrence, which can inform post-mastectomy radiation treatment decisions. There are no randomized trial data comparing outcomes with and without post mastectomy radiation therapy after neoadjuvant chemo therapy and mastectomy. Conversely retrospective studies (7-12) have many bias that the Physicians hat to take in account: often patients are included in several prospective trials with different chemotherapy, there have been advances over time in clinical staging, radiographic imaging, chemo-therapeutic agents, and surgical techniques that could affect loco-regional control rates. Retrospective studies have shown that post-mastectomy radiation therapy—when compared with no post mastectomy radiation—was associated with improved outcomes for selected patients with non-metastatic, non-inflammatory breast cancer who received neo-adjuvant doxorubicin-based chemotherapy and mastectomy at MD Anderson from 1974 through 2000 (9). Post mastectomy radiation was associated with reduced 10-year loco-regional recurrence for patients with clinical T3 and T4 disease at presentation, clinical N2–3 disease at presentation, pathological tumor size 2–5 cm at resection, pathological tumor size greater than 5 cm at resection, or involvement of > 4 nodes at resection. Conversely, a non-significant improvement in loco-regional recurrence was noted for patients with clinical N1 disease. Data regarding the benefit of post mastectomy radiation for patients with clinical T3 node-negative disease offer conflicting conclusions. Based on information from relevant published studies (13,14), patients with clinical T3N0 disease and nodal involvement after neoadjuvant chemotherapy have sufficient risk of loco-regional recurrence to warrant consideration of post-mastectomy radiation, while post-mastectomy radiation therapy may be omitted for patients with clinical T3N0 at presentation and no nodal involvement after neoadjuvant chemotherapy, considering that recurrence risk might be sufficiently low to omit radiation treatment. Another key point seems to be younger patients age. There is limited information on the benefit of post mastectomy radiation therapy for very young patients. A retrospective analysis of MD Anderson (8) on patients younger than 35 years with clinical stage IIA–IIIC disease (AJCC 2003 staging) who received doxorubicin-based neoadjuvant chemotherapy and mastectomy from 1975 to 2005 showed an improved loco-regional control and overall survival. Anyway not all the clinical stage were statistically significant, including women with IIB disease (p=0.033), IIIA disease (p=0.154), IIIB disease (p=0.064), and IIIC disease (p=0.56). Many studies showed as clinical response to neoadjuvant chemotherapy predicts loco-regional recurrence risk (11,15). In particular patients with clinical stage II disease and pathological complete response after neoadjuvant chemo therapy have a low risk of loco regional failure, whereas data for patients with clinical stage III disease and pathological complete response after neoadjuvant chemotherapy are often discordant. Anyway this feature may help tailor post mastectomy radiation treatment decisions. Although randomized clinical trials have established which patients might benefit from post mastectomy radiation therapy after upfront surgery, no randomized trial data exist to define which women benefit from post mastectomy radiation after neoadjuvant chemotherapy. Retrospective data suggest that disease at presentation and response to neoadjuvant chemotherapy can be used to tailor post mastectomy radiation treatment recommendations. These data may help guide appropriate design of future prospective studies. Randomized clinical trials are needed to assess whether post mastectomy radiation therapy can be safely omitted without compromising local control or breast-cancer survival.

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LA RADIOTERAPIA DOPO RECIDIVA: È POSSIBILE UN RITRATTAMENTO?

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In-breast local recurrence (IBR) rates after breast conserving therapy (BCS) increase by 1-2% per year. Although mastectomy is often felt unnecessary for small, localized lesions, for which a local excision would be technically more appropriate, this major surgery is recommended as the local treatment of choice when the failure is confined to the breast and is operable. Salvage mastectomy achieves a local control in 85%-95% of the cases. A further BCS is generally not accepted because second lumpectomy could yield an unacceptable cosmetic outcome. Moreover, subsequent local recurrence rate after conservative surgery alone is higher (range 19%-50%) compared with that after mastectomy. In a retrospective analysis carried out at European Institute of Oncology, a second IBR was reported to be 19% for patients treated with local re-excision alone compared with 3.3% in patients with salvage mastectomy. Anyway, no difference in overall survival and in time to second local recurrence between mastectomy and second lumpectomy was observed. This finding is in line with other specifically addressed studies. In a series reported by Salvadori, survival did not appear to be worse with repeat lumpectomy compared to mastectomy for IBR, but second local relapse rate was higher. Survival and time to subsequent local failure for patients with IBR after being treated with mastectomy or lumpectomy was similar in the EORTC and DBCG trials. An additional irradiation in the setting of a previous radiotherapy (RT) meets with the limitations related to normal tissue tolerance. A second course of radiation to the whole breast is discouraged as serious tissue damage is feared, while the re-treatment of only a part of the breast (PBI), minimizing the volume of healthy breast tissue reirradiated, seems to be safe. However, PBI leaves untreated most of the breast. This is the main concern related to the real effectiveness of adding a second radiotherapy course. As more than 20% of mastectomy specimens of ipsilateral breast recurrence after BCT could reveal residual disease in 2 or more quadrants, the outcome of a second BCS with respect to mastectomy is still under investigation. Besides, the importance of increasing local control with an additional course of radiotherapy after the first tumor relapse might be considered questionable if in-breast reappearance is not considered as an isolated event. Invasive local recurrence carries a significant risk for distant metastases and death: compared with patients without local failure, those experiencing recurrence have 3.4 to 4.6 increased risk of death for breast cancer-related events. It recalls the concept of local failure as predictor of distant metastases (DM) or source of DM. From an analysis of 2669 nodal positive patients included in 5 NSAPB studies, an interval of 5 years after IBTR found only 51.4% of the patients free of distant disease. One of the most important prognostic factors is the time interval between primary tumor and IBR. An early reappearance has been reported to be a negative prognostic factor and a second BCS after a short recurrence- free interval may have no benefit. If IBR occurred within 5 years after the primary event, the overall survival and the disease-free survival were 65% and 61%, respectively, compared to 81% and 80%, if the local failure occurred 5 or more years after the first event. The time prior to tumor reappearance is also used for discriminating true recurrence from new primary. These two kind of events carry different natural history, different prognosis and different implications. In fact, true recurrences might be the expression of a persistent radioresistant and drug- insensitive disease, revealing the intrinsic aggressiveness of the tumor and poor prognosis. True recurrences tend to occur within the same quadrant and present the same histology to the primary tumor in most of the cases. However, a strict distinction between true recurrence and new primary is difficult and some investigators used DNA flow cytometry as well. In the analysis carried out on the EORTC and DBCG trials, early loco-regional relapses resulted in a poor prognosis and salvage treatment only cured a limited number of patients, whether treated by mastectomy or lumpectomy. Other factors associated with an adverse effect on survival are dermal involvement, lymph nodal positivity at the time of the primary, size of local recurrence, negative estrogen status, high grading, patients' age. In a series of local recurrences reported by Gentilini, patients were treated either with mastectomy or second lumpectomy without any additional radiotherapy. Those who presented a IBR < 2 cm in size and time to relapse > 48 months, experienced a lower rate of further local failure (12.5%) and showed a better local-disease free survival. A matter of discussion would be if these patient category may further benefit from a repeat radiotherapy as to make the rate of failure comparable with the 3.3% obtained with mastectomy in the same Institution.

Local recurrence after primary treatment with mastectomy is associated with a worse prognosis than after BCS, particularly if the failure occurs within 2 years In the study led by Dunst, local relapse after chest wall irradiation was the highest risk factor for metastases and poor survival. Extended or limited reirradiation after previous radiotherapy to the chest wall should be considered in case of positive surgical margins and macroscopic residual disease, multiple recurrent lesions. The additional use of hyperthermia in combination with radiotherapy may improve local control in high-risk patients and has proven to be well tolerated. Reirradiation to the breast in the context of a second BCS, could be applied with various modalities, such as brachytherapy, intraoperative radiotherapy (IORT) or external beam radiation. IORT represents a novel option to treat recurrent tumors after previous RT. By sparing adjacent critical structures, IORT results in an acceptable toxicity. IORT single dose of 14-

21 Gy has been reported using either 50 Kv X-ray or intraoperative electrons. Very limited reports are published regarding reirradiation with MammoSite balloon, applying the scheme of 34 Gy at 3.4 Gy/fraction twice at day, whereas interstitial brachytherapy (HDR, PDR) presents the more extensive experience. Multicatheter pulse dose rate (PDR) brachytherapy following BCS for local IBR results in excellent local control. Kauer-Dorner reported an outcome comparable to mastectomy, with a 5-y actuarial control rate of 93% after a mean follow-up of 57 months. Regarding external beam reirradiation, the series from Mullen and Deutsch reported a local control of 76.9% after 50 Gy in 25 fractions using electron beams. Local control appears to be dose-dependent, with better results when a dose > 50 Gy is applied. Hannoun-Levi showed that a reirradiation dose of 30 Gy had more second IBR than 50 Gy using LDR-brachytherapy. The rate of severe late effects after a mean cumulative dose for late responding tissue of 113-140 Gy EQD2 was low. With a cumulative dose to the chest wall structures of 106 Gy (74-137.5 Gy), Dahlstrom reported a G3-G4 late toxicity in 4 out of 81 patients and no treatment variables was found associated with the development of toxicity. To sum up, in patients undergoing second lumpectomy a repeat course of RT applying various PBI modalities seems to be feasible with an acceptable burden of side effects. Regarding the advantage of providing a superior long-term control compared to lumpectomy alone, the biological heterogeneity of the recurrence and the lack of prospective specifically addressed clinical trials make it difficult to define the benefit of reirradiation. A selected group of patients with small relapse and long interval-time from primary treatment may be the ideal candidates, but further clinical studies are needed to assess the magnitude of the expected benefit. Up to date, mastectomy provides a higher local control compared to second lumpectomy, with no impact on survival. Reirradiation of the chest wall for excised local recurrence in mastectomy patients after previous RT should be considered with caution, not for technical feasibility, but for the high risk of the presence or fast development of metastatic disease.

THE ROLE OF RADIOTHERAPY IN INOPERABLE BREAST CANCER

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Breast cancer may be considered inoperable in various clinical situations: 1) at diagnosis in stage IIIA (T3N2), IIIB and IIIC; 2) in case of recurrent disease, if irresectable 3) in presence of co-morbidities, elderly, patient's refusal or other reasons that may contraindicate a surgical strategy. In this paper are briefly reviewed only topics 1) and 3)

1. Inoperable locally advanced breast cancer (LABC)

Introduction: LABC - despite modern efforts for early detection - remains an important public health topic and a challenging management problem in all the Oncologic Centers around the world.

Classification: According to the AJCC, "LABC" applies to a heterogeneous group of patients (pts) with either advanced nodal metastases (N2 – N3) with any T or any presentation with T3 – T4 with any N. These pts have in common a high propensity for both locoregional recurrence and distant metastases after therapies. Commonly, are considered not suitable for surgery patients affected by stage III breast cancer: III A (only T3 N2), III B (T4 N0, N1, N2) and III C (any T, N3).

Role of Radiotherapy in inoperable LABC: The prognosis for pts affected by LABC, over the past 15 years, has significantly improved with recognition of the efficacy of multimodal therapy: it offers excellent local control to 80% or more for pts with stage III B – C and even higher for III A. Multimodality treatment delivered with curative intent is considered the standard of care for pts with clinical stage III. In these cases surgery is generally limited to biopsy, to permit the determination of histology, estrogen/progesterone-receptor levels and human epidermal growth factor receptor 2 (*HER2*/neu) overexpression. Then, the use of neoadjuvant chemotherapy (± endocrine therapy ± trastuzumab if HER2 positive) is considered the standard of care, with the aim of tumor shrinking: it can result in successful tumor downstaging, enabling resection in most pts. In case of response to neoadjuvant chemotherapy (CHT), further local therapy may consist of surgery followed by postoperative radiation therapy (RT), and - if not completed preoperatively - completion of CHT + endocrine therapy and trastuzumab if Her2 positive, concurrent to RT. In case of minimal- or no-response to CHT, when primary systemic treatment fails to achieve operability, the optimal treatment remains uncertain (because of scarse evidence from randomised trials), and the therapeutic strategy should be determined in an interdisciplinary approach. In these cases, guidelines strongly suggests to recommend RT, because there is evidence that RT is significantly associated with a higher 10 year overall survival in the irradiated pts compared with non-irradiated (with concomitant CHT if possible and hormonal therapy if tumor is ER positive or unknown and trastuzumab if Her 2 positive, concomitant to RT). RT should be started 4-6 weeks after completion of the primary CHT; theoretically, it seems tempting to minimize to delay of local treatment by using concomitant RT-CHT, moreover, an additional radiosentizitation of tumor cells might be expected. For this reason some Authors suggest the use of concomitant RT-CHT for all inoperable patients in whom primary systemic treatment fails to achieve operability. However, simultaneous treatment yelds higher toxicity. In preclinical trials HER2 overexpression was associated with radioresistance relative to controls (low HER2 expression), a phenomenon that can be reversed with exposure to trastuzumab, that may be considered a radiosensitizer. A prospective study in advanced and CHT-refractory breast cancer demonstrated that adding trastuzumab to RT can potentially improve its efficacy, with better response rates (43% pathologic responses or microscopic residual disease) and without excessive cutaneous or cardiac complications (despite the typical inclusion of the IMN chain in the treatment); the study suggested that trastuzumab may increase the efficacy of the relative low radiation doses employed and pts seemed to have extended survival compared with that of

historical controls (other studies with concomitant other radiosensitizers such as paclitaxel or capecitabine reported increased toxicity). Other studies confirmed that no increased toxicity is observed when trastuzumab is applied simultaneously with RT; IMN irradiation is not recommended in this setting by some Authors (DEGRO Guidelines). Usually, in these patients there are no contraindications for simultaneous endocrine treatment and RT. RT volumes usually includes breast, supraclavicular and axillary lymph nodes; many Authors recommend to treat also internal mammary nodes. A question arises of whether to design RT treatment fields on the bases of the extent of tumor after initial CHT or on the clinical stage at presentation of the disease: for the majority of Authors, RT should be considered regardless of the response to initial CHT. In case of good response to RT, surgery should be keep into consideration: a Cochrane Review (2007) and a systematic review (Mauri 2005) suggest higher rates of loco-regional recurrence in patients who received RT without surgery after primary chemotherapy. On the other hand, some Authors suggest another option for LABC patients: a combination of exclusive CHT-RT, on the basis of an old Bonadonna's group randomised trial (CHT followed by surgery or RT: no difference in the outcome) and several subsequent reports. A systematic review (Shenkier 2004) included trials comparing mastectomy alone with loco-regional RT alone following primary CHT in patients with LABC: the results suggest that both treatments are equally effective in terms of recurrence and survival, after primary CHT in inoperable disease. As in locally advanced cancer of nasopharynx, oesophagus, cervix or anal canal, where concomitant or sequential CHT-RT are now the standard of care, also in LABC the use of surgery may be reserved for the treatment of residual disease or local recurrence. A recent published study (123 LABC patients; 30% had surgery at a mean of 15 months post diagnosis for residual disease or local recurrence) demostrated with CHT-RT (40 Gy/15 fractions + 10 Gy boost/5 fr.) + endocrine treatment, a complete remission rate of 65%, 5-year OS 54% and DFS 43%, with no significantly difference from surgical group patients: the delay in offering surgery did not appear to disadvantage pts with residual or recurrent disease. Finally, are available until now only few researches utilising hyperthermia (HT) in pts with LABC: the addition of HT to CHT-RT seems to increase response rates, but randomised trial need to be performed.

Role of Radiotherapy in a particular subgroup of LABC: inoperable Inflammatory Breast Cancer (IBC, T4d N0-3): IBC (1-5%) represents a rare and the most aggressive presentation of breast cancer, characterized by erythema and edema of a third or more of the breast skin, often without an underlying mass. A recent study clearly showed that the outcome of IBC is worse than that of non-inflammatory LABC and hence the current standard treatment for IBC, which is more or less similar to standard treatment for LABC, should be changed to fit the peculiarities of IBC. The current standard of care includes a multidisciplinary approach with primary CHT (strongly recommended trastuzumab in HER2 positive disease; some studies are evaluating the use of Lapatinib, a reversible inhibitor of HER1 and HER2), modified radical mastectomy, postoperative RT ± hormonal therapy. In case of no-response after primary CHT (so, in presence of inoperable disease), the use of high dose RT is mandatory, targeting the chest wall skin and soft tissues as well as the draining lymphatics; the skin is a target, and care must be taken to ensure adequate dose and skin reaction. Concomitant trastuzumab and hormon therapy are useful, if indicated. In case of good response, surgery should be then evaluated, but his role is unclear: a recent published UK study based on 232 pts demonstrated a significant improvement in locoregional disease control with addition of surgery, but no significant difference in OS or DFS; late toxicities were not different. Other French trial recently updated with 20 years of follow up, employing alternating CHT and two courses of RT (including breast, supraclavicular-axillary-IM nodes; each course: 25 Gy/10 f + boost 15-25 Gy/6-10 f), obtained good long term local control (82%) without surgery; metastasis-free survival and OS were similar to those obtained with primary CHT, mastectomy and RT. IBC is a relative radiation resistant breast cancer, compared with non IBC, so acceleration of RT regimens, giving increased dose in less time, may be an effective strategy against his aggressive biology: studies from MD Anderson Cancer Center during the last 40 years demonstrate good results in local control employing altered fractionation RT regimens, with the intent of intensifying the RT dose (twice-daily fractionation treatment of 1.5 Gy to a total of 51 Gy + a 15-20 Gy boost to gross disease): LC 54% in the RT once-a-day arm *vs* 73% with hyperfractionated RT. Other studies from MDACC demonstrate that dose escalation (60 *vs* 66 Gy) appeare to have the most significant benefit in high risk group: age < 45, negative receptor status, lack of taxane use, disease unresponsive to CHT; furthermore, other their results indicate that second line treatment with RT and capecitabine as radiosensitizer is feasible, well tolerated and effective in pts with IBC refractory to primary antracycline-based treatment. New trials with novel radiosensitizers are needed.

2. Patients not elegible to breast surgery (elderly, concurrent diseases, refusal)

The surgical option - standard treatment of breast cancer - may be discarded in elderly pts because the tumor is not operable (LABC stage III); for either contraindication to anaesthesia, severe disabling physical or mental disease, high risk of operative complications, very old age, patient refusal or a combination of these factors. Consequently, some interesting protocols of exclusive RT have been proposed and reported in the literature, frequently using definitive hypofractionated RT (HFRT) associated with hormonal therapy. In these (mainly French) studies, irradiation was delivered to a total dose of 32.50 Gy (whole breast), in five once-weekly fractions of 6.5 Gy, with a boost of 13 - 19.50 Gy, one weekly fractions; sometimes, according to each protocol, the axillo-supraclavicular axis was irradiated to a dose of 27.5-30 Gy in five/six weekly fractions. In all these retrospective series, with a mean follow up of 5-8 years, acceptable local control, early and late toxicity and good outcome were observed, suggesting that definitive HFRT in this elderly population would be a reasonable option, a good alternative in case of contraindication to surgery. However other studies

reported that surgery, whenever feasible, together with RT, offers in elderly pts a better outcome than definitive RT. Nevertheless, although the results of definitive HFRT French trials seem satisfactory, there are no prospective data that assesses the place of RT for the exclusive treatment of elderly pts: this strategy should be further assessed in large-scale randomised trials.

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Guidelines: (PDQ) NCI 2012, NCCN 3.2012, DEGRO 2008, NICE 2008.

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XXII CONGRESSO
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BOOST SIMULTANEO INTEGRATO (SIB): IMPLICAZIONI RADIOBIOLOGICHE E CLINICHE

C001

PHASE I-II STUDY OF HYPOFRACTIONATED SIMULTANEOUS INTEGRATED BOOST (SIB) USING VOLUMETRIC MODULATION ARC THERAPY FOR ADJUVANT RADIATION THERAPY IN BREAST CANCER PATIENTS: A REPORT OF FEASIBILITY AND EARLY TOXICITY RESULTS IN THE FIRST 50 TREATMENTS WITH A MINIMUM FOLLOW UP OF 12 MONTHS

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Between 9/2010 and 5/2012, 122 consecutive patients with early-stage breast cancer were submitted to adjuvant radiotherapy with SIB-VMAT approach by means of VMAT in our Institution (ICH). Fifty were treated until 5/12 and have a minimum follow up of 12 months. Of these 50 patients data collected are here reported in detail. Three out of 50 patients were irradiated bilaterally (53 tumors in 50 patients). All patients were enrolled in a phase I-II trial approved by the ICH ethical committee. All patients enrolled in the study underwent VMAT-SIB technique to irradiate the whole breast with concomitant boost irradiation of the tumor bed. Doses to whole breast and surgical bed were 40.5 Gy and 48 Gy respectively, delivered in 15 fractions over 3 weeks. Skin toxicities were recorded during and after treatment according to RTOG acute radiation morbidity scoring criteria. In the first 50 patients the median follow up was 16 months(range 12-20). Cosmetic outcomes were assessed with the RTOG Headquarters cosmesis forms.

Results: In the 50 patients analysed with a minimum follow up of 12 months,the median age of the population was 68 years (range 36-88). According to AJCC staging system, 38 breast lesions were classified as pT1, and 15 as pT2; 50 cases were assessed as pN0 and 3 as pN1. The maximum acute skin toxicity by the end of treatment was Grade 0 in 20/50 (40%) patients, Grade 1 in 32/50 (64%), Grade 2 in 0 and Grade 3 in 1/50 (2%) (one of the 3 cases of bilateral breast irradiation). No Grade 4 toxicities were observed. All Grade 1 toxicities had resolved by 3 weeks. There were no significant differences in cosmetic scores on baseline assessment *vs*. 3 months, 6 and 12 months after the treatment: all patients were scored as excellent/good (50/50) compared with baseline. No fair/poor judgment was recorded. No other toxicities or local failures were recorded during follow-up.

Conclusions: The 3-week course of postoperative radiation using VMAT with SIB showed to be feasible and was associated with acceptable acute skin toxicity profile in the first 50 patients analyzed with a minimum follow up of 12 months; no other side effects were reported. Long-term follow-up data are needed to assess definitively late toxicity and clinical outcomes.

C002

ANAL CANCER TREATED BY HELICAL TOMOTHERAPY WITH SIMULTANEOUS BOOST (SIB) WITH CONCOMITANT CHEMOTHERAPY: A MONO-INSTITUTIONAL EXPERIENCE

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Purpose: Randomized controlled trials have assessed con-

current chemoradiation as the standard treatment for anal squamous carcinoma with a high rate of sphincter preservation, local control and survival; conversely, the cost of acute morbidity may be significant since irradiation of sensitive normal structures plays a negative impact on clinical outcome. New technological advances could improve dose delivery and therapeutic index ratio. IMRT allows simultaneous delivery of higher RT doses to the gross tumor volume and lower doses to normal tissue in an attempt to reduce toxicity. Our purpose is to evaluate our initial experience in the treatment of anal cancers with chemotherapy combined with intensity-modulated radiation therapy with Simultaneous Integrated Boost (SIB) delivered by Helical Tomotherapy (HT). This novel technique could result in a better outcome in terms of tolerance and clinical results.

Materials and Methods: Between February 2009 and May 2012 26 patients, median age 62 years, with stage I (5 pts), II (4 pts), IIIA (10 pts), IIIB (7 pts) were treated with RT±CT. 14 pts underwent 2 courses of MMC and 5 FU (during the first and last week of RT); 2 pts received capecitabine concurrent with RT; 3 pts received Capecitabine and MMC. Radiotherapy was delivered by HT with SIB technique. The prescribed doses were 50.6-55 Gy to CTV1 (primary tumor, involved nodes and high risk area) and 41.4-45 Gy to CTV2 (low risk subclinical disease), delivered in 22-25 fractions. Dose constraints to minimize the dose to OARs were prescribed. Megavoltage CT scans were obtained for patient alignment before each treatment. The clinical status during RT was analyzed through the evaluation of supportive care type defined by analgesic need.

Results: All pts received the prescribed dose and none had treatment breaks due to acute toxicity, except for one, who refused to conclude treatment, receiving 50.6 Gy on CTV1 and 41.4 Gy on CTV2. For all patients, dose volumes results for PTVs and some of the critical structures are reported in the Table. The median follow-up is 15.5 months (range 1-36). The most significant severe genitourinary acute toxicities reported at treatment end were grade 3 vaginal bleeding (4%) and grade 2 vaginal burn (8%). Cutaneous grade 3 erythema was recorded in 19% of patients and grade 2 gastrointestinal toxicities in 15%. Generally skin toxicity appeared in the last week of RT and recovered in 2 weeks. 15 (58%) pts needed analgesic support (tramadol, codeine or major opioids). At a minimum FU of 4 months, 22 pts are alive and evaluable for clinical response: 19 (86%) pts achieved complete response (CR), 2 pts underwent local progression after initial partial response (PR) and one patient had progressive disease (PD). One patient died for PD.

Table.

Volume	*Prescription Dose (Gy)*	*Mean Dose*	*Max Dose*	*Min Dose*
CTV55	55	54.9	56.8	52
CTV50.6	50.6	51	52.9	46.7
CTV45	45	46.9	56.1	40.2
CTV41.4	41.4	42.5	52	38.5
Critical Structures		**Mean Dose (Gy)**		
Bladder		27.4		
Bowel		14.9		

Conclusions: HT with SIB achieves great homogeneity in the dose distribution and a significantly good sparing of the organs at risk, and also allows to shorten total treatment time. IMRT-SIB combined with CT (both in neo-adjuvant and concomitant regimens) is very satisfactory in terms of toxicity and local control.

C003

SIMULTANEOUS IN FIELD BOOST HELICAL TOMOTHERAPY FOR PATIENTS WITH 1-3 BRAIN METASTASES: MONOISTITUTIONAL EXPERIENCE

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Purpose: It is estimated that 20-40% of patients with cancer will develop brain metastases during the course of their illness. Surgery, whole brain radiotherapy, or radiosurgery represent the cornerstones of treatment, even if the optimal management of brain metastases remains controversial. Several trials have assessed the role of a more aggressive combined approach compared with WBRT alone in the management of brain oligometastatic disease. The objective of this study was to evaluate the overall survival, intracranial control and intralesional after image-guided-IMRT with simultaneous in field boost. Inclusion criteria were: maximum 3 brain metastases, ≤3 cm of diameter, Karnofsky performance status ≥ 70, no previous cranial RT and systemic stable disease.

Patients and Methods: Between May 2010 and November 2011, 21 patients with 44 brain metastases were treated with image-guided-IMRT with simultaneous in field boost. Median age was 52 years (range 35-72 yrs) with 12 females and 9 males. Primary cancers were non-small-cell lung cancer in the majority cases (n=11), breast cancer (n=6), colon cancer (n=1), melanoma (n=2) and other sites (n=1). Eight patients had a solitary brain lesion, 18 patients had 2 to 3 lesions. All patients were immobilized in the supine position in a tight thermoplastic head mask. Helical computed tomography images of 3-mm thickness were obtained. Gross tumor volume (GTV) was defined by the tumor on CT scans registered with magnetic resonance imaging. Planning target volume (PTV) was defined by adding a margin of 3 mm to GTV. In association with WBRT, a SIB was administered to all brain lesions. A composite IMRT plan was generated for all patients consisting in WBRT (30 Gy/10 fx) with a SIB of 6 Gy in 10 fractions. Patients were treated in with Tomotherapy Hi-ART, with positioning determined by co-registration of the simulation kV CT scan with a MVCT scan acquired on the treatment unit. Patients underwent clinical follow-up examinations every 3 months.

Results: At the time of the last follow-up conducted in May of 2012, 5 patients was alive, and 17 were died. The

median follow-up time of alive patients was 14 months (6-17 months). The median survival time was 12 months. The overall survival rate at 6 and 12-months was 94% and 30%, respectively. Two patients experienced intralesional progression and 5 developed new brain metastases. Intracranial control was observed in 15 patients. No acute toxicity was observed. Late toxicity consisting of grade 2-3 brain edema occurred in 5 patients, and it presented as uncontrollable headaches. Of the 17 patients who died, 8 died of extracranial disease progression, 6 died of intracranial disease progression and 1 each died of brain edema. The cause of death for the remaining 2 patients was unknown. The following factors were analyzed in order to determine whether they were related to the prognosis of survival and local tumor control: gender, age, number of brain metastases (1, >2), status of primary tumor, status of extracranial metastases, KPS , and RPA class. Controlled primary tumors and KPS >80 were advantageous prognostic factors of survival.

Conclusions: The delivery of 60 Gy in 10 fractions using a SIB technique was achieved with no significant toxicity. Stable systemic disease and KPS scores >80 were advantageous prognostic factors of survival. Overall survival benefits need to be confirmed by large randomized studies.

C004

INTENSITY MODULATED RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST (IMRT-SIB) AS TREATMENT MODALITY FOR NASOPHARYNGEAL CARCINOMA: A COMPARISON WITH CONVENTIONAL 2D AND 3D CONFORMAL RADIOTHERAPY

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Backgrounds and Purpose: Radio-chemotherapy is the first choice treatment in non-metastatic nasopharyngeal carcinoma. Intensity-modulated radiation therapy (IMRT) allows the sparing of parotid glands, improving the toxicity profile. The aim of this study is to assess the results obtained with IMRT compared to those obtained with conventional 2D (2DRT) and 3D conformal radiation therapy (3DCRT) in terms of tumor control and acute and late toxicity.

Materials and Methods: We reviewed the clinical records of 52 patients with histologically proven nasopharyngeal (AJCC 2002 stage I-IVB) treated with curative intent between January 2003 and August 2011: 26 patients were treated with 2DRT or 3DCRT and conventional fractionation (Arm A) and 26 with IMRT (Arm B) with simultaneous integrated boost (SIB). Fifty patients (96%) also received chemotherapy. Local control (LC), local-regional control (LRC), disease-free survival (DFS), overall survival (OS), acute and late toxicity were retrospectively evaluated.

Results: After a median follow-up of 37.6 months, 69% of patients were alive and disease-free, 10% were alive with disease and 21% died of disease, with an OS of 81%, a LC rate of 88%, a LRC rate of 80% and a DFS of 74% at 2 years, with no statistically significant differences between IMRT and 2DRT/3DCRT (Table 1). In multivariate analysis the TNM stage and the volume treated to high dose correlated with DFS. Chronic toxicity was not statistically different in the two study groups and in particular ≥ G2 xerostomia rates were 67% and 41% in Arm A and B respectively (p=0.10).

Table 1.

	2DRT/3DCRT	IMRT
2y-OS	81%	81%
5y-OS	77%	81%
2y-DFS	69%	80%
5y-DFS	65%	83%
2y-LC	81%	96%
5y-LC	72%	87%
2y-LRC	69%	92%
5y-LRC	65%	83%

Conclusions: The findings of this study confirm that IMRT associated with chemotherapy, even with moderately hypofractionated regimens, allows good disease control with better results in terms of late xerostomia, although without statistically significant differences compared to 2DRT and 3DCRT. The hypothesis of an impact of IMRT has yet to be confirmed. Further advances in technology will probably help to contain other important aspects of chronic toxicity.

C005

SIB (SIMULTANEOUS INTEGRATED BOOST) – IMRT (INTENSITY MODULATED RADIATION THERAPY) FOR OROPHARYNX CANCER (OC): ANALYSIS OF TOXICITY AND RESPONSE

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Aims. IMRT is associated with significant clinical improvements over three-dimensional conformal radiotherapy (3DCRT) for head and neck (H&N) cancer. The SIB-IMRT technique allows the simultaneous delivery of different dose levels to different target volumes within a single treatment fraction and represents a new method of accelerated fractionation. We compared two different fractionation strategies in SIB-IMRT treatment of OC in terms of acute and late toxicity and clinical response.

Materials and Methods: December 2006 through December 2011, 53 patients (pts) with OC were treated with radical SIB-IMRT at our Institution (M:F=40:13; squamocellular /indifferentiated histotype=50/3; Stage III-IV pts were 79%; 92,5% and 79.2% of pts had respectively MRI and US for diagnosis and staging). Dose to

clinically evident disease was 70 Gy (2 Gy/fraction SIB, NORMO) and 69 Gy (2.3 Gy/fraction SIB, HYPO), respectively, in 36% and 64% of pts. 72% of the pts had at least 4 concomitant chemotherapy cycles with platinum. Chi square test and KM curves were used when appropriate.

Results: Three categories of "radical CTV volumes" (I,<100cc, II, ≥100cc<200cc, III, ≥200cc) were considered. While the two fractionation schemes were evenly distributed according to stage (P=NS), the percentage of the pts treated with HYPO significantly decreased with increasing CTV volumes (100%, 50% and 28% in Group I,II and III, respectively - p=0.00). The majority of pts undergoing HYPO showed a mild-severe acute mucositis (CTCAE v. 3 scale) as opposed to NORMO pts (p=0.005). The same trend was observed for dysgeusia (p=0.028), pain (p=0.00) and dysphagia (p=0.01). For those pts with avalaible late toxicity data (at 12 and 18 months) xerostomia, dysphagia, pain, and weight loss incidence were not significantly different between HYPO and NORMO groups. Clinical response and early overall and disease free survival data did not significantly differ in the HYPO and NORMO groups.

Conclusions: The choice of HYPO in OC treatment can determine worse acute toxicity expression but not a worse late toxicity. Survival and late toxicity data should be confirmed in a larger group of cases, followed longer.

C006

A MONO-INSTITUTIONAL EXPERIENCE OF SIMULTANEOUS INTEGRATED BOOST(SIB)IN BREAST CONSERVING TREATMENT: DOSIMETRIC AND RADIOBIOLOGICAL CONSIDERATION AND PRELIMINARY RESULTS

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Purpose: Helical Tomotherapy (HT) has recently been introduced in breast cancer treatment and some very little data are available on the dosimetry and feasibility of HT in the context of whole breast radiation with SIB. In our institute all the breast patients receive hypofractionated radiotherapy including WBRT with SIB by HT.

Materials and Methods: In our institution from 2009 to December 2011 we treated 22 conservatively operated breast cancer patients with loco-regional adjuvant radiotherapy by HT. The median age was 58 years (range 36 – 81). Eighteen patients (81%) had a histological diagnosis of ductal carcinoma, and ten of them with a locally advanced tumor (LABC). The supraclavicular lymph nodes were irradiated in all the patients and in eleven patients the internal mammary lymph nodes were irradiated too. The SIB schedule used was: 2.3 Gy x20 fraction (whole breast and regional nodes) and 2.6 Gy x20 fraction (tumor bed). Breast and boost CTVs were expanded with a margin of about 5 mm to generate the breast and boost PTVs, sparing irradiation of organs at risk (heart and lung. The breast CTV ranged from 192.3 cm to 2558.3 cm and the SIB CTV ranged from 7.3 to 257.9 cm. The CTV margin is reduced compared with conformational 3D-CRT, due to HT IGRT system that allows to check a correct patient position before each treatment. The biologically effective dose (BED) for the innovative treatments was calculated using the linear-quadratic (LQ) model with parameters previously derived for breast cancer from clinical data (alpha/beta=4Gy). It may be appropriate to consider the time factor. The comparison between the standard fractionated treatment BED (WBRT 50Gy/25fr + sequential boost 10Gy/5fr) and the hypofractionated treatment BED with HT (WBRT 46Gy/20fr + SIB 6 Gy/20 fr, for a 52 Gy total dose to the tumor bed) shows that the two treatment schedules have the same radiobiological effectiveness, with a BED value of 82,5 Gy and 81 Gy respectively.

Results: At the end of hypofractionated RT with SIB given by HT we observed a moderate grade 1-2 erythema toxicity in about 86% of the total patients. The 63% of them showed a decrement in toxicity (mild hyperpigmentation) in three months approximately. The remaining 36% of the "acute-toxicity patients" showed a total resolution of it in the same period of time. About the late results (at six months) only 36% of the patients showed a G1-G2 toxicity in terms of fibrosis. Even if in absence of an adequate follow up the preliminary aesthetic and functional results were favorable and we have not observed unsatisfactory outcomes.

Conclusions: Hypofractionated radiation therapy with SIB administered by TomoTherapy seems to have the same effectiveness in terms of radiobiological parameters, it is a well-tolerated treatment and allows a reduction in the number of the patient's accesses to the radiotherapy centre.

C007

NORMAL TISSUE COMPLICATION PROBABILITY MODELING OF ACUTE BLADDER TOXICITY IN PATIENTS TREATED WITH SIMULTANEOUS INTEGRATED BOOST FOR PROSTATE CANCER

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Purpose: To test the hypothesis that increased bladder mean dose is associated with acute genito-urinary (GU) toxicity in prostate cancer patients treated with Simultaneous Integrated Boost (SIB) technique, using a previously derived normal tissue complication probability (NTCP) model.

Materials and Methods: Forty-five patients with Stage I-III prostate cancer treated with SIB were enrolled. Patients received a total dose of 80 Gy fractionated into 2Gy/die to the prostate, and a total dose of 72 Gy fractionated into 1.8 Gy/die to the Seminal Vesicles. Acute bladder toxicity was collected in thirty-nine patients using the Radiation Therapy Oncology Group scale. Equivalent uniform doses (EUD) used as dose reduction method were calculated for patient without toxicity (group A) and

patients with any toxicity grade (group B). A logistic model was used to test correlations between acute GU toxicity and bladder dosimetric parameters (EUD).

Results: Acute bladder toxicity was G0 in 9/39 (23%) patients, G1 in 17/39 (43%), G2 in 10/39 (26%) and G3 in 3/39 (8%). G4 grade toxicity was never found. Mean treatment bladder doses were significantly higher in group B (group A 23.89 Gy vs group B 42.76 Gy, p=0.02). EUD were also significantly higher in patients with GU toxicity (group A 25.10 Gy vs group B 42.13, p=0.02). The DVH-reduction model based on estimated complication probability (NTCP) under uniform irradiation (EUD) of the bladder showed that logistic model parameter estimated were 50=0.53 and a =1.4. Moreover, on multivariable logistic regression, TCD50 was 18 Gy.

Conclusions: In our patients there is 50% probability of acute bladder toxicity with a mean delivered uniform dose of 18 Gy. Our results support the hypothesis that increasing bladder mean dose is significantly correlated with increased GU toxicity in prostate cancer patients undergoing SIB-IMRT. Because of the large confidence intervals calculated, a higher number of patients would be needed in order to increase the reliability of the model.

C008

SIMULTANEOUS INTEGRATED BOOST IN NEOADJUVANT CHEMO-RADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER: PRELIMINARY RESULTS OF P CR AND ACUTE TOXICITY

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Purpose: To evaluate rates of pathological complete response (p CR) and acute toxicity in patients (pts) with locally advanced rectal cancer undergone to neoadjuvant chemotherapy concomitant to radiotherapy with three-dimensional conformal simultaneous integrated boost (SIB).

Materials and Methods. Between October 2009 and May 2012, twenty patients (median age, 62 years, range 45-72) with locally advanced rectal cancer (T3) were treated with neoadjuvant radio-chemotherapy. Patients treated by radiotherapy at whole pelvis (45 Gy, 1.8 Gy/fraction) with hyperfractionated simultaneous boost to the mesorectum corresponding to the GTV (10 Gy, 1.0 Gy twice a week). The daily dose of the boost was delivered twice a week concomitant to daily dose administered to the pelvis for a total dose of 55 Gy associated to chemotherapy with Capecitabine (1650 mg/m2 chronomodulated, during the whole treatment time). Surgery was performed 6-8 week after radiotherapy. Tumor response was assessed with Mandard tumor regression grading (TRG). Acute toxicity was assessed with RTOG toxicity scale (Radiation Therapy Oncology Group/).

Results: Seventeen pts were evaluated. A complete pathological response (TRG1) was observed in 12/17 pts (71%), one patient (6 %) had TRG 2 and 4 (24%) TRG 3. No significant G3-G4 acute toxicities were observed except one patient who refused xeloda's dose due to gastrointestinal toxicity G3 grade.

Conclusions: In our series complete pathological response rates (TRG1) in patients treated with SIB and chronomodulated capecitabine seems to be greater than complete response rate obtained with a conventional radiotherapy scheme of 50.4 Gy (1.8 Gy/day) combined with chemotherapy using capecitabine 825 mg/m2 twice daily.

APPROCCI INTEGRATI NELLE NEOPLASIE LOCALMENTE AVANZATE DEL TORACE

C009

TOMOTHERAPY AFTER PLEURECTOMY/DECORTICATION OR BIOPSY FOR MALIGNANT PLEURAL MESOTHELIOMA ALLOWS THE DELIVERY OF HIGH DOSE OF RADIATION IN PATIENTS WITH INTACT LUNG

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Purpose: To asses the safety of high doses of radiation delivered with Tomotherapy to the intact lung after radical Pleurectomy/Decortication (P/D) or biopsy for malignant pleural mesothelioma (MPM).

Materials and Methods: Twenty-eight patients were enrolled in this prospective study and underwent adjuvant or definitive Tomotherapy after radical P/D (n=20) or pleural biopsy (n=6) for MPM. The dose prescribed to the Planning Target Volume, defined as the entire hemithorax, including chest wall incisions and drain sites and excluding the intact lung, was 50 Gy delivered in 25 fractions. All patients underwent FDG-PET for staging after surgery. Any FDG-avid areas or regions of particular concern for residual disease were given a simultaneous boost of radiotherapy to 60 Gy. Specific lung dosimetric parameters were reported. Toxicity was graded using the modified Common Toxicity Criteria v3.0.

Results: The median follow-up was of 19 months (range, 6-29 months). Five (17.8%) patients experienced severe respiratory symptoms corresponding to Grade 2 pneumonitis in 3 cases, and Grade 3 pneumonitis in 2 cases. No fatal respiratory toxicity was reported. Controlateral lung V5 was strongly correlated with the risk of pneumonitis. Patients who developed Grade 2 and 3 pneumonitis had a higher controlateral lung V5 (mean V5=32%) than those without pneumonitis (mean V5=17%) (p=0.002). Other two Grade 3 toxicities were registered: one severe pain to the chest wall, and one severe thrombocytopenia.

Conclusions: Tomotherapy allows the safe delivery of high dose of radiation to the hemithorax of MPM patients with intact lung.

C010

HYPOFRACTIONATED RADIATION THERAPY IN PATIENTS WITH ADVANCED NSCLC: A SINGLE INSTITUTION EXPERIENCE

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Backgrounds: At present, the standard evidence-based treatment for locally advanced non-small-cell lung cancer (NSCLC) is concurrent chemotherapy-radiation therapy (RT) with a platinum-based regimen. Hypofractionated radiotherapy (HypoRT) can potentially improve local control with a higher biological effect and shorter overall treatment time. We aimed to evaluate toxicity rates, local control and survivals of patients with advanced non-small cell lung cancer that received HypoRT +/- IGRT.

Materials and Methods: Thirty patients with advanced NSCLC were enrolled: 27% had stage IIIA, 50% had stage IIIB, and 23% had stage IV disease. Patients were staged according to the American Joint Committee for Cancer Staging System (AJCC) 2002. All patients underwent curative HypoRT with total dose prescribed 60 Gy in 20 fractions of 3Gy/each. Radiation treatment was delivered using a 3 dimensional conformal technique (3D-CRT) and in 21 (70%) patients an IGRT (Image-Guided Radiotherapy) technique was associated to verify correct position. Toxicities were grading according to the RTOG morbidity score. Survivals were estimated using the Kaplan-Meier method.

Results: The median follow up was 13 months (range: 4-56 months). All patients completed radiotherapy and received the total dose of 60 Gy to the primary tumor and positive lymph nodes (BED=78 Gy). The overall response rate after radiotherapy was 83% (3 pts with CR and 22 pts with PR). The 2-year overall survival and progression free-survival rates were 38.1% and 36%, respectively. Loco-regional recurrence/persistence occurred in 11 (37%) patients. Distant metastasis occurred in 17 patients (57%). Acute toxicities occurred as follows: hematological grade 1-2 in 5 pts (17%), grade 3 in 1 patient; esophagitis grade 1-2 in 12 pts (40%), grade 3 in 1 pt; pneumonitis grade 1-2 in 6 pts (20%), grade 3 in 2 pts (7%). The 33% of the patients developed grade 1-2 late toxicities. Only 3 pts developed grade 3 late adverse effects: esophagitis in 1 pt and pneumonitis in 2 pts.

Conclusions: Hypofractionated curative radiotherapy is a feasible and well-tolerated treatment for patients with locally advanced non-small cell lung cancer. Randomized studies are needed to compare HypoRT to the conventional treatment.

C011

MULTIMODALITY TREATMENT IN ELDERLY PATIENTS FOR LOCALLY ADVANCED NSCLC: RESULTS AND ANALYSIS OF TOXICITY FROM OUR EXPERIENCE

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Purpose: To evaluate the outcome and toxicity in elderly patients (aged 70 or older) with locally advanced non-small cell lung cancer (NSCLC) after combined-modality therapy, comprehending surgery, chemotherapy and radiotherapy (RT).

Materials and Methods: We retrospectively reviewed 56 patients affected by NSCLC from January 2005 to December 2010 at the "Sapienza" - University of Rome, Policlinico Umberto I, Department of Radiation Oncology (follow up range 24-84 months). Forty-six patients were male (82%) and 10 female (18%). The mean age was 77.8 years (range 70- 92). Forty-two patients (75%) were classified as IIIA stage and 14 patients (25%) as IIIB, according to TNM classification. Histology evidenced squamous cell carcinoma in 21 patients (37%) and adenocarcinoma in 35 patients (63%). Forty-four (78%) patients underwent surgery: lobectomy was performed in 95% of patients and pneumonectomy only in 5%. All patients underwent sequential radio-chemotherapy, 46 as neodjuvant treatment (82%) and 10 (18%) as adiuvant therapy. RT was delivered with a range of dose between 50-70 Gy with a daily fraction of 180/200cGy, with a 6-MV linear accelerator, using a three-dimensional external conformal radiotherapy (3D-ECRT) technique.

Results: Median overall survival (OS) was 37 months (range 11-80 months). Thirty-eight patients (66%) showed a response (22% complete and 43% partial response) to multimodality therapy, while 12 patients (21%) had disease stability and only 6 patients (10%) showed disease progression. As side effects related to RT, we observed dispnea and cough (G2 RTOG) in 19 patients, disphagya (G1 RTOG) in 17 patients, in 13 patient mild effects as low- grade fever, anemia e leukopenia (G1 RTOG), and no significant side effects in 7 patients. During RT no patient interrupted the treatment and the quality of life remains good.

Conclusions: Older age, higher N stage, high mean lung dose were associated with increasing pulmonary toxicity on univariate analysis. In the last two decades the use of new technologies and multimodality strategies reduced toxicity related to anticancer therapies also in elderly people. Our experience demonstrated that a combined therapy in NSCLC in elderly patients promotes a good response and is well tolerated, tough the old age, the high RT doses and comorbidities age-related.

C012

RADIATION THERAPY IN THE MENAGMENT OF LOCAL ADVANCED NSCLC: WHEN PATIENTS ARE REFERRED TO RADIATION ONCOLOGIST?

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Aims: a recent italian survey has shown how daily prac-

tice differs in some ways from the guidelines for care of advanced non-small cell lung cancer (NSCLC). We report the daily oncological medical practice in our centre on lung cancer pts referred to our observation before 2011.

Materials and Methods: We retrospectively assessed data relating to the management of pts with locally advanced NSCLC referred to the Radiation Therapy Department of Taranto from 2002 to 2011. We evaluated 190 pts (175 male/ 15 female - mean age of 70 years) with histologically proven NSCLC and clinical stage IIIa/b (107/83). We classified pts in 4 groups according to the international treatment guidelines. Group I: 76 inoperable pts but potentially elegible to curative concomitant RCT; Group II: 37 pts operated and elegible to adjuvant treatment (post operative CT and RT); Group III: 37 inoperable pts (very advanced disease and severe comorbidities) with indication to a palliative RT; Group IV: 40 pts not elegible to RT.

Results: in the group I, 67/76 pts came to our attention after induction CT (42 pts after 2-4 cycles of CT and 25 pts after 5-6 cycles). The remaining 9/76 pts were naïve because presenting comorbidities. Twenty-three out of 76 pts were treated in a different centre for our long lasting waiting list. Among the 53 pts treated in Taranto, concomitant RCT was delivered to 36 pts while the remaining 17 received RT only. Concomitant RCT platinum based was delivered in 23/36 pts while low dose monochemotherapy was given to 13 pts. In the subset of the naïve group 5/9 pts had concomitant RCT and 4 pts exclusive RT. Mean total dose delivered to Group I was 64 Gy (60-66 Gy) with standard fractionation. In the group II, no pts received neoadjuvant CT; 29 pts were observed after adjuvant CT (28 pts after II-IV cycles and 1 after VI cycles). The remaining 8 pts came to our attention immediately after surgery. Patients with postoperative margins status R1-R2 (7/37) after CT received RCT. Thirty pts out of 37 received adjuvant RT after CT. Total dose of RT was 50 Gy for R0 pts and 60-66Gy for R1-R2. In the group III, 24/37 pts came to our attention for palliation during CT; 15 pts during II-IV cycles and 9 during V-VI cycles. The remaining 13 pts were send to our observation naive after diagnosis. Three pts out of 37 received vinorelbine monochemotherapy concomitant with RT while 34 pts received RT only; RT delivered total dose was from 16 to 40 Gy. In the group IV, 38/40 pts came to our attention during CT, while the remaining 2 pts were naive. For these 40 pts there was no indication to RT due to IK < 60, progressive disease or respiratory failure.

Conclusions: on 190 observed pts, 40 pts (21%) had no indication to RT while from the remaining 150 pts 76 (51%) received RCT or were refferred for RCT to other centres; only 5/76 pts (6.6%) were not treated with induction CT and could start RCT according interntional guidlines for locally advanced NSCLC. Thirty out of 37 pts (81%) were correctely treated in adjuvant setting; 6 pts were refferred to us after 6 cycles of CT. In our daily practice patient initial management diverted from the standard approach and could have compromised patients possibility to be cured. These results supported the urgency for a multidisciplinary team creation in our centre from 2011 to straighten pts to a correct and in-time therapeutic strategy.

C013

A PHASE I STUDY OF SHORT COURSE ACCELERATED RADIATION THERAPY (SHARON) FOR ADVANCED THORACIC TUMORS

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Aims: To define the maximum tolerated dose (MTD) of a short course accelerated radiotherapy in the symptomatic treatment of advanced thoracic tumors.

Patients and Methods: A phase I clinical trial was designed, escalating the dose in three steps: 16, 18 and 20 Gy. A twice daily fractionation in two days was delivered. The dose limiting toxicity was defined as any acute toxicity >Grade 3, according to RTOG scale. Information on status of symptoms, ECOG performance status, and quality of life (QoL) was recorded and compared at baseline and 3 weeks after treatment.

Results: Twenty-eight patients were enrolled (M/F: 22/6; median age: 66.4 yrs). All patients had baseline symptoms: dyspnea (43%), pain (28%), dysphagia (11%) and haemoptysis (7%). Three patients (11%) showed superior vena cava syndrome. Three patients showed grade 1-2 acute lung toxicities (10.7%). One patient experienced early death 15 days after treatment (grade 5 acute lung toxicity). Overall, no other patient experienced DLT in all 3 dose levels. With a median follow-up time of 5 months (range, 0.5-36 months) no late toxicities have been observed. Three weeks after treatment, 26 of 28 (92.9%) symptomatic patients showed an improvement or resolution of their baseline symptoms. Four patients (14.3%) with baseline haemoptysis or dyspnea had complete symptom relief. One patient (3.5%) was stable and 1 patient (3.5%) showed symptoms worsening. Overall, palliative response rate was 92.9% (CI 0.95: 71.6% - 99.3%). A significant reduction of pain, as evaluated by VAS, was recorded (pre- treatment vs post- treatment mean VAS: 7.7 + 1.3 vs 5.0 + 0.9; p=0.019).

Conclusions: Short course radiotherapy was tolerated up to a total dose of 20 Gy. A phase II study has been planned to confirm the efficacy on symptoms control and QoL.

C014

SURGICAL RESECTION VERSUS RADIOTHERAPY AFTER CDDP/DOCETAXEL INDUCTION CHEMOTHERAPY IN LOCALLY ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)

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Purpose: Induction chemotherapy (ICT) could increase survival compared with surgery alone in stage III NSCLC patients candidate to surgery and/or allow resection when surgery is not indicated upfront. We here report a series of patients treated with ICT and treated either with surgery or radiotherapy (RT) on the basis of response.

Methods: From July 2005 to April 2011, 33 patients with a histological or cytological proven Stage III NSCLC (30 IIIA, 3 IIIB-T4 disease) received 2, 3 or 4 cycles of Cisplatinum-Docetaxel (CDDP 75 mg/m2, TXT 75 mg/mq, every 21 days). Patients in CR, PR or SD were evaluated by a multidisciplinary team including a thoracic surgeon and underwent resection or radical full dose radiotherapy (60- 66 Gy). Patients with a pathological stage N2 and/or R1 received adjuvant RT (50- 54 Gy). Statistical analyses were performed with SPSS. Survival rates were estimated using Kaplan - Meier analyses.

Results: After ICT 21 patients were in PR, 6 in SD and 6 in PD. Fifteen patients were resected after ICT (45.4%, 2 pneumonectomy and 13 lobectomy), and 12 received radical RT (36.3%). Postoperative RT was performed in 7 patients. Out of 21 partial responders, 13 underwent surgery (62%) and 8 RT (38%). With a median follow up of 26 months (range 3-71), the Progression Free Survival (PFS) rates at 2 years for resected patients vs patients treated with RT were 76% and 51%, respectively (p=0.032), while the Overall Survival (OS) rates were 86% vs 65%, respectively (p=0.12). Local-progression free survival rates were similar for surgery and radiotherapy. Patients in Partial Response after ICT showed higher PFS and OS rates at 2 years (74% vs 36%, and 80% vs 33%, p=0.003 and p=0.002) than patients in SD or PD.

Conclusions: Responders to ICT have better outcomes, in terms of both PFS and OS, then non-responders (PD or SD). A statistically significant difference in terms of PFS (mainly represented by distant failures) was recorded in favor of surgery, without difference in OS. This difference could be explained by a selection bias for surgical resection after ICT (lower T stage, younger age, better PS, major response). The low resection rate after ICT (45%) suggests that a better selection prior to ICT could be crucial in offering upfront concomitant chemoradiotherapy to patients who will not be addressed to surgery even if partial responders (around 40%).

C015

EFFICACY OF FARINGEL IN PREVENTIG RADIATION-INDUCED ESOPHAGITIS IN LOCALLY ADVANCED LUNG CANCER: A COMPARISON WITH A CONTROL GROUP TRETED WITH CONCURRENT CHEMORADIATION

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Purpose: Esophagitis is the most frequent side effect in patients treated with radiation therapy for cancers located in the thoracic district. The aim of this study is to evaluate the efficacy and tolerability of Faringel (a propoli-based syrup) in preventing or delaying esophagitis in locally advanced lung cancer patients treated with concurrent chemoradiation.

Materials and Methods: FARINGEL was prescribed at the beginning of treatment to a group of 22 consecutive lung cancer patients undergoing chemo-radiotherapy at our institution. between October 2010 to June 2012. Patients with GERD were excluded from the analysis. Three-dimensional conformal radiation therapy was delivered with total dose ranging from 59,4 Gy to 70,2 Gy on the chest district with daily fraction doses of 1,8 Gy, 5 days for week. During treatment a weekly clinical visit with physical examination, complete blood count and hematochemical analysis was performed for acute toxicity. Toxicity was recorded according the NCI Common Toxicity Criteria 3.0 scale. Results were compared with a control group of 57 patients previously treated with concurrent chemoradiation without the administration of the syrup.

Results: All patients in the Faringel group have completed the administration of the syrup with good levels of tolerance. The two groups are comparable for treatment plan constraints. They were compared according to dosimetric characteristics (V5,V10,V20, V30, V40, V45, V50, V55, V60, esophageal volume) and no statistically significant differences were recorded (p>0.05). Grade 2 esophagitis was lower in FARINGEL group in comparison with the control group (28.6% and 36,4%), even if statistical difference was not reached (p=169). Instead, mean dose delivered at the onset of esophagitis was higher in the FARINGEL group (40.7 Gy and 25.9 Gy of the control group) with a highly significant difference (p<0.001). Mean numbers of interruption days in patients with or without esophagitis were 0.6 and 2.6, respectively (p=0.10). The mean number of interruption days was 1.6 in FARINGEL group and 5 in the control group (p=0.021).

Conclusions: Study results highlights the possibility that Faringel action could be effective in protection of the esophageal mucosa with effectiveness either in prevention and either in delayng esophagitis induced by chemoradiotherapy for locally advanced lung cancer.

C016

LOW DOSE RADIOTHERAPY AND CONCURRENT CISPLATINUM AND GEMCITABINE CHEMOTHERAPY REGIMEN IN UNRESECTABLE STAGE III AND IV NON SMALL CELL LUNG CANCER (NSCLC): A FEASIBILITY STUDY

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Aims: Low-dose radiotherapy (LDR) (<50 cGy) induces enhanced cell killing *in vitro*. The safety and efficacy of platinum-based doublets as a neoadjuvant regimen in patients with unresectable Stage III and IV NSCLC are well known. Aim of this study was to evaluate the safety and efficacy of regimen combining cisplatinum, gemcitabine and LDR (as a chemopotentiator) in stage III and IV NSCLC

Methods: Patients (pts) with unresectable NSCLC received gemcitabine (1000 mg/m2/die on days 1 and 8), cisplatinum (80 mg/m2/die on Day 1) and concurrent LDR (40 cGy bid on days 1, 2, 8 and 9); this cycle was repeated for 2-4 cycles every 21-day. LDR was delivered to PET positive pulmonary and nodal lesions. The response was assessed by CT scan and/or PET-CT. If no progression, patients were treated with neoadjuvant concurrent radiochemotherapy (RT-CT) consisting of cisplatinum (20 mg/m2/die for 4 consecutive days, every 4 weeks) and gemcitabine (350 mg/m2/die, weekly) and radiotherapy (Total dose 50.4 Gy, 180 cGy/die) delivered to PET positive pulmonary and nodal lesions.

Results: From March 2009 to February 2012, 33 pts (median age 68, M/F: 25/8), affected by unresectable lung cancer (1 pt Stage IIB, 16 pts Stage IIIA, 8 pts Stage IIIB and 8 pts Stage IV) were enrolled. Only 3 pts developed G3 haematologic toxicity. No lung and oesophageal toxicity was recorded. All patients are evaluable for clinical response: among them, 22 (66.7%) had a response (complete or partial response), 6 (18.1%) had a stable disease and 5 (15.1%) had a progression disease. After multidisciplinary evaluation 3 pts directly underwent surgical resection. Eighteen pts (54.5 %) were treated with RT-CT. Among these pts, 8 (44.4 %) underwent surgery (5/8 pts (62.5 %) had a pathological nodal response and 2/8 pts had a pathological complete response), 6 (33%) had a progression disease and 4 (22.2 %) were under RT-CT treatment at the data analysis time.

Conclusions: The addiction of low-dose radiotherapy to induction cisplatinum and gemcitabine chemotherapy regimen is feasible and safety; the response rate of this novel approach is encouraging. Further scientific investigations on this new treatment approach are required.

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Oral Communications

C017

ASSOCIATION STUDY OF COMMON GENETIC VARIANTS WITH THE RISK ACUTE SKIN TOXICITY IN BREAST CANCER PATIENTS RECEIVING RADIOTHERAPY AFTER BREAST CONSERVING SURGERY

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Purpose: In order to provide new insights into the genetic basis of normal tissue radiosensitivity, we evaluated the association between eighteen polymorphic variants located in fourteen genes related to DNA repair mechanisms (XRCC1, TP53, MSH2, MSH3, XPD, PARP1, BRCA1, RAD51, LIG3), oxidative stress response (GSTP1, GSTA1, eNOS, SOD2) and fibroblast proliferation (TGF 1), and the risk of acute skin toxicity in breast cancer patients receiving radiotherapy.

Materials and Methods: Skin toxicity was scored according to the Radiation Therapy Oncology Group criteria in a retrospective series of 286 breast cancer patients who received radiotherapy after breast conserving surgery. Genotyping was conducted by PCR-RFLP analysis and real-time PCR allelic discrimination assay on genomic DNA extracted from peripheral blood. The association between genetic variants and the risk of moderate to severe acute skin toxicity was evaluated by either univariate and multivariate logistic regression analysis.

Results: In the multivariate analysis, eNOS G894T polymorphisms (TT *vs*. G carriers, OR: 2.561, 95%CI: 1.259-5.210, P=0.009), XRCC1 T-77C (T carriers *vs*. CC, OR: 2.293, 95% CI: 1.034-5.087, P=0.041), LIG3 rs4796030C>A (AA *vs*. C carriers, OR: 1.919, 95%CI: 1.003-3.670, P=0.049), breast diameter (OR: 1.148, 95%CI: 1.010-1.306, P=0.035) and boost dose-fractionation (3 Gy *vs*. no boost, OR: 4.652, 95% CI: 1.372-15.777, P=0.014) emerged as independent predictors for grade 2 acute skin toxicity after radiotherapy in breast cancer patients. The analysis of classificatory power of the model showed low value of sensitivity (0.29), high specificity (0.91), and an overall prediction correctness (0.72).

Conclusions: Our results suggest that approaches based on multiple polymorphic variants and factors related to radiotherapy and to clinical characteristics of patients have the potential to predict normal tissue radiosensitivity in breast cancer patients. Further investigations based on a larger number of candidate polymorphic genes are warranted to identify more comprehensively the SNPs of clinical usefulness for the identification of patients at greater risk for the development of acute radiation injury.

C018

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AND RADIATION-INDUCED LATE TOXICITY IN PROSTATE CANCER

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Purpose: The aim of this study was to explore the possible relationship between SNPs in genes involved in the DNA repair pathways and radiation-induced late toxicity in patients treated for prostate cancer.

Materials and Methods: Analysis includes 63 patients

who underwent radiotherapy at the Radiotherapy Centres of Florence, Pistoia, Arezzo, Siena and Brescia. 20(31.7%) patients received postoperative radiation on prostate bed volume, 22(35%) patients were treated with radical radiotherapy on the prostatic volume and 21(33.3%) patients received radiotherapy on prostate and seminal vesicles. The mean dose was 75 Gy. Late rectal and bladder toxicities were graded according to Common Terminology Criteria for Adverse Events v3.0. Peripheral blood lymphocytes were collected and analysis of SNPs was performed using HRMAnalysis. SNPs of GSTP1A313G; XRCC1c.1196A>G; XRCC3c.722C>T; RAD51c.3429G>C; RAD51c.3392G>T were evaluated. Allele frequency for each gene in the studied group was compared with the frequency in Caucasian population.

Results: The genotype frequencies of XRCC3c. 722C>T; RAD51c.3429G>C; RAD51c.3392G>T were consistent with previously reports in Caucasian population. 71.4% of patients did not develop any toxicity. 18 patients have developed genitourinary and/or gastrointestinal toxicity 359 days (mean-time) after radiotherapy. None of the patients who developed late toxicity showed homozygous GG for the GSTP1 gene and homozygous for the allele A with regard to the gene XRCC1c.1196, then this condition could be considered as a protective element. Only two patients with homozygous allele GG for GSTP1 had not developed late toxicity. DVH analysis of this subset of patients even showed an unfavorable rectum dose relative to Quantec. Also 7.6% of patients with homozygous allele AA for XRCC1c.1196A>G had not developed late radiation-induced toxicity, despite for one patient DVH analysis showed unfavorable. This data furtherly confirms the hypothesis that the homozygous GG for GSTP1c313A>G11 and homozigous AA for XRCC1c1196A>G could be a protective factor for the development of late radio- induced toxicity.

Conclusions: Our findings suggest an association between development of less late rectal and bladder radiation-induced toxicities in prostate cancer for the homozygous allele G at GSTP1 c.313 and for the homozygous allele A at XRCC1 c.1196. Further studies are in progress on a genome wide scale in order to confirm our data.

C019

PLASMATIC CYTOKINE LEVELS IN LUNG CANCER PATIENTS UNDERGOING DEFINITIVE RADIATION THERAPY

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Purpose: To assess the kinetics of plasmatic cytokines during the course of definitive radiation therapy (RT) for locally-advanced or early-stage Non-Small Cell Lung Cancer (NSCLC).

Materials and Methods: This prospective study was conducted on 28 patients: 15 early-stage NSCLC patients underwent Stereotactic Body RT (SBRT) consisting of 52 Gy in 8 fractions; 13 locally-advanced NSCLC patients underwent Intensity Modulated RT(IMRT) consisting of 60 Gy in 25 fractions. All patients were treated with Helical Tomotherapy. For patients undergoing SBRT, EDTA-peripheral blood samples were collected the first day of SBRT (TFd), the last day (TLd) and 45 days (T45d) after the end of RT. For patients undergoing IMRT, blood samples were collected at TFd, at two weeks (T2w), at TLd, and at T45d. A multiplex parametric technology was used for quantification of the following cytokines: IL-1, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17A, EGF, FGF-2, INF- , MIP-1 , MIP-1 , TGF- , TNF- , VEGF, PDGF- , and PDGF-. Cytokine levels measured at different RT time were compared using a two-tailed Student's t test; statistical significance was claimed for $p < 0.05$.

Results: No difference in baseline levels of cytokines was documented between SBRT (early-stage) patients and IMRT (locally-advanced) patients. For SBRT patients, a mean IL-10 and IL-7 plasma level reduction of 5 pg/ml ($p<0.05$) and 2 pg/ml ($p<0.05$), respectively, was noted between TLd and TFd. IL-10 and IL-17 returned to pre-RT levels 45 days after completion of SBRT. For IMRT patients, a statistically significant ($p<0.05$) mean plasma level reduction was noted between T2w and TFd for all the following cytokines: IL-1 (4 pg/ml), IL-1ra (33 pg/ml), IL-2 (5 pg/ml), IL-12 (35 pg/ml), FGF-2 (42 pg/ml), MIP-1 (2 pg/ml), MIP-1 (13 pg/ml), TGF- (2 pg/ml), TNF- (7 pg/ml), VEGF (105 pg/ml), PDGF- (3784 pg/ml), and PDGF- (47875 pg/ml). All theses cytokines returned to pre-RT levels the last day of IMRT.

Conclusions: The present study was conducted to examine the effect of different schedule of radiation therapy on levels of inflammatory markers in NSCLC patients. We show that several cytokines are sensitive to irradiation. A reduction of plasmatic cytokine levels during the course of radiation therapy both for early-stage and locally advanced NSCLC patients was documented. If such cytokine kinetics might have an impact in outcome or in radiation toxicity has to be investigated.

C020

ROLE OF PHARMACOLOGICAL INHIBITORS OF THE RHO/ROCK PATHWAY AND THEIR FIBROLYTIC ACTION IN DIFFERENT ANIMALS MODELS OF RADIATION-INDUCED FIBROSIS: STUDIES *IN VIVO* AND *IN VITRO*

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Objectives: Among signalling pathways involved in radiation fibrosis, the activation of Rho/ROCK pathway

has been shown in intestinal fibrosis.Moreover,we showed that Rho/ROCK pharmacological inhibitors (Pravastatin, Simvastatin and Y-27632) displayed antifibrotic efficacy in lung fibrosis. We investigated the molecular basis of their antifibrotic action and postulated that they could trigger fibrolytic action involving MMP2/TIMP2 axis. In addition, in order to evaluate whether irradiation and Pravastatin could induce gelatinases activity, in an *in vitro* approach, we have studied MMP2 and 9 expression in lung fibroblast after different irradiation and Pravastatin doses.

Materials and Methods: Involvement of Rho/ROCK pathway and fibrolytic action exert by Rho/ROCK inhibitors,via MMPs altered expression, was investigated by histology and immunohistochemistry in: a model of rats delayed radiation-induced enteropathy treated with pravastatin in both mitigating and curative approaches;a model of pulmonary fibrosis in mice C57BL6 by IP injection of bleomycin and thorax irradiation (19Gy) treated with pravastatin, simvastatin and Y-27632; and by zymography on primary cultures of lung fibroblasts irradiated and incubated with Pravastatin.

Results: Fibrotic lesions observed in the intestine were improved by Pravastatin prophylactic and curative administration. In the animals preventively treated with pravastatin an increased expression of MMP2/TIMP2 was observed after-IR, suggesting a sustained and delayed activation of fibrolysis. In rats curatively treated with pravastatin, the expression of MMP2/TIMP2 at late time point was not observed,suggesting that pravastatin fibrolytic action is actived only in a mitigating approach. In lungs, in a curative approach, study of MMP2/TIMP2 expression show an increased staining at 15 weeks after IR. Also in this model, Pravastatin exert fibrolytic action but this activation is limited at the first phases after treatment. Modulation of gelatinases activity was investigated by zymography in cellular lysed and culture conditioned medium after irradiation and Pravastatin exposure: both irradiation and Pravastatin seem to be induce gelatinases activity.

Conclusions: Our results support the hypothesis that Rho/ROCK cascade is a signalling pathway essential for control and maintenance of fibrosis. The antifibrotic action of Rho/ROCK pharmacological inhibitors trigger a different fibrolytic action in preventively and curatively administration.

C021

INHIBITION OF THE MET ONCOGENE SENSITIZES TUMOR CELLS TO RADIOTHERAPY

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Backgrounds: Radiotherapy (RT) is successfully employed to loco regionally treat primary cancer. Recent experiments have indicated that RT promote positive selection of the "cancer stem cell" subpopulation, which is intrinsically radioresistant, thus proposing an attractive mechanistic explanation for radiation-induced tumor progression. After RT, a few radioresistant cancer cells can survive, and cause disease relapse with metastatic progression. The MET oncogene is a prominent regulator of "invasive growth", a regenerative and pro-survival program unduly activated in cancer metastasis.

Methods: *In vitro*, RT upregulates MET expression through a molecular pathway involving the DNA-damage sensor ATM and transcription factor NF- B. We reasoned that MET upregulation could prevent cell death induced by RT, and that Met inhibition could increase the efficacy of radiotherapy. In human tumor cell lines culture (eg, glioblastoma) in the presence of Met inhibitor and in non permissive conditions for cell proliferation, we reduced viability of irradiated cells by more than 50%, 48 hr after exposure to RT (10 Gy). To define whether Met inhibition radiosensitizes tumor cells *in vivo*, we xenotransplanted cells in immunocompromised mice.

Results: Combination with the Met inhibitor induced significant tumor regression and enhanced the efficacy of RT to stop the growth of or to induce the regression of xenografts (P=.01). The Met inhibitor could also convert an ineffective low-dose RT protocol into a very effective treatment, capable of reducing tumor volume by an average 75%. Analysis of tumor sections at day 2, 4 and 6 after RT showed that the number of apoptotic cells was significantly increased in tumors undergoing combined therapy. These results indicate that inhibition of Met activity sensitizes cells to RT *in vitro* and *in vivo*, likely by decreasing resistance to RT-induced apoptosis and by reducing the ability to resume proliferation after treatment.

Conclusions: MET is expressed in the stem/progenitor compartment of several normal tissues and is also expressed in cancer stem cells, which often derive from direct transformation of normal stem cells or proliferating progenitors. Met overexpression and activation boosted by RT could contribute to cancer (stem) cell radioresistance and invasive ability, thus increasing the chance of their positive selection and dissemination. Drugs targeting MET increase tumor cell radiosensitivity and prevent radiation-induced invasiveness, so we should soon be ready to start a phase I study.

C022

ROLE OF NEOADJUVANT RADIOTHERAPY IN THE TREATMENT OF SOFT TISSUE SARCOMAS: RETROSPECTIVE EXPERIENCE BY RADIATION ONCOLOGY UNIT OF FLORENCE

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Purpose: The aim of this study is to evaluate disease free survival (DFS), overall survival (OS) and toxicity of patients who underwent preoperative therapy for soft tissue sarcoma.

Materials and Methods: Data of 38 consecutive patients affected by soft tissue sarcoma were retrospectively analyzed. Six (15.8%) patients were treated only

with neoadjuvant radiotherapy (NRT), thirty-two (84.2%) with neoadjuvant chemo-radiation therapy (NCRT). Surgery was performed within 4-6 weeks after the completion of neoadjuvant treatment.

Results: Median follow up was 4.9 years (range: 1-13.7 years). All patients received preoperative external beam radiotherapy. The most part of patients (84.2%) underwent a neoadjuvant chemotherapy treatment associated with radiotherapy. After neoadjuvant treatment the majority of patients underwent wide excision (32 out of 38) and 5 patients had a marginal surgery, only one patient underwent amputation. Local recurrence was observed only in 2 patients (5.2%). 14 (36.8 %) patients experienced metastatic relapse. At the time of our analysis 13 patients (34.2%) were dead due to metastatic spread of the disease. In our series disease free survival (DFS) in relation to distant metastases (DM) showed a significant result for lower limbs involvement (p=0.038) and marginal excision (p=0.024) predicted a worst DFS, histology resulted statistically significant but it was not evaluable the risk for specific histology due to the low number of events in the different subtypes.

Conclusions: Results obtained from our study are encouraging about the feasibility and efficacy of preoperative RT considering results in terms of local control, limbs sparing and safety.

C023

ADJUVANT TREATMENT OF SOFT TISSUE SARCOMA: UNIVERSITY OF FLORENCE EXPERIENCE

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Purpose: The aim of this study is to evaluate disease free survival (DFS), overall survival (OS) and toxicity of patients who underwent adjuvant radiotherapy for soft tissue sarcoma.

Materials and Methods: Data of 255 consecutive patients affected by soft tissue sarcoma were retrospectively analyzed. All patients underwent surgery and had histological confirm of soft tissue sarcoma. 195 (76.5%) patients were treated only with radiotherapy (RT), 60 (23.5%) with adjuvant chemo-radiation therapy (CRT).

Results: Median follow up was 3.6 years (range: 1-20 years). All patients underwent surgery, the surgical approach was of wide excision (47.4%) in most cases. The most representative histological types were liposarcoma (23.1%), leyomiosarcoma (12.5%) and fibrosarcoma (10.6%). Eighty (31.4%) patients received a brachytherapy treatment associated to external beam radiotherapy, ten (3.9%) received exclusive brachytherapy. Radiotherapy was well tolerated, no radiotherapy interruption was recorded. Sixteen(6.3%) patients experienced edema of the limbs with reduction of the functionality and only 9 (3.5%) patients had a grade 3 skin toxicity. Sixty patients (23.5%) underwent an adjuvant chemotherapy treatment associated to radiotherapy. Chemotherapy consisted of Epirubicine (60 mg/m2 e.v. days 1,2) and Ifosfamide (1800 mg/m2 e.v. 1-5 days) every 28 days. Local recurrence was observed only in 104 patients (41%). 91 (36 %) patients experienced metastatic relapse. At the time of our analysis 26 patients (10.2%) were dead due to metastatic spread of disease and 219 (85.9%) patients were alive. At statistical analysis local disease free survival (LDFS) and distant disease free survival (DDFS) at 5 years were 59% and 64% respectively.

Conclusions: Results obtained from our study are encouraging about the efficacy of postoperative RT considering results in terms of local control, overall survival and good toxicity profile.

C024

MULTIMODALE TRATMENT OF SOFT TISSUE SARCOMA OF LIMBS: THE ROLE OF HIGH DOSE RATE BRACHYTHERAPY

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Aims: The purpose of this study is to evaluate the feasibility, methods, advantages and limits of use high dose rate brachytherapy associated to external radiotherapy in soft tissue sarcomas of limbs, presenting results of our experience. Indications to perform the brachytherapy were: - margins positive or however uncertain - possible contamination of the surgical field - deep location makes it difficult to follow-up. - the presence of a recurrence in a site previously treated with external beam radiation therapy.

Patients and Methods: From 2003 to the present, on a total population of 68 cases of patients with soft tissue sarcoma of the limbs, 12 patients were treated with wide or marginal surgical excision and adjuvant treatment with high dose interstitial brachytherapy (HDR) followed by external beam radiation therapy. The series that we analyzed consists of 12 patients aged between 83 and 30 years, with a mean age of 54,91 years, including 6 men and 6 women, with a M: F 1:1. The treated sarcomas were located in the deep in the lower limbs, including one in the gluteal region (8.33%) and all others in different regions of the thigh (91.67 %). All lesions treated were large (>5 cm), of which 9 of 12 (75%) exceeded 10 cm at diagnosis with a range of values from 5.5 cm to 44 cm in maximum diameter. Hystotypes were: high grade Malignant Fibrous Histiocytoma (4 cases); Solitary Fibrous Tumor (2); Leiomyosarcoma, (2) one high and one low grade; Dedifferentiated Liposarcoma (1); Myxoid Liposarcoma (1); low-grade Mixofibrosarcoma (2). Extensive or marginal surgical excision were performed in all cases. All patients underwent high-dose interstitial brachytherapy (HDR) with floodlight charges "remote after-loading". The carries were not loaded before the fifth postoperative day in order to reduce the risk of problems of scar and to minimize any hematoma that could dislodge the carries. A total of three patients received adjuvant chemotherapy after the end of EBRT and one patient received neoadjuvant chemotherapy.

Results: Mean follow-up period was of 61 months, (range from 9 to 109 months). No patients death. In the cases examined we had two cases of lung metastases, one had metastatic disease at diagnosis. Three cases (25%) had local recurrence of disease: hystotype was malignant fibrous histiocytoma pleomorphic high-grade, size at diagnosis >10 cm, deep with staging IIB (in two cases) and IIIB. In the series analyzed there were 3 cases (25%) of local hematoma, of these only required surgical drainage. Two cases of local infections were reported: one case of post-actinic abscess drained surgically about 3 months after the excision, without sequelae, and the other was an infection with Gram-negative bacteria treated with medication and antibiotic therapy. No signs or symptoms of toxicity or nerve, neither vascular injury occurred in our series.

Conclusions: Although the literature brachytherapy is indicated for high-grade lesions, we believe that such treatment, being saddled with a low rate of major complications, also on neurovascular bundle, almost identical to those of the surgery or other adjuvant treatments, may also be indicated in low-grade lesions that, for large size or proximity to neurovascular structures, are difficult to be resected with wide margins.

C025

PREOPERATIVE CHEMO-RADIATION THERAPY FOR LOCALIZED RETROPERITONEAL SOFT TISSUE SARCOMA (STS): A PHASE II STUDY FROM THE ITALIAN SARCOMA GROUP

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Backgrounds: Retroperitoneal sarcomas are rare tumors accounting for only 1%-2% of all solid malignancies. Of all sarcomas, the majority occur outside of the retroperitoneum. Only 10%-20% of sarcomas are retroperitoneal sarcomas, and the overall incidence is 0.3%-0.4% per 100000 of the population. The peak incidence is in the 5th decade of life, although they can occur in any age group. Despite 'complete' resections, 5- and 10-year survival rates are poor, being 51% and 36% respectively. Local recurrence after complete surgical resection represents the leading cause of death in retroperitoneal soft tissue sarcoma (RSTS). Radiation therapy (RT) is widely used in STS of the extremities, but is problematic post-operatively in RSTS. High dose long-infusion Ifosfamide (HLI) as a single agent is known to be active in advanced sarcoma and may be a radiosensitizer. We then decided to study the feasibility, safety and activity of the combination of HLI and RT as preoperative treatment for resectable localized RSTS.

Methods: Patients received 3 cycles of HLI (14 g/m2), given as a continuous infusion in 14 days. RT was started in combination with the onset of the 2nd cycle and administered up to a total dose of 50.4 Gy in 28 fractions, using 3DCRT, IMRT and Arc-therapy (Rapidarc). Response rate was evaluated by RECIST at the time of surgery. Surgery was scheduled 4-6 weeks after the end of RT. An intraoperative boost (IORT) was allowed when clinically indicated. 3-yr local relapse-free survival (LRFS), distant recurrence-free survival (DRFS) and overall survival (OS) were calculated from the time of surgery.

Results: Between December 2003 and December 2010, 86 patients were recruited. 2 patients were ineligible following central pathological review. The overall preoperative treatment plan was completed in 61 patients. CT was completed in 65 patients, while RT in 74 patients. A partial response was obtained in 7 patients, while stable disease was observed in 62. One patient had systemic progression during preoperative therapy and was not operated. 79 patients underwent surgery (macroscopically complete in 70). IORT was delivered in 15 patients (median dose 12,0 Gy). At a median follow-up of 1.8 years (IQ range=0.6-3.7), 3-yr LRFS, DRFS and OS were 66%, 79% and 80%, respectively.

Conclusions: The combination of preoperative HLI and RT was feasible in two thirds of patients, while preoperative RT could be completed in most (74/84). Though a systemic coverage can be added to RT when this is felt to be appropriate in clinical practice, a Phase III trial should preferably explore the role of RT alone. Potential advantages for preoperative RT are: 45-50 Gy is expected to inactivate a large percentage of tumour cells as well as to minimise the risk of tumour implantation during surgery (peritoneal sarcomatosis); possible reductions in tumour size as well as thickening of the pseudocapsula may allow complete surgical resection (increase in resection rate) and large tumours will usually displace the adjacent uninvolved abdominal viscera (decreased risk of complications)

C026

NOVEL TECHNOLOGIES IMPROVE ACCURACY IN HIGH DOSE RATE BRACHYTHERAPY IN CHILDHOOD SOFT TISSUE SARCOMAS

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There is a strong incentive in minimizing radiation dose and volume in children because their high likelihood of survival and great impact of side effects. Because brachytherapy (BT) tends to be a substitute for radiation therapy (EBRT), the specter of EBRT side effects has no specific bearing on its use, while most will contend side effects can be reduced with BT because of enhanced conformity of the highest doses. From June 1998 till December 2012, 43 children, 17 males and 26 females (median age 7 years, range 3-17) with soft tissue sarcoma, underwent BT at the IOV-IRCCS of Padua.

Histology showed: Embryonal RMS 19; Alveolar RMS 11; Nos-RMS 2; PNET 8; LMS 2, Myoepithelial Carcinoma 1. Primary sites were: limbs 17; vagina 11; head and neck 10; pelvis 4, trunk 1. All were treated at diagnosis, except 2 at relapse, after evaluation by post contrast T1 with fat saturation and T2 sequences MRI. A cutaneous localizer has been used for small superficial lesions and in front of scars on limbs. Occasionally a 3 mm reconstruction slice post contrast CT scan was done to exclude subtle bone involvement. Thirty nine patients received only BT, while 4 had BT as boost. Doses ranged from 15 to 42 Gy, but 32 patients had a treatment up to 36 Gy in 12 fractions, in 8 days, 2 times daily, with 2 day split after 6 applications. CT has supplanted orthogonal films in planning. The accrued axial CT images and reconstructed sagittal and coronal images made applicator identification easier. Target volumes have been modeled using contouring. MRI has been used to delineate differences in soft tissues not readily seen on CT scan. Nineteen children had treatment under general anesthesia. At a median follow up of 7 years (range 6 m-14 y), 2 patients had local relapse in the treatment field, 2 had metastatic progression and 1 developed a second tumor: all relapsed children dead of disease. Thirty eight children are alive in first complete remission. Regarding late effects, 1 girl presented hematocolpos at menarche and 2 children presented esthetically unacceptable scars on their arm, very well corrected by plastic surgery. Delivery of limited margin RT using HDR-brachytherapy provides a high rate of local tumor control without marginal failure. A close radiological preoperative staging and the use of CT and MRI in planning may allow to limit the extent of the implant. Further follow-up is required to determine whether normal tissue effects are minimized using this approach.

C027

VMAT BASED SBRT WITH FLATTENING FILTER FREE(FFF) BEAMS FOR ISOLATED ABDOMINAL/PELVIC LYMPH NODES: REPORT OF TECHNICAL AND CLINICAL FEASIBILITY IN THE FIRST 33 IN OLIGOMETASTATIC PATIENTS

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Objectives: Radiotherapy can play a role to achieve local control of oligometastatic focal disease. Here we reported data on technical feasibility and acute toxicity of SBRT with FFF beams in isolated lymph node oligometastatic patients.

Materials and Methods: Between 10/2010 and 3/2012, a total of 33 patients were treated with SBRT and FFF beams for isolated lymph node metastases in abdomen. The inclusion criteria were the presence of isolated or few lymph nodes(maximum of 3) in the same lymph node region, in absence of other active sites of cancer disease. Prescription doses was 45 Gy in 6 consecutive fractions. CT scans for planning were acquired for all patients positioned supine immobilized by means of a thermoplastic body mask. In all FFF cases 6 and 10 MV beam energy were used. Clinical evaluations were planned on first day of treatment, before SBRT-FFF session (visit 0); visit 1 during the the treatment; visit 2 at the end of the last fraction; visit 3 within 60-90 days from the end of thetreatment. Unscheduled visits were performed if necessary or asked by the patients. Acute radiation induced toxicities were scored according to CTCAE version 3.0. Although obviously very early, a first assessment of initial treatment outcome, was performed at first and second follow up visits and will be reported in terms of local response rate(PERCIST CRITERIA).

Results: All 33 FFF SBRT patients completed the treatment, as programmed. The median follow-up was 8 months for all patients(3-20). Five cases of nausea G1 and only one diarrhea G2 were recorded in acute setting.No late toxicity was found. In 24/ 33, early clinical outcome was assessable with diagnostic evaluation with PET and/or CT: at last control complete response was achieved in 11/24 patients, partial response was in 8/24, and in 5/24 disease remained stable. Progression in irradiated area was not found in all 24 irradiated lesions, while progression outside the treated region was documented in 7 of 24 evaluated patients.

Conclusions: The end pont of the study was to assess the technical and clinical feasibility of SBRT with FFF, and this finding was largely confirmed: all plan objectives were met and no toxicity were recorded in acute setting. Longer follow up is needed for definitive assessing.

C028

CLINICAL OUTCOME OF STEREOTACTIC RADIOTHERAPY FOR ABDOMINAL LYMPH NODE TARGETS IN OLIGO-METASTATIC PATIENTS

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Purpose: Several reports have shown that stereotactic body radiotherapy (SBRT) may play a major role to improve local control and clinical outcome in a significant subset of patients with either organ-confined primary tumors or oligo-metastatic disease. When ablative doses of RT have been delivered, high rates of local control have been reached in the treatment of metastases to the liver, adrenal gland, lung, brain and bone. Apart from hepatic primary and secondary lesions, the potential of SBRT for abdominal lymph node metastases is still to be fully investigated, although early reports have demonstrated its feasibility and efficacy. We report our preliminary experience on SBRT in oligometastatic patients (max 5 sites) with abdominal or pelvic lymph node lesions arising from gastrointestinal or genito-urinary tumors.

Materials and Methods: Between April 2011 and April 2012, 25 consecutive patients with a total of 31 lesions

were treated with SBRT. Treatment was delivered with an Elekta Synergy linear accelerator or with Cyberkinfe robotic radiotherapy. The dose was prescribed to the 70-80% isodose line to encompass the PTV; the prescribed doses ranged from 24 to 36 Gy in fractions from 1 to 5. Acute and late toxicity were evaluated according to RTOG and EORTC-RTOG scale respectively. Late toxicity was evaluated according to scale. Local response to treatment was scored as complete response, partial response, stable disease, or failure on the basis of imaging/metabolic evaluation no prior than 2 months after treatment(RECIST criteria). Median follow-up was 5 months.

Results: Of the 31 lymph node lesions treated, 18 (58.1%) were abdominal and 13 (41,9%) were pelvic. Of the 25 patients enrolled,distribution by histology was as follows: 12 prostate (48%), 7 ovary (28%), 2 endometrium (8%), 2 bladder (8%), 2 colorectal (8%). The 6-months actuarial rate of freedom from local progression for all treated lesions was 66%. Complete responses occurred in 8 of 23 lesions (34%). Eight patients (34%) showed progressive local and/or distant disease at follow-up. Treatment was very well tolerated: no>G2 adverse acute and late events were observed so far.

Conclusions: Our preliminary results support the use of high dose stereotactic radiotherapy as an effective and safe strategy for lymph node abdominal and pelvic lesions in selected, oligometastatic patients. Improved local control might result in better oncologic outcome, delay the need of further systemic therapies and preserve quality of life. Longer follow-up is needed to further assess the impact of SBRT on outcome and to monitor late toxicity. Prospective studies are required to better define the role of SBRT in the context of abdominal oligometastatic patients.

C029

WHOLE BRAIN IRRADIATION WITH SIMULTANEOUS INTEGRATED BOOST AND HIPPOCAMPAL SPARING FOR SELECTED PATIENTS WITH BRAIN METASTASES: OUR EXPERIENCE WITH TOMOTHERAPY

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Purpose: Several authors have reported the technical feasibility of whole brain radiotherapy and simultaneous integrated boost (SIB) to obtain homogeneous whole brain dose distribution, hippocampal sparing and radiosurgically-equivalent dose distributions to individual intracranial lesions (1-2). We report our clinical experience in treating selected patients with this technique.

Patients and Methods: We retrospectively reviewed seven patients submitted to whole brain irradiation with a total dose of 32.25 Gy in 15 fractions (2.15 Gy per fraction) and to a simultaneous integrated boost with a total dose of 63 Gy (4.2 Gy per fraction) to individual brain lesions. All patients had 1-4 brain metastases but a good Performance Status. Treatment was carried out using helical tomotherapy. CT and MRI images were fused together to contour the whole brain and contrast-enhanced lesions. The hippocampus was contoured as a dose-limiting structure.

Results: Between October 2010 and October 2011 seven patients were treated with the above technique and in all we achieved homogeneous whole brain dose distribution. The recorded average dose delivered to the hippocampus was 9.5 Gy. Only one patient reported neurological symptoms at the first check-up 3 months after irradiation. No intracranial progressions were recorded.

Conclusions: Our results show the feasibility and tolerability of whole brain irradiation and SIB with hippocampal sparing. Further studies are needed to evaluate the potential of this treatment for improving cerebral tumor control and preventing neurocognitive dysfunction (1) Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. Gutiérrez AN, Mehta MP et al. Int J Radiat Oncol Biol Phys. 2007 Oct 1;69(2):589-97. (2) Whole brain radiotherapy with hippocampal avoidance and simultaneous integrated boost for 1-3 brain metastases: a feasibility study using volumetric modulated arc therapy. Hsu Fet al. Int J Radiat Oncol Biol Phys. 2010 Apr;76(5):1480-5.

C030

RADIOTHERAPY IN PAINFUL BONE METASTASES: CORRELATION BETWEEN FUNCTIONAL MAGNETIC RESONANCE AND VISUAL ANALOGIC PAIN SCORE

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Purpose: To investigate the response to EBRT treatment of painful bone metastases by using diffusion-weighted magnetic resonance imaging with apparent diffusion coefficient (ADC) correlated to variations of Visual Analogic Pain Score (VAS).

Materials and Method: 18 patients (median age 63,8) with painful bone metastases were enrolled in single arm study. Pain palliation was evaluated by Visual Analogic Pain Score (VAS) before the treatment and during the follow up (1 and 3 months). All patients underwent MRI pre-treatment and in the follow-up(1 and 3 months). MRI protocol included DWI sequences and ADC maps were obtained.

Results: Statistically significant difference between baseline and follow up VAS value was noted. ADC coefficient increased after treatment. Progressive decrease of VAS value was correlated with an increase of ADC value.

Conclusions: Radiotherapy was the first line therapy in painful bone metastases.The functional MRI may be able to a predictor of palliative response to radiotherapy.

C031

STEREOTACTIC BODY RADIATION THERAPY FOR LUNG LESIONS IN OLIGOMETASTATIC PATIENTS

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Purpose: Hypofractionated stereotactic body radiotherapy (SBRT) is an emerging non invasive technique for the treatment of oligometastatic cancer. The aim of this study is to evaluate the efficacy and tolerability of SBRT for the treatment of lung lesions in oligometastatic patients.

Materials and Methods: Patients with lung detectable metastases were treated with SBRT at our institution. For each lesion, the primary cancer sites, tumor histololgy, site of metastasis, gross tumor volume and prescribed dose were described. SBRT doses ranged from 36 to 40 Gy in three or four fractions, with a median BED of 79,2 Gy at PTV margin. Adverse events were recorded according to the NCI Common Toxicity Criteria 3.0 scale. Acute toxicity was evaluated 45 days after the end of radiotherapy by CT torax scan. Clinical response was valuate 3 months after the end of radiotherapy with CT and thereafter with 18FDG PET/CT.

Results: Between December 2006 and December 2011, 34 patients with 42 lung metastases were treated at our institution. The number of targets treated for patients ranged from one to four. The primary involved organs were lung (n= 19), colorectum (n=12), breast (n= 5), parotid gland (n=4), kidney (n=1) and thymus (n=1). Treatment was well tolerated. Grade 1 pulmonary toxicity occurred in 11 cases (26,1%); grade 2 of pulmonary toxicity were observed in one case (2,3%). No grade 3-4 toxicity was recorded. According to RECIST and EORTC criteria (for CT and PET/CT respectively), local complete response was achieved in 18 lesions (42,8 %), partial response was observed in 16 lesions (38%), and in 6 cases (14,2%) stable desease. Local progression occurred in 2 cases (4,7%). Metastases from lung cancer reported a poorer LC with a 26,3% of complete local response, while lesions from breast cancer were better controlled, with a 100% of complete local response. Median follow-up was 45,5 months (range 8,9 to 74,6 months). Actuarial local control at one and three years after SBRT was 95,7% and 87% respectively. The 1-, 2- and 3-year overall survival rates were 90%, 77% and 57% respectively, with a median survival time of 58 months.

Conclusions: Stereotactic body radiotherapy can be considerated an effective treatment of pulmonary oligometastases with high local control rates. This treatment is well tolerated with a very low toxicity profile.

C032

CLINICAL OUTCOMES AND NEUROCOGNITIVE FUNCTION IN OLDER PATIENTS WITH BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY

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Purpose: To evaluate the clinical outcomes and neurocognitive function of stereotactic radiosurgery as initial treatment for brain metastases in patients of 65 years and older.

Materials and Methods: Between April 2008 and June 2011, 144 patients of 65 years and older with 1 to 4 metastases were enrolled in this prospective study. The primary end point of the study was overall survival. Secondary end points were local and intracranial control, cause of death, toxicity of treatment, and neurocognitive function.

Results: At a median clinical follow-up of 8.7 months (range 1-42 months) median survival and brain control rates were 12.8 and 10 months, respectively. The 1-year and 2-year survival rates were 58% and 31%, and respective brain control rates were 50% and 22%. Sixty-four (80%) patients succumbed to their extracranial disease and 16 (20%) patients died of progressive intracranial disease. Eleven patients recurred locally after SRS. The 1-year and 2-year local control rates were 92% and 81%, respectively. Neurological complications were recorded in 17 (12%) patients, being severe (RTOG Grade 3 and 4) in 7 (5%) patients and requiring surgery or medical treatment. Evaluation of neurocognitive function using the Mini-Mental State Examination (MMSE) showed no significant neurocognitive decline after SRS. MMSE score improved in 27% and deteriorated in 15% of patients, mainly caused by intracranial progression.

Conclusions: Initial treatment with SRS with close monitoring may represent a safe treatment strategy associated with survival benefit and preservation of neurocognitive function in older patients with newly diagnosed brain metastases.

C033

A NATIONAL-BASED PROGRAM ON PALLIATIVE RADIOTHERAPY IN END OF LIFE PATIENTS: CARE MODEL AND SPECIFIC SOFTWARE

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Purpose: Painful bone metastasis is the most common reason for the delivery of palliative Radiotherapy (RT)

that provides successful palliation of painful bone metastasis and has been associated with very few side effects. However, it is currently underused in patient care because logistical, economical and cultural aspects delay the access to treatment. This work describes the experience of our Institution in the implementation of a National-based Program on cancer palliative care, called "Relief Net", for the connection and integration of different care settings to guarantee the multidisciplinary care continuity and to facilitate the access to palliative single-fraction radiotherapy in end of life patients.

Materials and Methods: The National Net among patients, care settings (Primary care, Home care, Hospice) and the Radiation Oncology Departments was realized following a specific road map. In the first step, a multidisciplinary working group has analyzed the possible paths of care for symptomatic patients and studied the possible tools for clinical evaluation; a National Governance was realized after the identification of the referral for each italian region. In the second step, the project was introduced in each regional assistance program thanks to the communication with policy makers and we created an "e-infrastructure", called S.P.I.N. (Software for Palliative Italian Network), to store, manage and share patients' clinical information in the multidisciplinary setting. Programmers specialized in medical software have identified the tools and methods of storage, management and sharing of clinical information.

Results: From January 2012 we started the implementation phase of the project. The first report, from January to May 2012, was analyzed, in terms of accrual and epidemiology. Sixty-four Italian Centers applied the software, and data from 554 patients were stored. Fifty-two percent of patients are male, 65% are older than 60 years. Twenty-eight percent of patients have bone metastases from breast cancer, 24% from lung and 48% from other sites.

Conclusions: Our Project is feasible and it is in progress in the implementation phase. From the second year also clinical outcome data will be available. The systematic evaluation and monitoring the effectiveness of the palliative single fraction radiotherapy in the control of symptoms will support the development of methodology for research in this specific field. Since it is a Population-based Program, it can be a source for research also at the international level.

C034

TREATMENT OF BRAIN METASTASES WITH CYBERKNIFE RADIOSURGERY. OUR EXPERIENCE

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Introduction: To evaluate efficacy and feasibility of stereotactic radiosurgery with Cyberknife in the treatment of the metastatic brain lesions, in association or not with whole brain radiotherapy (WBRT).

Methods: From July 2007 to October 2009 we have treated 102 patients and a total of 143 lesions. 25/102 patients (25%) were in RPA class 1, 58/102 patients (56%) in RPA class 2 and 19/102 patients (19%) in RPA class 3. Twenty six patients were affected of extracranial disease, 20 patients had already been treated with WBRT, 5 patients had already been treated with both WBRT and temozolomide. 9/102 patients were scheduled for a WBRT after 30 days of the stereotactic radiosurgery. Median volume of the lesions was 1.9 cc (range 0.06-22.9 cc), the median dose delivered was 20 Gy, in single dose, (range 11-24 Gy) prescripted to 80% isodose line (range 60-90%). The patients were immobilized with a thermoplastic mask (Orfit). Treatment planning was based on TC imaging and contrast-enhanced MRI that had been coregistered from the TPS (Multiplan). CTV was considered to be identical to GTV plus an isometric margin of 2 mm that was defined as the contrast - enhanced lesion on the MRI imaging. Follow up examinations were carried out 2, 6 and 12 months after RS and, following, every year.

Results: The follow-up periods ranged from 1 to 50 months. 15/102 patients were lost to follow up, therefore we have evaluated 87 patients. The overall survival was 63% and 55% at 1 and 2 years respectively. In regard to the RPA class the mean survival was 14, 7.6 and 4.8 months for RPA class 1, 2 and 3 respectively. 80% of the patients treated with SRS only were alive at 40 months *versus* 43% of the patients treated with SRS plus WBRT, 20% of them treated with WBRT plus SRS and temozolomide and 19% of the patients treated with WBRT and temozolomide. In regard to the size of the lesions at 50 months 78% of the patients alive had been lesions ≤2.5 cm *versus* 43% of the patients with lesions >2.5 cm. We have observed early and late neurological effects in 15/87 patients (emiparesis, headache and seizures), in all cases the lesions were located in eloquent brain. All symptoms were well controlled with corticosteroid therapy.

Conclusions: Our study confirms the efficacy and feasibility of the Cyberknife stereotactic radiosurgery in the treatment of the brain metastases. The best results were obtained with patients in RPA class 1, with size of the lesions ≤2.5 cm and in patients without or controlled extracranial disease. Furthermore, the preliminary data of this study suggest that SRS without WBRT is the best modality of treatment for oligometatstic patients.

C035

FEASIBILITY OF IN-FIELD AND OUT-FIELD LUNG REIRRADIATION WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT): OUR EXPERIENCE

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Purpose: To asses feasibility to reirradiate the same lung with SBRT after prior SBRT for primary non-small cell lung cancer (NSCLC) or lung metastases.

Materials and Methods: We reviewed 11 patients (pts) reirradiated with SBRT on 17 lung lesions (LL) for in- or out-field relapse. Male/female ratio was 9/2, median age 66 y (range,40-71). Pre-treatment KPS ranged from 90 to

100 (median 100). First SBRT was done in 3 pts with local recurrence of primary NSCLC and in 8 pts with lung metastases from NSCLC, colon-rectal cancer and sarcoma (5,2 and 1 pts, respectively). Reirradiation was administered on metastases in the same lung for out-field, in-field or both in- and out-field relapse in 5, 4 and 2 pts, respectively. 8 pts received reirradiation of only one LL, remaining three received a second, third and forth reirradiation. Relapse was defined in-field when more than 95% of the recurrence volume was within the original 50% isodose, and out-field in the other cases.

Results: Median follow-up was 20 months (range, 9-82). Dose prescribed at first course of SBRT was 5x 10Gy (6 pts) for peripheral LL and 5x 8Gy for central ones (5 pts). Reirradiation doses were 5x 8Gy in 6(35%), 5x 10Gy in 4(23%), 5x 6Gy in 3(18%), 5x 5Gy in 3(18%) and 5x 4Gy in 1(6%) pts. Median number of retreated LL were 2 (range, 2-4), 10 central and 7 peripheral, respectively. The PTV ranged from 9 to 55 cc (median 17). Reirradiations, performed at least 6 months (median 22) after previous SBRT, were always well tolerated. No acute grade II-III toxicities were observed. One patient with out-field relapse receiving reirradiation for two LL developed an asymptomatic pneumonia. Two pts receiving 3 and 4 reirradiations for in and out-field relapses reported thoracic pain and two pts, retreated on the same central LL, had mild dyspnoea and mild dysphagia, respectively. One patient, treated with 5x 10Gy SBRT for a peripheral metastases and retreated with 5x 8Gy SBRT for an in-field-relapse, had a lib fracture 13 months after reirradiation. Local control was obtained in 100% of the LL with the following response rates: CR in 7(41%), PR in 2(12%) and SD in 8(47%) LL. All but one pts are alive. No grade II-III iatrogenic late toxicity was registered.

Conclusions: Reirradiation with SBRT was feasible and well tolerated with a high local control rate. This satisfying results could be related to an accurate patient selection and appropriate interval between prior SBRT and reirradiation.

C036

SINGLE-FRACTION STEREOTACTIC ABLATIVE RADIATIONTHERAPY FOR 1-3 LUNG METASTASES: EXPERIENCE AT UNIVERSITY OF TORINO

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Purpose: Hypofractionated stereotactic ablative radiotherapy (SABR) is a noninvasive technique for treating a limited number of lung metastases from a known primary cancer. Purpose of this study is to evaluate efficacy and tolerability of a single-fraction SABR in a cohort of patients affected by one to three lung metastases treated at our Institution.

Materials and Methods: A total of 67 patients with lung metastases from August 2003 to February 2012 were included in the study, for a total of 90 lesions: single in 46 patients, 2 in 19 patients and 3 in 2 patients. Primary tumor was NSCLC in 25/67 patients (37.3%), colorectal cancer in 27/67 patients (40.3%) and a variety of other origins in 15 patients (22.4%). Median disease-free interval (from diagnosis of primary tumor to SABR for lung metastases) was 26 months. Seventeen patients had other sites of disease, thoracic or extrathoracic. Seventeen patients received previous chemotherapy for metastatic disease. All patients received either 26 Gy to 80% isodose or 30 Gy to 95%, with 3D conformal or Volumetric Modulated Arc Therapy. Acute and cronic toxicities were evaluated with RTOG scale; treatment response was assessed by total-body CT and evaluated with RECIST criteria.

Results: With a median follow up of 24 months, local relapse, nodal relapse and systemic failure were 14.4%, 11.9% and 55.2%, respectively. Cancer-Specific Survival (CSS) rates at 1 and 2 years were 90% and 76%, respectively, while Progression-Free Survival (PFS) rates were 72% and 55.4%, respectively. At univariate analysis (UV), patients with disease free interval longer than 24 months had better CSS (p= 0.04). Systemic chemotherapy combined with SABR had a positive impact on PFS at UV (p= 0.02), while receiving other local therapies prior to SABR had a detrimental effect at UV (p=0.006) and also at multivariate analysis (OR 7.8). No statistically significant differences were observed forother factors such as age, number of metastases, histology and GTV volume. Toxicity profile was good for majority of patients, with only 7 cases of grade 1 radiation pneumonitis and 8 case of grade 2-3 late toxicity.

Conclusions: This experience shows that single-fraction SABR is a safe and effective procedure to control one to three lung metastases, with good loco-regional and systemic control rates, comparable to fractionated SBRT. Especially when combined with systemic chemotherapy, SABR is able to obtain very interesting PFS and CSS rates.

C037

CERVICAL LYMPH NODE METASTASES FROM OCCULT PRIMARY TUMOR. THE OUTCOME IN 90 PATIENTS AFTER COMBINED-MODALITY THERAPY

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Aims: The aim of this study was to analyze the results of treatment of patients with cervical lymph node metastases from occult primary tumor.

Materials and Methods: A retrospective review of 90 patients treated with combined surgery and postoperative radiotherapy was conducted. The median time between

surgery and radiotherapy was 34 days. For all patients the Planning Target Volume included the primary site of disease (oropharynx, larynx, hypopharynx) and bilateral neck. The median dose delivered was 50 Gy in 25 fractions. Eighty-six patients received an electron beam boost to the involved nodes up to a dose of 66 Gy in the presence of ECE (extracapsular extension) or 60 Gy in the absence of ECE. The nasopharynx was irradiated only in those cases with lymph nodes metastasis in Ib and V level or undifferentiated histotypes; likewise, the oral cavity was irradiated only in patients with submandibular lymph nodes disease.

Results: Nodal control was achieved in 72 patients (80.0%). In multivariate analysis the nodal control rate was negatively associated with the involvement of levels IV and V. The 5 years actuarial rate of neck disease control and developing head and neck primary tumors was 68,8% and 9,9% respectively, while the rate of developing distant metastases was 19.1%. In multivariate analysis, a statistically significant difference in the rate of distant metastases and in disease-specific survival was obtained when patients were stratified according to the level of nodal involvement and the presence of ECE. Actuarial disease-specific survival at 2 and 5 years was 73.6% and 62.8% respectively.

Conclusions: Despite the increase toxicity patients receiving bilateral neck plus mucosal irradiation had a higher survival rate than those who received ipsilateral irradiation. Lymph node metastatic level and the presence of ECE were the major cause of treatment failure.

C038

MANAGEMENT OF NECK METASTASES FROM AN UNKNOWN PRIMARY: UNIVERSITY OF FLORENCE EXPERIENCE

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Purpose: We retrospectively reviewed the treatment of patients with cervical lymph node metastases of carcinoma of unknown primary site, focusing on toxicity and survival.

Patients and Methods: A total of 70 patients (78,8 % M) with N1-3 stage (N1 14,2%, N2 77%, N3 8,5%), treated between 1988 and 2011 were retrospectively evaluated. Histologically, squamous cell carcinomas were 62,8%, undifferentiated carcinoma were 34,2 % and only 2 cases were neuroendocrine carcinoma.Patients diagnosed as having unknown primary cancer in our practice undergo, with few exceptions, imaging studies and examination under anesthesia with panendoscopy. Patients were examined by 1 or more of 4 different radiologic studies: CT scan (37 patients [52,8%]), MR imaging (11 patients [15,7%]), PET scan (28 patients[40%]), or PET-CT fusion scan (9 patients [12,8%]). Use of PET at our institution began in 2001 and the PET-CT fusion scans became available at our institution in 2008. A total of 42 patients (60%) underwent surgical resection before radiotherapy. Radiochemoterapy was employed in 10 patients out of 70. Radiotherapy of bilateral neck nodes+Waldeyer region was performed in 67 patients (95,7%) and radiotherapy of unilateral lymph nodes in 3 patients with a medium dose of 64,21 Gy.

Reuslts: 50 patients (71,4%) had a complete response to treatment. 8 patients had a local relapse after a medium time of 11,3 months. At the time of analysis, 9 of 70 patients died with confirmed disease: 7 patient developed widespread distant metastasis. The estimated 3- and 5-year overall survival (OS) rates were 71,5 ± 7% and 71,5 ± 7%, respectively. Disease-specific survival (DSS) rate at 3- and 5-years were 76,9 ± 7% and 76.9% ± 7%, respectively. The most commonly reported Grade 3+ acute toxicity was related to mucositis which occurred in 67% of patients. No treatment-related deaths occurred.

Conclusions: Results obtained from our experience, according to the most recent studies, are encouraging about efficacy of RT-CMT association. We reported a 5-year OS and a 5-years disease specific survival rate of 71,5% and 76.9% respectively, which are in line with other series.

C039

DOSIMETRIC ANALYSIS OF PATIENTS WITH HEAD-AND-NECK CANCER OF UNKNOWN PRIMARY ORIGIN TREATED WITH INTENSITY-MODULATED RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST: TOXICITY AND OUTCOME EVALUATION. EXPERIENCE OF THE RADIOTHERAPY OF FLORENCE

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Aims: To analyze survival, failure patterns, and toxicity in patients with head- and-neck carcinoma of unknown primary origin treated with intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB).

Materials and Methods: The medical records of 13 patients with head-and-neck carcinoma of unknown primary origin treated during the period 2007–2012 with IMRT-SIB were reviewed retrospectively. Nodal staging ranged from N1 to N3. Seven patients underwent neck dissection, the other six patients underwent just exeresis of the lymphoadenopathy. All patients were staged using CT, PET was prescribed in 11 patients, while MRI in 4 patients. Doses prescribed to high, intermediate and low risk areas were 70, 60 and 54 Gy respectively in 33 fractions or 66, 60 and 54 Gy in 30 fractions. Eleven patients received also chemotherapy.

Results: with a median follow up of 42.7 months (range 9.1-64.5 months), two patients died for progression of the disease for lung metastases, after 15 and 20 months from the end of the treatment. Two patients experienced locoregional recurrence, after 28 and 35 months from the end of radiotherapy. All other patients remained free of disease until the last follow up visit. The 2 and 4-year actuarial PFS were 83,3% (+/- 0,10) and 54,6% (+/- 0,18) respectively; the 5-year actuarial OS was 90,3% (+/- 0,08). 6 patients experienced some form of G3 acute toxicity during radiotherapy, no G4 toxicity was recor-

ded. Regarding chronic toxicity, no G3-4 toxicity was recorded. Mean dose and V30 to the controlateral parotid gland were 29 Gy and 35,38% respectively. 7 patients experienced mild chronic xerostomia. Mean dose to cochlea was 32 Gy.

Conclusions: IMRT-SIB is a feasible treatment for patients with laterocervical metastases from head-and-neck carcinoma of unknown primary origin, with a good local control and survival. Acute and chronic toxicity of the treatment is acceptable.

C040
SIMULTANEOUS INTEGRATED BOOST IN THE MANAGEMENT OF CERVICAL LYMPH NODES METASTASES FROM UNKNOWN PRIMARY SITE

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Purpose: The aim of this study is to evaluate the outcomes of patients with cervical lymph node metastases of carcinoma from unknown primary site, treated with SIB using Helical Tomotherapy.

Materials and Methods: From February 2009 to January 2012, 5 patients with cervical lymph node metastases from unknown primary site underwent concomitant radiochemotherapy. Excisional biopsy of cervical nodes resulted positive for poorly or not differentiated carcinoma. Involved levels were II – IV and clinically staged as N2a-N2c. MRI, PET and additional biopsies of suspected areas resulted negative for primary lesion detection. Patients were treated by Helical Tomotherapy with Simultaneous Integrated Boost (SIB) technique in 30 fractions. PTV1 (positive cervical nodes), PTV 2 (pharyngeal axis), PTV 3 (negative cervical nodes) were irradiated to a total dose of 66 Gy, 60 Gy, 54 Gy, respectively. Cisplatin 100 mg/m2 was administered every three weeks.

Results: All patients completed the planned radiotherapy, without any interruption due to the treatment toxicity. Median follow up was 24 months (range 4 – 38). No major (≥G3) acute toxicity occurred. Four patients developed G2 acute toxicity (2 cases of dermatitis, 1 of mucositis and 1 of dysphagia). No late toxicity superior than G1 was registered. Complete response on positive cervical nodes was achieved in all patients (100%), in terms of clinical and nuclear/radiological findings. In the course of follow up, no primary tumor was detected.

Conclusions: Simultaneous Integrate Boost by means of HT allows to obtain excellent results in terms of clinical response and tolerance to the treatment; therefore, it can be considered a safe and effective option in this setting.

C041
RE-IRRADIATION OF LOCALLY RECURRENT BREAST CANCER: OUR EXPERIENCE

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Aims: Despite the success of both breast conserving surgery and mastectomy, some women will experience a local-regional recurrence (LRR) of their breast cancer. The aim of our study was to review the institution experience involving irradiation and re-irradiation of the breast, chest wall or lymphatics for locoregional recurrence of breast cancer and report toxicity and clinical outcomes.

Materials and Methods: Between 2004 and 2011, 19 patients were treated for locoregional recurrences of breast cancer. In this group 8 locoregional recurrences were re-irradiated in 6 patients. The mean age was 60, 7 years (range 35-79) and the mean interval between the initial treatment and diagnosis of recurrence was 82 months. The mean total dose of initial radiotherapy was 46 Gy (range 26 – 50 Gy) and the mean dose of re-irradiation was 46, 6 Gy (range 30 – 50 Gy). The second course of radiotherapy was delivered using 3D- conformal radiotherapy in 3 patients with 2 Gy/fraction five times weekly on chest wall and supraclavicular nodes, while other 3 patients were treated using electron beam radiotherapy with 2 Gy/fraction five times weekly on chest wall skin.

Results: The median follow-up from time of completion of re-irradiation was 12 months (range 12 – 96). Local control was achieved in all patients. At time of analysis all patients were alive and one of them had distant metastases. Mean survival since re-irradiation was completion was 38, 4 months. Acute side effects were mild to moderate (skin erythema grade 1 to 2) in all patients with no grade 3 and 4 toxicity. Late skin and soft tissue toxicity manifested as hyperpigmentation and telangiectasia in 4 patients.

Conclusions: Re-irradiation of locoregional recurrence of breast cancer is well tolerated as salvage treatment and provides durable locoregional control.

C042
PROGNOSTIC SIGNIFICANCE OF NODAL RATIO IN NODE POSITIVE BREAST CANCER PATIENTS TREATED WITH CONSERVITIVE SURGERY: A SINGLE INSTITUTION ANALYSIS

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Purpose: data in litterature suggest a prognostic role of

axillary nodal ratio (number of positive nodes/number of excised nodes) for locoregional recurrence and survival. We retrospectively analysed the data of patients treated with radiation therapy after conservative surgery, looking for a correlation between nodal ratio and prognosis

Materials and Methods: we analysed data from clinical records of 699 consecutive patients treated with radiation therapy after conservative surgery and axillary dissection. Patients with clinical supraclavicular or internal mammary nodes were excluded.

Results: Mean age of patients was 54 years, 58% of them were premenopausal. About half of the patienst had right tumors, mainly located in the superoexternal quadrant. T1 lesions accounted for 76% of cases and surgical margins were clear in 96%.84% were ductal carcinomas, in 25% intraductal component was detected. 50% had low grade lesions, in 29% grading was not assessable. 65% had ER positive cancers. All patients had positive axillary nodes. Mean removed nodes were 19, median number of positive nodes was 4. Nodal stage was re-classified following last TNM reccomendations: 73% of patients were N1, 19% were N2. All but 12 patients received adjuvant therapy: 71% of patients received chemotherapy, mainly CMF and 46% hormones. All patients received whole breast irradiation, less than half (47%) also supraclavicular. Less tha 10% of patients were irradiated with Cobalt Unit. During follow-up we identified 33 local recurrences, mainly out quadrant, 16 nodal recurrences, 130 distant metastasis and 39 controlateral breast cancers. A Multivariate analisis on locoregional recurrence, dfs, distant recurrence and survival was obtained. All the relevant prognostic factors were included in the test model as well as nodal ratio as continous or categorical variable with the cut-offs already reported in litterature. The final model for locoregional recurrence included age, T stage and nodal ratio; for distant metastasis only age and N Stage following last TNM definitions were significant; for dfs and survival nodal ratio had a stronger predictive value than N Stage. Higher nodal ratios determined worse outcomes for all end-points, also in patients submitted to nodal irradiation.

Conclusions: although the role of nodal ratio in breast cancer patients remains unclear, in our patients this predictive factor results stronger than nodal stage, confirming already published data.

C043

DOES 18FDG-PET/CT MODIFY THE TREATMENT STRATEGY IN LOCALLY ADVANCED OR HIGH RISK BREAST CANCER PATIENTS?

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Aims: Evaluate the sensitivity and specificity of 18FDG-PET/CT in high risk or locally advanced breast cancer and its impact on treatment volumes delineation.

Materials and Methods: 132 breast cancer patients (pts), median age 61 (34-87), have been staged with PET/CT if: invasive carcinoma (ca) ER-, PR-, c-Erb-B2- (triple negative); invasive ca >3 positive axillary lymph nodes; locally advanced/inflammatory ca; locoregional relapse. Patient tumour demographics included the following: 104 infiltrating (inf) ductal, 15 inf lobular, 1 inf tubular, 3 inf papillar, 1 inf mucinous and 4 mixed carcinomas. PET/CT as staging analysis has been prescribed in 104 pts while in 28 pts it has been part of the precudures for radiotherapy (RT) treatment planning. In this second group of pts PET has been carry out immediately after the planning TC with the pts in the treatment position; CTV/PTV and OaRs were then delineated on the blended PET/CT images.

Results: PET modified the stage, and consequently the treatment strategy, in 10 pts (7.5%); we detected and cyto/histologically confirmed axillary metastatic lymph nodes (LN) in 6 pts, retrosternal metastatic LN in 2 pts and bone metastases in 2 pts. In addition the PET images showed internal mammary metastatic LN outside the standard location and allowed us to delineate them correctly in the PTV.

Conclusions: The selective use of optimal diagnostic techniques, higher sensitible and specific in comparison to the standard staging precedures (chest Xray/CT, abdomen US/CT), in these subgroups of pts is suggested as it may help to better define the surgical approachs well as the appropriate neo or adjuvant chemo-hormonal therapy. Their use in the RT planning procedures increases the visualization of structers such as retrosternal LN and allows an optimal definition of the PTV and the OaR.

C044

ACCELERATED PARTIAL BREAST REIRRADIATION USING HIGH-DOSE-RATE CATHETER-BASED INTERSTITIAL BRACHYTHERAPY FOR LOCAL RECURRENCES AFTER PRIOR BREAST EXTERNAL BEAM RADIOTHERAPY: TECHNICAL FEASIBILITY AND PRELIMINARY CLINICAL RESULTS

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Purpose: To evaluate technical feasibility and toxicity using catheter-based interstitial high-dose-rate (HDR) brachytherapy as adjuvant treatment in previously irradiated recurrent breast cancer.

Methods: Between January 2011 and April 2012, 15 consecutive patients with histologically confirmed recurrent breast cancers were reirradiated by adjuvant interstitial HDR brachytherapy using a remote afterloading unit.

The median time from first treatment until salvage surgery for local recurrence was 9.6 years (range, 3.3-27.9 years). All women were retreated with conservative surgical resection with (7 patients) or without (8 patients) axillary dissection or sentinel node biopsy. All patients but one (grade 2 intraductal carcinoma, DIN2) had infiltrating ductal (12 patients) or lobular (2 patient) carcinoma. All patients had oestrogen receptor-positive tumour, 11 patients had progesteron receptor-positive tumour and 9 patients had a Ki-67 value higher or equal to 20% (median 23%; range, 8-28). None of the brachytherapy implant was performed during the quadrantectomy procedure. At the time of the implant, the median age of the patients was 56 years (range, 41-74 years). Number of and spacing between catheters were individually chosen to adequately cover the width and thickness of the target. The median number of catheters was 9 (range, 6-18) with a median maximal active length of 6 cm (range, 5-9.5 cm). A dose of 34 Gy in 10 fractions, 3.4 Gy per fraction, 2 fractions per day with a minimal gap of 6h in-between was delivered, over a period of 5-6 days.

Results: No complications involving the implant, such as bleeding or infection, were noted. Procedure resulted to be well tolerated for all patients. No epidermitis or soft tissue acute side effects higher than grade 2 were recorded, with good cosmetic results in all patients. After a median follow-up of only 10 months (range, 1.6-15 months), the disease free and overall survival was 100%. No patient developed distant metastases.

Conclusions: Our retrospective analysis showed that the repeated course of radiotherapy by means of HDR brachytherapy to the new surgical bed is a feasible treatment for recurrent breast cancer, offering very low-complications rate and good cosmesis. Main limitations of our study include small number of patients and short follow-up. The technique reduces the treatment time to one week in contrast to the 5-7 weeks typically associated with conventional EBRT.

C045

RADIATION THERAPY AFTER NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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Purpose: The aim of our study was to retrospectively review outcome in terms of overall survival and disease free survival of patients referred to our institution with locally advanced breast cancer treated with neoadjuvant chemotherapy.

Patients and Methods: Between March 2001 and December 2008 a total of 34 women with locally advanced breast cancer were treated at our institution. All patients had histologically proven ductal or lobular carcinoma, all underwent mammography, breast ultrasound, chest radiographs (or CT scans), bone scan and breast magnetic resonance. Clinical stage was cT3-4, cNO or CN+. Neoadjuvant chemotherapy was FEC (5-fluorouracil, epirubicin, and cyclophosphamide) or doxorubicin-cyclophosphamide (AC) followed by taxanes. Preoperative revaluation always consisted in magnetic resonance. In 21 patients (60%) mastectomy was performed, while 13 patients underwent breast conserving surgery. Indication for radiotherapy was essentially based on initial conditions. 90% of patients who had undergone mastectomy received irradiation on chest wall and nodal stations (50 Gy); remaining 10% of patients received treatment on chest wall only. Patients who had undergone breast conserving surgery received irradiation on breast (50 Gy) and boost on tumor bed with an electron field.

Results: Observed median overall survival was 60 months, disease free median survival was 48 months, local recurrence-free mean survival was 60 months. 5 patients (16%) experienced local relapse, 7 patients (21%) had lung and/or liver metastases, 4 patients.

C046

HYPO-FRACTIONATED RADIO-HYPERTHERMIA IN BREAST CANCER RECURRENCES. A PILOT STUDY

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Purpose: Patient affected by breast cancer recurrence after mastectomy or systemic chemotherapy (without radiotherapy) have a poor prognosis. Palliative treatments are often necessary due to bleeding and pain symptoms. Hypo-fractionated radio-hyperthermia would allow a shorter course of radiation treatment improved by the effectiveness and radio-sensitizing of the heating treatment. The purpose of this study is to evaluate the feasibility and tolerance of an hypo-fractionated schedule of radiotherapy combined with superficial hyperthermia.

Materials and Methods: From January 2010 to May 2012, 8 patients were enrolled in the study. Mean age was 61.25 years, KPS was 70-100. Histological features were 87.5% ductal infiltrating (grading G3) and 12.5% inflammatory carcinoma. Immuno-histochemistry phenotype were Luminal B (62.5%), HER+ type (25%) and basal-like or triple negative (12.5%). Two patients were treated on the chest wall (group A), and the other patients on the residual or the whole breast (group B). Lesion size was <1cm in group A and <4cm in group B. Hypo-fractionated radiotherapy, delivering a total dose of 42.56Gy in 16 fractions (2.66Gy/fr), was performed by electron beam in group A and by field-in-field photon beams in group B. Hyperthermia was performed by a superficial microwave machine (434 MHz/45-75W) delivered twice a week (60 min-session). Seven patients were treated by and one by applicator connected with a bolus. The average temperature Bolus was 40°C in all sessions. Follow-up was performed at the end of treatment (T0), and 3 (T1), 6 (T2)

and 12 months (T3) later. We evaluated palliation of symptoms, toxicity and local response (by ETG and MR).

Results: Treatment temperature was analyzed in 48 sessions. A mean temperature of 42°C was reached in the center of the field, and 40.5°C peripherally. The average latency time of hyperthermia was 5.48min. Median follow up was 9 months. All patients showed optimal palliative response. Skin acute toxicity was G1 in 7 patients and G2 in only one patient. No late toxicity was referred. Patient of group A showed CR at T0 and never recurrences. In group B 87.57% of patients showed PR at T0, 87.57% CR at T1, 14.28% PD at T2, 14.28% SD at T0 and T1.

Conclusions: According to these findings we aimed to extend the Hypo-fractionated radio-hyperthermia to all patients affected by breast cancer recurrence (without local radiotherapy)and to evaluate the statistical significance on a larger sample.

C047

EXTERNAL BEAM RADIOTHERAPY (EBRT) IN THE TREATMENT OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA (DTC): A RETROSPECTIVE MULTICENTRE STUDY FROM THE AIRO'S RADIOMETABOLIC STUDY GROUP

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Purpose: The role of EBRT in the treatment of DTC is still not well defined. Many Institutions rely on 131I alone to destroy both benign or malignant remnants. While the efficacy of 131I on ablation of normal tissue is well documented, the reduced uptake of 131I in tumour cells makes this treatment option alone insufficient to eradicate microscopic and even more gross residual disease in many patients (pts). The AIRO's Radiometabolic Study Group conducted a multicentre retrospective study to evaluate the outcome of pts with DTC treated with EBRT due to persistent disease (micro or macro), or at high risk of recurrence, as part of primary treatment or at relapse.

Materials and Methods: From 2000 to 2012, 54 pts underwent EBRT in 5 Italian RT departments (24 Bologna AOSP and USL, 15 Aviano, 11 Padua and 4 Florence); 29m, 25f, median age at diagnosis 59 years. EBRT was part of the primary treatment in 16 pts, performed at recurrence in 38. Histology was: 44 papillary, 7 follicular and 3 Hurtle cell. Stage at diagnosis was: 1 IVc, 3 IVb, 24 IVa, 22 III, 1 I, not available in 3. Surgery was previously performed in all: 21 total thyroidectomy (TT), 2 sub-TT, 30 TT plus lymphadenectomy, 1 unknown. Surgical margins were: 12 neg, 26 R1, 2 close, 14 unknown. After surgery 131I was administered in 50 pts, average dose 123 mCi. In the 38 pts treated at relapse, median 131I dose was 307 mCi. EBRT (24 3D-CRT and 30 IMRT) was performed on the thyroid bed (TB) plus lymph nodes in 50 cases on the TB alone in 4. Median dose was 6288 cGy with IMRT, and 5867 cGy with 3D-CRT.

Results: After a median FU of 80.8 months from DTC diagnosis, and 35.8 months from the end of EBRT, 43 pts (80%) are alive (29 in CR, 2 with local-regional disease, 10 with metastasis (mets), 2 with both local-regional disease and mets), 9 pts (16.5%) died (6 due to mets, 3 due to other causes), 2 pts, with mets at the last control, were lost to FU. Overall, 47 pts (87%) were free from local relapse, and 34 (63%) from mets.

Conclusions: Our data confirm that EBRT allows a high rate of local control when performed both at diagnosis or at relapse in pts with DTC with positive surgical margins and in pts at high risk of local relapse due to unfavourable stage or histology. In comparison to 3D-CRT, IMRT allows higher EBRT doses. Even if larger studies are desirable, our data are in favour of an important role of EBRT in the treatment of pts with high-risk DTC.

C048

ANAPLASTIC THYROID CARCINOMA: EXPERIENCE OF A SINGLE INSTITUTION

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Purpose: Anaplastic thyroid carcinoma (ATC) is an aggressive malignancy with a generally poor prognosis and a median survival of less than 6 months. A multidisciplinary approach, combining surgery and radiotherapy, is recommended in order to increase local control and overall survival rates. The present study analyzes retrospectively the outcomes of 15 patients treated at our institution from February 2007 to March 2011.

Patients and Methods: The medical records of 15 patients (9 males, 6 females, mean age 67 years) affected by ATC were retrieved and analyzed. Patients underwent either surgical resection followed by adjuvant external beam radiotherapy (EBRT)/chemoradiotherapy (9 out of 15) or definitive EBRT (6 out of 15). An elective tracheostomy was performed in 4 out of 6 patients treated with exclusive radiotherapy for the evaluation of the residual respiratory space. Regarding patients who underwent surgery, an extra-thyroidal involvement became evident after surgery in two cases, while concomitant chemotherapy with doxorubicin was associated to radiotherapy in three cases. A Kaplan Meier curve was used to evaluate disease free survival and overall survival rates.

Results: Median disease free survival and overall survival rates were respectively 2.9 months (96% confidence interval 1.1-4.6 months) and 3.6 months.

Conclusions: Despite the chosen strategy, prognosis of ATC remains poor. Loco-regional control is often but not always feasible and treatments basically aim managing symptomatic local disease and prevention of overlap complications, mainly respiratory. Validation of new tar-

geted therapies, especially monoclonal antibodies is of crucial importance, in order to achieve a better prognosis.

C049

RADICAL RADIOTHERAPY FOR LOW-RISK PROSTATE CANCER FOLLOWING INITIAL ACTIVE SURVEILLANCE: RESULTS FROM A PROSPECTIVE OBSERVATIONAL STUDY

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Introduction: The use of active surveillance (AS) as a treatment option for low risk prostate cancer (PCa) is increasing in response to high rates of overdiagnosis. Current guidelines from American Urological Association (AUA), European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) propose AS as a management option for men with low- risk PCa. However, these guidelines by and large do not dictate the criteria for patient selection, schedule for patient follow up, or triggers for delayed intervention. These shortcomings are due to the fact that to date, no study has prospectively compared the outcomes of varying published AS protocols. To get better insight into the effectiveness of protocol based active therapy recommendations, we evaluated the results for deferred treatment and reported the outcome in patients with low risk PCa who underwent initial or delayed radical radiotherapy (RT) in our AS cohort. Purpose/Objectives To determine clinical outcome of men with low risk PCa who underwent initial radical RT or delayed RT following initial AS.

Materials and Methods: 77 patients (pts.) 65 years old or older with low-risk PCa (clinical stage </= T2, Gleason score </= 6 , PSA </= 10 ng/mL and one or two positive biopsy cores) referred between 2004 and 2011 to our department were identified. Of the 77 pts., 49 (64 %) underwent AS, 15 (19 %) underwent initial RT and 13 (17%) pts.underwent radical prostatectomy (RP). In the AS group, PSA was measured every 3 months and the study recommends RT in case of risk reclassification on repeat biopsy at least after 1 year (Gleason Score >6 and/or more than two positive cores) or a PSA doubling time </= 3 years. Median follow up for pts. who remained on AS was 26 months after diagnosis (range 8-68 months) while for pts. initially treated with RT median follow up was 40 months (range 6-84 months).

Results: In the AS group, 24 pts. (49 %) had biochemical progression and underwent delayed RT at a median time of 15 months (range 6-48). Unfavourable results were found in 13% of As group. After delayed RT actuarial 5 years biochemical recurrence-free survival was 87% and overall survival was 100 %. In the initial RT group 5 years biochemical recurrence-free survival and overall survival was 96% and 100 % respectively. It is reported that in 31% of patients who underwent RP in the first instance the histological examination showed a higher stage of disease. (>pT2,GS>7) A cause of treatment failure in pts suffering from Pca may therefore be the initial downstaging of the disease.

Conclusions: Consistent with these data, others (Klotz L, Zhang L, Lam A, et al. Clinical results of long term follow up of a large, active surveillance cohort with localized prostate cancer. J.Clin Oncol 2010; 28:126-131) have reported similar disease-specific survivals of 97-100% at 5 years follow up for initial RT or RT deferred treatment after initial AS in pts with low risk PCa. The choice of curative intervention or AS for men with low risk PCa should depend on age, health status and pts. preferences and the possible side effects of curative management.

C050

LOW-RISK PROSTATE CANCER: ROLE OF MAGNETIC RESONANCE IMAGING (MRI) IN STAGING AND TREATMENT

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Purpose: The main diagnostic tools to diagnose prostate cancer (PCa) include digital rectal examination (DRE), serum concentration of PSA and transrectal ultrasound guided biopsies. Sometimes, patients with PSA ≤10 ng/dl or Gleason score ≤6 , are submitted to surgery with any further exams [EAU Guidelines on Prostate Cancer, Eur Urol. 2011 Jan;59(1):61-71]. Magnetic resonance imaging (MRI) is an emerging tool in prostate cancer staging. We have evaluated the role of MRI in staging patients with low risk prostate cancer in order to assess the ability of such exam to detect an over-staging.

Materials and Methods: Between January 2008 and December 2011, 225 patients with histologically proven prostate cancer (PCa) have been evaluated for radical Radiotherapy. Eighty-three patients (36,9%) were defined as low risk class for PSA ≤10 ng/dl and Gleason Score ≤6. Among them, sixty-nine patients (83.1%) underwent to MRI at 1.5 T before Radiotherapy. In 14 patients (16.9%) MRI was contraindicated for pace-maker or metallic implants or due to severe claustrophobia.

Results: Median age was 76 years (range 60-84). Only in 54 patients (78.3%) organ-confined prostate cancer was confirmed. Fifteen patients (21.7%) had extra-prostatic disease: 8 capsular perforation, 6 seminal vesicle invasion, 1 nodal involvement. In the last patient, nodal disease was confirmed by PET/CT scan. Thus, MRI had identified high risk disease in more then 20% of patients with PSA ≤10 ng/dl and Gleason Score ≤6.

Conclusions: Actually a 20% of patients with low-risk prostate cancer classified by means of PSA and Gleason Score only, have a high risk T-stage. MRI could identify such patients.

C051

CYBERKNIFE SIMULATING HDR BRACHYTHERAPY FOR LOCALIZED PROSTATE CANCER: TECHNIQUE, TOXICITY AND PSA RESPONSE

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Objectives: The CyberKnife is an imaging-guided device for delivering high radiation doses to a precisely defined three-dimensional target volume. With CyberKnife is possible to emulate the fractionation, the prescription and the distribution of dose of the HDR brachytherapy. This modality is indicated for patients with localized prostate cancer (Tl-T2b) with favorable prognosis (Gleason score <6, PSA <10 ng/ml) and selected patients with intermediate prognosis (Gleason score of 7, PSA 10-20 ng/ml). The low a/ß (1-2 Gy) of the prostate cancer requires, for tumor control, an high radiation dose and a scheme of hypofractionated dose. We report our preliminary experience using a treatment planning that simulate HDR brachytherapy dose distribution for the treatment of patients with localized cancer prostate.

Methods: In our institution, in a period of 42 months, 20 patients with a median age of 78 (range 70-86) years and a median Gleason score of 6 (range 5-7) underwent CyberKnife body fSRT. The planning target volume (PTV), defined with fusion MRI and CT imaging, included the prostate and proximal seminal vesicles, plus 2 mm of expansion for favorable prognosis or 5 mm for intermediate prognosis in all directions, except posteriorly. The prescription dose was 38Gy (9.5Gy/Fx) in four fractions with an extra-urethral PTV Dmax of at least 150% of the prescription dose. The Fiducial Tracking System was used for the localization of fiducials that are placed one week before.

Results: A dose of 38Gy in four fractions with a median prescription dose of 59% (range 56-75%) was prescribed for all patients. No biochemical failures were observed in a median follow-up of 11 (range 3-42) months.All patients are without evidence of biochemicalor clinical progression to date, and favorably low PSA nadirs have been observed with a current medianPSA nadir of 0.15 (range 0.02-1.4). The median value of pretreatment PSA was 9.4 (range 4.5-14.3) ng/ml.The rectal toxicities of grade 2-3 was observed in the 6% of patients that regressed at G0 after a six months. No G2-3 urinary toxicity was observed. One patient died for other causes.

Conclusions: The CyberKnife may effectively simulate brachytherapy HDR. It is noninvasive and turned out to be safe at the short-term follow up for low-intermediate risk prostate cancer with sensible reduction of PSA values and minimal toxicity.Further studies are warranted to investigate possible late complications and tumor control rate.

C052

THE CHOICE OF RADICAL TREATMENT MODALITY OF LOCALIZED PROSTATE CANCER. DIFFERENT QUALITY OF LIFE (QL) OUTCOME AFTER BRACHYTHERAPY (BT) OR RADICAL PROSTATECTOMY (RP): MEDIUM-TERM RESULTS FROM A PROSPECTIVE MONOINSTITUTIONAL STUDY

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Purpose: Different therapies with similar disease control rates but relevant differences in terms of QL impact may be considered in radical treatment of localized prostate cancer. We attempted to evaluate the changes of QL after BT or RP.

Materials and Methods: From March 2005 to July, 2010, we evaluated a consecutive series of 420 pts treated with RP (192 pts) or BT (228 pts) for localized prostate cancer. All pts were requested to fill a self-filled QL questionnaire a week before, one-two months (one for BT, two for RP) and yearly after. The questionnaire (listing 64 items) derived from a validated instrument previously used in a prospective study (Int J Radiat Oncol Biol Phys 2006; 66: 31-7). The items identify the following QL subscales: physical well-being (PHY), psychological well-being (PSY), relational life (REL), physical autonomy (POW), rectal (REC), urinary (URI), erectile (ERE), and sexual functioning (SEX). Differences in terms of subscales value means between RP and BT at the different assessment time-points were statistically analyzed by one-way variance analysis.

Results: The findings observed at the different assessment time-points are reported, comparing the subscales value means. BT produced a statistically significant better outcome in terms of urinary, sexual, and erectile functions, compared to RP, whereas rectal function was significantly less impaired after RP. The differences concerning not functional scales favored IB but they were limited to the period immediately after treatment.

Conclusions: Relevant differences between treatment groups persisted in our medium term analysis. These results provide relevant information for clinical decision making and can aid in the controversial choice of radical treatment modality of localized prostate cancer.

C053

LOW RISK PROSTATE CARCINOMA: BRACHYTHERAPY EXPERIENCE IN 208 CONSECUTIVE PATIENTS TREATED IN RADIOTHERAPY DEPARTMENT OF LUCCA

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Purpose: Several radiotherapy techniques are used in the treatment of low risk prostate's cancer treatment. These are, by now, external beam radiotherapy (3D or IMRT) or bra-

chytherapy. Another management of this particular type of cancer could be also watchful waiting or surgery. Radiotherapy Department of Campo di Marte Hospital, Lucca choosed, from 2004, 125Iodine seeds transperineal brachytherapy as standard therapy. Aim of this work is to evaluate results in terms of biochemical failure and toxicity.

Materials and Methods: Between April 2004 and May 2012, 294 patients with prostate cancer were treated with transperineal 125I seeds implants at the Radiotherapy Department of Lucca. Among them, 208 patients were classified "low risk carcinoma". Median age was 67 years (range 50-80), stage was cT1c. Gleason score was 3 in 2% of patients, 4 in 24 %, 5 in 21%, 6 in 50 % and 7 in 3%. Average pre-treatment PSA was 6.0 ng/ml. Hormonal therapy was prescribed in 9% of patients. 125I seeds, with activity of 0.464 mCi, were implanted transperineally with transrectal ultrasound guidance. The urethral location was estimated using a Foley catheter. Median prostate volume was 33 cc and an average of 69 seeds were implanted. A post-implant geometric and dosimetric evaluation was performed one month after implant, with 3 mm- CT slices for reconstruction and pixels dimension of 0.3 mm (FOV of 150 mm). Prostate' s prescription dose was 145 Gy, with an average post-planning D90 of 145 Gy and an average post-planning V100 of 89%.

Results: No patients died for prostate cancer (3 and 5-years Overall survival 100%). Biochemical failure occurred in the entire group in 15 patients. Biochemical failures failures were observed to a maximum period of 36 months (range 6-36), with a median of 18 months. Urinary toxicity occurred in 2% of case. Only one patient experimented rectal complication.

Conclusions: Transperineal 125Iodine seeds brachytherapy in low risk prostate cancer achieves a good clinical control, and overall survival with acceptable late toxicity.

C054

DIFFERENT PSA KINETICS AFTER BRACHYTHERAPY OR EXTERNAL BEAM RADIATION THERAPY IN LOW-RISK PROSTATE CANCER PATIENTS

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Purpose: To evaluate PSA kinetics in a cohort of low-risk prostate cancer patients treated either with Brachytherapy (BRT) or External Beam Radiotherapy (EBRT).

Materials and Methods: We retrospectively analyzed 150 consecutive low-risk prostate cancer patients, who underwent BRT (with permanent implant of 125I as monotherapy, n=69 patients) or EBRT (n=81 patients) at our Institution, between April 2003 and December 2009. Exclusion criteria were: a) follow-up time < 24 months; b) administration of any form of Androgen- Deprivation Therapy (ADT) prior to RT; c) < 4 PSA measurements during the follow-up. Median age was 67.4 years (range: 53-77) in BRT group and 68.9 years (range: 56-80) in EBRT group. Biochemical Failure (BF) was defined either with the ASTRO Phoenix definition (nadir+2 ng/mL, dated "at call") or the introduction of ADT after RT. Bounce PSA (bPSA) was defined as a post-treatment PSA rise >0.4 ng/ml followed by a spontaneous decrease to pre-bounce level or lower. Survival functions were determined using Kaplan-Meier method and Cox regression with proportions tested with the log-rank test.

Results: Median follow-up was 51 months (range: 24-101 months) in BRT arm and 55.6 months (range: 24-99.3 months) in EBRT arm. Three-years biochemical Disease-Free Survival (bDFS) was 96.7% for the BRT arm and 98.8% for EBRT arm (p=0.72). Median time to BF was 31 months (range: 31-90 months) after BRT and 52.92 months (range: 11-72 months) after EBRT. Median nPSA was 0.18 ng/mL (range: 0-0.94 ng/mL) in the BRT group and 0.28 ng/mL (range: 0- 2.01 ng/mL) in the EBRT group (p<0.001). Median time to the nPSA (TnPSA) was longer after BRT than EBRT (38.47 months *vs*. 26.37 months; p<0.01). Twenty-six patients (37.7%) in the BRT group and 11 patients (13.6%) in EBRT group experienced a bPSA at any time during follow-up (Chi-square test, p=0.001). Bounce PSA occurred earlier after BRT (median time to bPSA: 22 months; range: 10-40 months), than after EBRT (median time to bPSA: 31 months; range: 9-47 months) (t Student p=0.04).

Conclusions: In low-risk prostate cancer patients, PSA kinetics after BRT or EBRT significantly differs. Lower nPSA values and a longer TnPSA are expected after BRT, probably due to the higher dose delivered. Rising in PSA levels in the first 24-36 months after BRT/EBRT should be considered with caution (as nearly 40% of BRT patients experienced a PSA bounce, which may cause anxiety and unnecessary start of hormonal therapy).

C055

CORRELATION BETWEEN AGE, COMORBIDITY, PRETREATMENT ERECTILE FUNCTION AND DOSE TO PENILE BULBO WITH ERECTILE DYSFUNCTION AFTER CONFORMAL RADIOTHERAPY FOR LOW RISK PROSTATE CANCER PATIENTS: OUR EXPERIENCE

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Aims: To evaluate the correlation between age, comorbidity, pretreatment erectile function and dose to penile bulb with erectile dysfunction (ED) after conformal radiotherapy in low risk prostate cancer patients.

Materials and Methods: From January 2010 to February 2012 we enrolled 22 patients affected by low risk prostate cancer submitted to exclusive 5-fields conformal radiotherapy (3DCRT) to the prostate gland, with a total dose of 76 Gy/2 Gy die/38 fractions. None patients received an antiandrogen treatment. The median age was 72 years old with a range between 66-77 years. Ten patients underwent trans urethral resection of the pro-

state (TURP), 13 were affected by hypertension and 3 patients by diabetes mellitus type 2. To evaluate the ED we used the International Index of Erectile Dysfunction (IIEF) questionnaire, personally given by a physician, based on 15 questions before the start and six months after the end of 3CDRT. The median follow-up was 17.5 months with an range from 3 to 25 months.

Results: The erectile function and satisfactory sexual performance score of the IIEF declined after radiotherapy, instead the sexual desire score did not change after external beam radiation. In particular severe, moderate and low ED were observed in 55% (12 patients), 9% (2 patients) and 27% (6 patients) of patients, respectively. Two patients (9%) reveled no deterioration of erectile function six months after radiotherapy. The statistical analysis showed significant differences in clinical features between patients who maintained erectile function and those who had worsening erectile function six months after radiotherapy. In our small cohort of patients, in univariate analysis hypertension (r=0.87), TURP (r=0.71) and mainly diabetes (r=0.94) correlates with ED. No correlation was found with the age of the patients. Furthermore, 6 patients (27%) submitted to TURP started 3DCRT with a severe o moderate ED. Finally among the ten patients with severe ED after 3DCRT, seven affirmed having a compromise sexual function even before the start of oncological treatment. Regarding the dose to the penile bulbo, we compared the mean radiation dose of post-RT potent and impotent patients and, as showed by the current literature, we didn't find a correlation between the exceeding of the dose constraint and ED. All patients resulted with no biochemical evidence of disease (bNED).

Conclusions: Our analysis showed a correlations between comorbidity and potency preservation. TURP lead to impotence and its potential sexual morbidity should be taken into consideration in the comparative risk-benefit analysis of different therapeutic strategies.

C056

"TO INCLUDE OR NOT TO INCLUDE?" INCLUSION OF SEMINAL VESICLES IN THE TARGET VOLUME AND RECTAL TOXICITY IN LOW-RISK PROSTATE CANCER

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Purpose: Definitive External Beam Radiotherapy (EBRT) results in a significant rectal dose which is clinically translated in acute and late rectal toxicity. This latter, can be consistently reduced excluding totally or partially the seminal vesicles from the planning target volume (PTV). The aim of the present study was to evaluate the variation of the rectal dose on the basis of three different contouring approaches.

Materials and Methods: The medical records of 22 patients affected by low risk prostate cancer were evaluated and 3 different three-dimension conformal radiotherapy (3D-CRT) treatment plans were generated; PTV coverage varied according to a partial, total or no inclusion of the seminal vesicles. The mean doses to the rectum were also calculated and dose-volume histograms (DVH) were compared.

Results: Total exclusion of seminal vesicles in the PTV, resulted in a decreased dose to the rectum (18%, $p<0.05$), in comparison to their total inclusion, while the inclusion of the third proximal of seminal vesicles was not translated in a dosimetric benefit.

Conclusions: According to our data, whereas inclusion of seminal vesicles can be omitted (low risk prostate cancer, low probability of vesicle involvement), this can be safely performed, as significantly reduced dose to the rectum and better patient compliance, is expected.

C057

VESTIBULAR SCHWANNOMA: MICROSURGERY OR RADIOSURGERY? A COMPARISON OF DELIVERY TECHNIQUES IN STEREOTACTIC RADIOSURGERY OF VESTIBULAR SCHWANNOMA

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Introduction: Vestibular Schwannomas (VS) are benign tumors of the vestibulocochlear nerve which induce symptoms such as hearing loss, tinnitus, vertigo, and equilibrium problems. Following diagnosis with contrast enhanced MRI,the tumor could be kept under observation or treated by means of microsurgery, radiosurgery, or radiotherapy. Stereotactic radiosurgery (SRS) typically involves the combination of an invasive immobilization frame with the delivery of radiation with a very tight precision level. This allows delivering the dose to the tumor with the most appropriate degree of conformation and, in turn, increasing the dose which is delivered in a single fraction.

Materials and Methods: This study compares quantitatively the dose distributions arising from the treatment planning of the VS designed with three different RT modalities: GammaKnife (GK), IMAT and Helical Tomotherapy (HT). Dose distributions were compared in terms of: Dose conformation by means of the Paddick Index (PI);Dose homogeneity by means of Homogeneity Index (HI);Dose fall-off outside the target by means of Gradient Index (GI).Three patients were involved for the study. The comparison GK-HT was performed for two patients with different tumor volumes (1,6 cc and 0,4 cc) while the comparison IMAT-HT was performed for a single patient with tumor volume of 0,22 cc. For a correct comparison, different dose prescriptions were used in order to achieve a marginal dose of 13 Gy to the tumor.

Results: Table 1 reports the values of HI and PI obtained for planning, higher HI values results in less homogeneity to the target while higher PI values correspond to better dose conformity to the target. Figure 1 shows the GI difference (GI) for the three cases. The HT capability

of reducing the doses outside the target results poor with respect to the other two techniques. The GI increases according to the decrease of the isodoses and the treated volume. GK results as the most appropriate technique in terms of normal tissue sparing.

Conclusions: HT was compared to the GK and IMAT for the treatment of the VS. HT results as the technique capable to deliver the most homogenous and conformal dose distribution with respect to the others. On the other hand, HT is more inclined to spread the medium and low doses outside the target with respect to GK in particular. This effect seems to be related to the treatment volume, since it resulted more pronounced for small volumes.

Table 1. Homogeneity Index (HI) and Paddick Index (PI) resulting from the different treatment planning techniques.

vol	1,6 cc		0,4 cc		0,22 cc	
	TOMO	GK	TOMO	GK	TOMO	IMAT
HI	1,07	1,99	1,07	2	1,1	1,2
PI	0,88	0,78	0,69	0,51	0,54	0,44

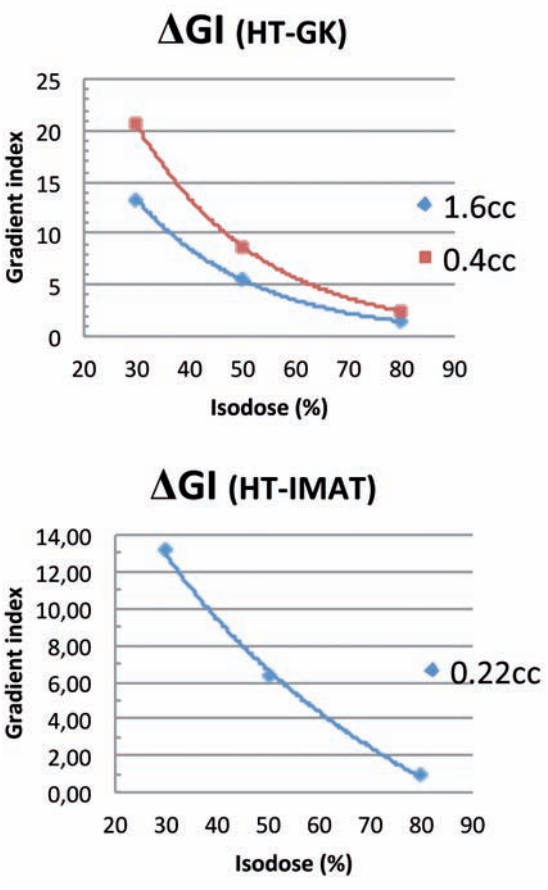

Figure 1. Gradient Index GI difference between HT and GK (diagram above) and HT and IMAT (diagram below).

C058

COMPARISON OF DOSE IN THE MANAGEMENT OF ARTERO-VENOUS MALFORMATION (AVM) WITH STEREOTACTIC RADIOSURGERY (SRS)

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Purpose: Certain AVMs, are inoperable due to their large size, eloquent location, deep venous drainage, and/or other anatomical considerations that are associated with unacceptably high rates of morbidity and mortality. In those cases SRS is generally recommended. In this paper we reviewed our experience to evaluate clinical response and toxicity with different delivered dose.

Materials and Methods: From January 2009 to November 2011, 22 patients with diagnosis of AVM were treated at San Camillo Forlanini Radiotherapy department. Median age at SRS was 36,14 years (range 11-63). 12 AVMs (54,5%) were located in brain left side with a prevalence involvement of the frontal lobe (5 left/2 right), parietal lobe (4 left/2 right), temporal lobe (3 left/2 right), occipital lobe (1 left/2 right) and one sited in left cerebellum. We compared two groups of patients: in the first group (15 pts-68%) delivered dose was 20 Gy with a median volume of 2.03 cc (0.1 – 6.7 cc); the latter group (7 pts-31,5%) received 16 Gy or less on a median volume of 8.97 cc (0.2-39.3 cc). Low SRS dose was justified by larger volume, clinical history and critical anatomical location. Fixation was performed with a 3D-Line invasive frame, and all the patients underwent Angiography/CT/MR fusion for the localization of the target and the organ at risk. SRS was performed with 6 MV LINAC and MMLC of 3 mm. The radiation treatment was administered generally using five noncoplanar arcs with a single isocenter.

Results: All the patients completed the SRS procedure without toxicity. Follow-up RM revealed complete obliteration of all AVM nidus in 7 out of 22 patients (32%) after 19 months of median follow up (range 12-36).Complete response was seen only when 20 Gy were administered. After 12 months of follow up RM documented partial obliteration in 3 patients (13%) treated with 16 Gy. Median 15 months RM (3-24 months) showed persistent AVM nidus in 12 out of 22 patients (55%).

Conclusions: Good response rate seen in higher dose SRS (20 Gy) confirm results already described in literature. Low dose SRS is an effective and relatively safe mean of treating large, complex AVMs that are not amenable to surgery or higher dose SRS. In our experience 16 Gy or less can achieve a partial obliteration of those AVMs. Overall obliteration rates are further probably limited by shorter gap between SRS and radiological check. A longer follow up (almost 36 months) will be usefull to confirm are early data.

C059

APPLICAZIONE DELL'FMEA IN PROTON TERAPIA

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Purpose: Failure mode and effects analysis (FMEA) represents a prospective approach for risk management. A multidisciplinary working group including Radiation Oncologists, Medical Physicists and risk managers applied FMEA to the planning process in proton therapy with the aim of preventing accidental exposures to the patient. Actively scanned proton beams for fixed target irradiation and the procedures adopted at the National Center for Oncological Hadrontherapy (CNAO) were considered.

Materials and Methods: FMEA was applied to the proton therapy planning process and consisted of three steps: 1) identification of the involved sub-processes; 2) identification and ranking of the potential failure modes, using the risk probability number (RPN) scoring system, based on the product of three parameters (severity, occurrence and detectability, each ranging from 1 to 10); 3) identification of additional safety measures.

Results: Thirty-four sub-processes were identified in the treatment planning phase. Forty-four potential failure modes were found and scored, in terms of RPN, in the range of 20-196. Events with score 10 for severity (death of patient) were found, but since they were easy to detect, did not influence in critical way the RPN score. The most critical failure modes consisted of 1. incorrect delineation of CT artefacts and metal implants, 2. use of an outdated CT scan for planning; 3.wrong definition of the reference system origin for absolute positioning.Potential causes of failure included human error, lack of documentation from the referring clinicians,incorrect HU number assignment or inaccurate delineation of artifact regions. The main potential consequences of failures were represented by wrong dose distribution, PTV under dosage and unintended normal tissue irradiation. Some additional safety measures to implement proton therapy planning process, preventing potential errors, were identified: higher attention to the collection of details concerning either unknown or unusual prosthesis material; the acquisition of software filters to minimize the CT artifacts, double check procedures, verification of the contours of metal implants on different datasets (*e.g.* MRI) were some of the strategies suggested.

Conclusions: FMEA appeared a useful tool for prospective evaluation of patient safety in particle radiation therapy leading to identify the most critical failure modes and additional safety measures for risk mitigation.

C060

CLINICAL RISK MANAGEMENT IN RADIOTHERAPY: PERSONAL EXPERIENCE

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Purpose: The radiation oncology, as always, can be considered a complex system for the combination of several variables: the characteristics of the therapeutic agent used, the need for teamwork with different specificities professional, strong technological component in continuous evolution. In view of the fact that in any complex organization of the error and the possibility of an event can not be eliminated, it becomes a moral and ethical obligation to implement all possible measures to prevent errors and minimize their possible consequences.

Materials and Methods: In the hospital Belcolle of Viterbo was set up UO of Clinical Risk Management, through training first introduced and, after that take the concept of "Clinical Governance". The OU radiotherapy were then set up training courses, workgroups of formats from medical radiation, radiation therapy technician, registered nurse and physical health. It 'was identified a team leader for the coordination of teamwork, and produced a list of processes using simple and effective tools. Was adopted methodology estimates that achieves high levels of reliability of complex systems (FMECA-Failure Mode, Effects and Criticality Analysis). We proceeded first with the identification of processes in radiation therapy and then we proceeded with the study of the processes (steps 1 and 2 of FMECA). It 's good to remember that the "critical processes" are to be found in the processes of radiation and therefore there must be clarity of what the context of the processes under study, radiation therapy has been repeatedly described as "four-engine times" : 1) Acceptance and visit, 2) Treatment planning, 3) Execution radiotherapy 4) Follow up. For each process listed above were defined stages that make up the process and identify the activities that the individual process steps (step 3 of FMECA).We proceeded to the implementation of steps 4 and 5 of FMECA.

Results and Conclusions: Since 2008 in radiotherapy of Viterbo was formed a working group for clinical risk management, we made use of the tools of analysis and control proposed in FMECA. In 4 years of observation could be identified 2 cases of minor event (injury or no increase in hospitalization or standard of care). It can be assumed then that the steps proposed in the FMECA, if strictly applied, reduce the percentage of occurrence of an error reduction of possible damage to patient health and reducing the costs of the NHS.

C061

APPLICATION OF FAILURE MODE AND EFFECTS ANALYSIS (FMEA) IN SINGLE-FRACTION STEREOTACTIC INTRACRANIAL RADIOTHERAPY

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Purpose: Radiotherapy (RT) technology greatly improved over the last decades reaching a very high level of complexity and sophistication. A high-precision techniques, such as stereotactic RT, represents an adding value for the patients in terms of clinical outcome, however it need special assurance protocols and adequate measures for patient safety. This study aims to contribute at increasing the safety of patients undergoing RT, with particular emphasis to single-fraction stereotactic intracranial RT.

Materials and Methods: The study is performed through a proactive analysis of the potential risk of incidents, "near misses", and, in general, events leading to a deviation from the scheduled treatment, in terms of over- or under-dosage. We considered the Failure Mode and Effects Analysis (FMEA), that is a prospective tool successfully applied in industry, and recommended by the International Commission for Radiological Protection [ICRP, 2009] for use with modern RT techniques. FMEA was performed by a multidisciplinary team, including 8 radiation oncologists, 3 physicists, 4 radiation therapists, and a nurse. The analysis considered of the following tasks: (1) create a visual map of the process, (2) identify possible failure modes; (3) assign risk probability numbers (RPN) to each failure mode based on tabulated scores for the severity, frequency of occurrence, and detectability, each on a scale of 1 to 10; and (4) identify improvements that are both feasible and effective.

Results: The RT process is described, and the detailed process tree of the treatment process presented. In particular, the stages: 1) assessment of patient, 2) decision to treat, 3) prescribing treatment protocol, 4) positioning and immobilization, 5) imaging acquisition, 6) volume identification and outlining, 7) planning, 8) patient set-up, 9) treatment delivery, 10) response assessment and follow-up are analyzed. Finally, potential failure modes, their causes and effects are identified and discussed.

Conclusions: The study is still ongoing and failure modes for SBRT with the highest risk priority numbers will be considered for implementing adequate measures for process improvement.

C062

RISK MANAGEMENT IN RADIATION THERAPY: THE EXPERIENCE OF RADIOTHERAPY UNIT OF "R. DIMICCOLI" HOSPITAL IN BARLETTA

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Aims: Radiotherapy is a risk intensive process; therefore the department daily activities have to be oriented to quality assurance and risk management. Errors can occur at every step of the porcess, from patient initial evaluation to delivery and follow-up. Radiation Therapists play a crucial role in the achievement of high quality and well-managed risk. We reviewed our activities aimed to assure quality and minimize errors.

Methods: We usually try to minimize clinical risk by the following activities: Independent check of Radiation Treatment Plan Parameters before starting every new treatment course Acquisition of a patient's face photograph, to minimize error in correct identification; Establishment of internal written guidelines (Procedure Manual and Protocols) about primary evaluation, prescription, simulation, contouring, dose constraints and follow-up for each diagnosis, after accurate review of literature and international guidelines; Weekly meetings to discuss clinical cases and to share evidence-based guidelines, to consult with seniors and to reduce the risk of non homogeneous clinical behaviours; Acquisition of patient's photo during TC treatment simulation in the cases of complex or difficult positioning, to minimize errors in patient's setup; Regular imaging of patients during treatment to verify that patient position remains correct throughout a course of treatment and to ensure the accuracy of the delivered radiotherapy; Written recording of medical errors with precise identification of direct causes, stage of the treatment process and corrective actions and prevention of future incident, to optimize weak points of the process; Full informed written consent form, to minimize the risk of misunderstanding about aims, modalities and side effects of radiation treatment; Minimize oral information transfer and paper archive data, optimizing electronical recording and transferring of clinical and planning data.

Results: In our experience, the most frequent errors (60%) concern the information transfer about patients' setup. These informations are usually written on medical records without using a form. A possible solution is filling out a prescribed form. In past, errors in pre-RT evaluation, prescription and patients' setup during simulation occurred with a moderate frequence (30%): these kind of errors have been minimized thanks to internal written protocols and weekly meetings. We reported a low incidence (5-10%) of errors during treatment delivery, thanks to electronical recording of treatment planning data, independent check and regular portal imaging, and of incorrect patient's identification, thanks to ID number and photos.

Conclusions: We found a low frequence of errors during the steps of radiation therapy process in which we have adopted standardized procedures, independent checks and planned activities. The transfer of information about patients setup from simulation to treatment is the phase in which we recorded the highest incidence of errors: now we plan to use a prescribed form to record patient setup, considering the benefical effect of prescribed forms in other areas.

C063

PANCREATIC CANCER: FROM STAGING TO TREATMENT IN PREOPERATIVE SETTING

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Backgrounds and Purpose: An accurate diagnosis folllowed by multimodality therapy is essential to achieve long-term survival patients with pancreatic cancer. Based on radiographic criteria patients with pancreatic tumors are classified in resectable disease, borderline resectable disease, or clearly unresectable disease. The subset of patients with marginally resectable tumors is emerging as a cohort who may benefit from neoadjuvant radiochemotherapy prior to surgery. Dynamic contrast-enhanced computed tomography (CT) is helpful to evaluate local extension of the tumor and to verify the presence of metastases and it is the current staging test of choice. Additionally, endoscopic ultrasonography (EUS) is useful to detect local infiltration, FDG-PET/CT and laparoscopy are important for diagnosis of distant metastases or small peritoneal metastases. All these exams are useful for staging, restaging, and to evaluate the response to treatment and the prognosis. The optimal management of patients with pancreatic cancer isn't fully defined, so we have proposed a protocol that included all mentionated exams to select better patients for a neoadjuvant treatment.

Materials and Methods: Between January 2009 and December 2011, forty-two patients with pancreatic cancer underwent to preoperative imaging including multidetector computed tomography (CT), endoscopic ultrasound (EUS), PET-CT and laparoscopy with peritoneal washing. Patients were defined as potentially resectable, unresectable or borderline resectable disease. Borderline resectable and unresectable patients were referrred for neoadjuvant therapy with external beam radiation and concomitant radiation-sensitizing chemotherapy. Approximately 3-4 weeks after the completion of radio-chemotherapy, an evaluation was performed regarding tumour response and resectability with clinical examination, laboratory test, tumor markers, CT scan, PET-TC and laparoscopy.

Results: Of the forty-two patients who underwent to preoperative imaging and laparoscopy, seventeen (40.4%) patients presented metastatic disease. Nine patients were known to have distance metastases at PET-CT, eight patients peritoneal nodules at laparoscopy, unrecognized on CT scan. Twenty-five patients (fourteen women and eleven men) were treated with preoperative protocol of chemoradiation. Following completion of neoadjuvant treatment, patients were reevaluated clinically and through diagnostic imaging and laparoscopy. Of these patients, five demonstrated peritoneal carcinosis at laparoscopy, and four patients metastatic disease at CT scan. Surgery was then scheduled for patients demonstrating lack of progression of disease and who were determined physiologically suitable. Eight patients (32%) underwent radical surgery, six patients (24%) underwent palliative surgery. Eleven patients (44%) didn't undergo to surgery (seven showed distant progression of disease, two had poor performance status and two patients showed persistent vascular infiltration).

Conclusions: The most important issue in the management of patients with pancreatic cancer is the accurate identification of staging disease. An advantage of neoadjuvant radiochemotherapy include the optimal patient selection for pancreaticoduodenectomy through exclusion of patients with rapidly progressive metastatic disease.

C064

PRELIMINARY RESULTS OF THE EUDRACT STUDY: NEOADJUVANT CHEMORADIOTHERAPY FOLLOWED BY SURGICAL RESECTION COMPARED TO SURGERY ALONE FOR RESECTABLE PANCREATIC CANCER

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Preliminary results of the EUDRACT study: neoadjuvant chemoradiotherapy followed by surgical resection compared to surgery alone for resectable pancreatic cancer. Purpose: The assessment of the outcomes of patients who received preoperative gemcitabine-based chemoradiation and pancreaticoduodenectomy or surgery alone for resectable pancreatic adenocarcinoma.

Materials and Methods: Patients were randomly assigned to receive induction chemoradiotherapy (CHRT) followed by surgical resection (Group A: 14 patients) or surgery alone (Group B: 18 patients). Preoperative CHRT consisted in 6 weekly intravenous infusions of Gemcitabine (1000 mg/m2), followed by concomitant radiation (delivered to a dose of 45 Gy to the gross tumor volume and regional lymph nodes by using conventionally fractionated radiation regimens and small-volume boost radiation with 9 Gy) and Gemcitabine 50 mg/m2, days 1-5 for 6 weeks.

Results: From March 2007 to June 2012, 32 patients (14 females, 18 males) were enrolled. 11 out of 14 (78,6%) patients of Group A completed the neoadjuvant therapy and underwent surgery; 2 patients interrupted treatment because developed liver metastasis and one patient died for acute myocardial infarction. In Group B, 1 out of 18 patients (5,6%) died immediately after surgical resection for postoperative complications (anastomo-

sis dehiscence). During follow up, 2 patients (18,2%) of group A developed metastasis, while extrapancreatic diseases were found in 10 patients (55,6%) of group B.

Conclusions: Our results indicate the effectiveness of the CHRT followed by surgical resection for locally advanced pancreatic cancer, that may increase the progression-free survival and improve the overall survival. The rationale for neoadjuvant chemoradiotherapy (CHRT) may be to improve local control, increase rates of potentially curative resections with clear margins, develop overall survival benefit and reduce the incidence of late relapse. Due to the small number of patients, larger prospective studies are needed.

C065

CHEMORADIOTHERAPY FOR LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA

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Purpose: The prognosis of patients with pancreatic adenocarcinoma is poor. Surgery is the only curative option but even after radical resection, the median overall survival is 18 months due to both local and distant failures. The treatment of locally advanced disease is controversial. Multimodality approach is currently used in the clinical practice, although literature data do not support it. This is a retrospective analysis of a monoinstitutional experience, evaluating the outcomes of patients with locally advanced disease submitted to radiochemotherapy as definitive treatment or after resection (if the surgical approach was feasible).

Materials and Methods: We reviewed our database looking for patients with histologically confirmed locally advanced pancreatic disease (stage II-III), receiving adjuvant or definitive radiochemoterapy. Radiochemotherapy (adjuvant or definitive) consisted of 2 phases: chemotherapy with gemcitabine (1000 mg/m2/week/6 weeks) followed by concomitant gemcitabine (300 mg/m2/week) and radiotherapy. Patients received 3D conformal radiotherapy to the tumor site (or surgical bed after surgery) plus regional nodes to a total dose of 45-54Gy. Toxicity was evaluated according to RTOG-EORTC score systems. Survival analysis was calculated from the date of diagnosis (biopsy or surgery) by the Kaplan-Meier method and log-rank method was used to evaluate the role of prognostic factors.

Results: From January 2000 to August 2011, 52 patients meeting the eligibility criteria, were included in the analysis. Characteristics of patients were as it follows. Gender M/F: 31 (59.5%)/21 (40.5%); median age 61 years (range 37-75); median KPS 100% (range 70-100); site of disease: head 37 (71%), body/tail 15 (29%) patients; stage: II 17 (32,5%), III 35 (67,5%) patients. Twenty-seven patients received surgery with curative intent (15 pancreaticoduodenectomy e 12 spleno-pancreasectomy), while 11 underwent laparotomy or palliative surgical digestive bypass. Seven patients had biopsy while in 8 the diagnosis was radiological. Globally all patients completed the scheduled treatment. The median delivered radiation dose was 50.4 Gy (range 45-64.8) in 28 fractions. Grade III-IV acute toxicity was observed in 25% (13/52) of cases. Seven patients experienced haematological, five gastrointestinal and one both toxicities. No patient showed late toxicity. The median follow-up was 19 months (range 4-126). Eleven (21%) patients experienced local event (relapse or progression), while 32 (61,5%) systemic event (distant metastasis). The median overall survival (OS) and the median event-free survival (EFS) of all patients were 20 (range 4.2- 126.8) and 12 months (range 2.4-126.8), respectively. The 2-y and 3-y OS were 44.8% and 27.1%, while the 2-y and 3-y EFS were 19.% and 13.7%. Stage of disease (II *vs* III), gender (female *vs* male), anatomical site (head *vs* body/tail), surgery and surgical margin status (R0 *vs* R1 *vs* R2) represent prognostic factors in term of OS e EFS.

Conclusions: Combined modality treatment as adjuvant or definitive option, seems safe, feasible and effective in terms of local control and survival. Distant metastases in pancreatic cancer is an unsolved problem. An intensification of both chemotherapy and radiotherapy is necessary in order to improve clinical outcome.

C066

4D-COMPUTED TOMOGRAPHY (4D-CT) IN THE NEOADJUVANT TREATMENT OF PANCREATIC CANCER

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Purpose: In neoadjuvant pancreatic cancer treatment, to account for inter-fractional and intra-fractional variations, a personalized planning target volume (PTV) was added to cover the clinical target volume, determined by four dimensional computed tomography (4D-CT) that allows to reconstruct three-dimensional CT scans at various phases of the respiratory cycle. Toxicity and outcome has been related to the 4D-CT volumes.

Patients and Methods: Ten patients with pancreatic adenocarcinoma underwent implantation of single fiducial marker. Intrafraction and interfraction uncertainties were assessed on simulation four dimensional computed tomography (4D-CT) and megavolt cone beam CT (MVCBCT) respectively. Respiratory correlated 4D-CT was retrospectively reconstructed into eight respiratory phases, using the amplitude of the waveform obtained by the respiratory sensor. Based on 4D-CT, PTV margins were personalized. All patients recieved neoadjuvant 3D conformal radiotherapy concurrent with gemcitabine based chemotherapy, to a total radiotherapy dose of 54 Gy on the tumor site and 45 Gy to the nodal areas.

Results: No morbidity related to the fiducial marker implantation was recorded. Main acute toxicities were gastrointestinal and haematological. Outcome, acute and late toxicities are similar to the main series published.

Conclusions: 4D-CT treatment plans permits to tailor the radiotherapy treatment on the specific target movement of the patient. Despite it often results in augmented volumes, it demonstrated the best coverage of the PTV, without increasing toxicity.

C067

FEASIBILITY STUDY OF HYPOFRACTIONATED REGIMENS IN PARTIAL BREAST IRRADIATION (PBI) USING RADIOBIOLOGICAL MODELS

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Aim of the Study: To evaluate the feasibility of hypofractionated regimens of PBI in terms of tumor control and cosmetic outcomes using Normal Tissue Control Probability (NTCP) and Tumor Control Probability (TCP) models.

Materials and Methods: Seventy patients were treated with external beam, forward intensity modulated PBI at a prescribed dose of 40 Gy in 10 fractions. Dose Volume Histograms (DVHs) were extracted and the average NTCP of subcutaneous fibrosis was estimated using a Lyman model based on biologically effective uniform dose (BEUD) [1]. Average NTCP on the patient population was recalculated using each patient DVH rescaled to total dose and dose per fraction in the treatments considered. NTCP iso-level curves were visualized in a plot of total dose *versus* fraction number. In this graph the curve of total dose to the tumor equivalent to 50 Gy in 25 fractions was also plotted. A formula of biological equivalent dose (BED) corrected for repopulation of tumor cells was used to calculate equivalent breast tumor doses [2]. A clinical trial in which the number of treatment fractions is to be decreased from 10 to 7, 5 and 3 fractions was designed. Average NTCPs on the patient group were recalculated for these hypofractionated regimens. A first group of patients was treated with 35 Gy in 7 fractions and the incidence of toxicity was assessed.

Results: Treatments with total prescribed doses of 35, 30, 24, Gy in 7, 5 and 3 fractions, respectively, were considered feasible. The NTCPs for these treatments were 14.5%, 11.7%, 10.1% which were considered acceptable risks of 2nd grade Radiation Induced Fibrosis. Twenty five patients were treated in 35 Gy, 7 fractions. The average NTCP on these patients was 10.8% and the incidence of fibrosis was 4% after an average follow-up of 2 months.

Conclusions: Hypofractionated treatments are considered feasible on the basis of NTCP and BED to the tumor. Early results on patients treated in 7 fractions are promising. Accrual of patients to a prospective study will provide clinical validation of this hypothesis in due course.

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C068

SUBJECTIVE AND OBJECTIVE MEASURES OF LATE MORBIDITY AND ONCOLOGICAL OUTCOME AFTER RADICAL HYPOFRACTIONATED RADIOTHERAPY IN MEN WITH PROSTATE CANCER

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Aims: To test the hypothesis that three-dimensional hypofractionated radiotherapy (3D-HFRT) is well tolerated and not worse than 3-D conventional RT (3D-CRT) for oncological outcome.

Methods: In all, 162 men with histologically confirmed prostate adenocarcinoma were included in the analysis. In all, 82 men were treated with 3D-HFRT (15 fractions of 3.62 Gy delivered 3 times/week; a total dose of 54.3 Gy). This group was retrospectively compared with 80 men who met the same inclusion criteria and who were treated with 3D-CRT (39 fractions of 2 Gy delivered daily; a total dose of 78 Gy). A short course of hormone therapy was administered concomitantly with the RT.

Results: Only one (1.7%) patient in the 3D-CRT group and two (4.0%) in the 3D-HFRT group had Grade 3 genitourinary toxicity. There was late gastrointestinal morbidity of ≥ grade 3 in only 5.1% of men treated with 3D-HFRT and in 4.0% of men treated with 3D-CRT. In both groups there was no Grade 4 toxicity. Significant changes in storage-symptoms were not found. The assessment of voiding-symptoms and maximum urinary flow rate (Qmax) showed that no significant difference was measurable at 12 and 28 months. For PVR, a transient increase at 12 months with a subsequent decrease at 28 months was measured. No significant increase in alpha-blockers usage and in the percentage of men with pathological non-intubated uroflowmetry (NIF) was observed at 12 and 28 months. Finally, patients did not perceive any clinical worsening in their quality of life (QoL) as attested by the International Prostate Symptom Score (IPSS)-QoL. At the median (range) follow-up of 45 (39.4-51) months for the 3D-HFRT group and 57.5 (54.9-59.1) months for 3D-CRT group the progression rate was 18/82 (21.9%) and 20/80 (25.0%), respectively, with no significant worsening in the risk of biochemical failure (BCF; log-rank test, P= 0.222).

Conclusions: In the present study, men with clinically localized prostate cancer had similar levels of morbi-

dity irrespective of whether they received HFRT or CRT without any worsening in the early risk of BCF. Thus, the present data provide some clinical evidence to justify trends already emerging toward HF regimens for treating clinically localized prostate cancer.

C069

HYPOFRACTIONATED RADIATION THERAPY IN THE ADJUVANT SETTING OF BREAST CANCER: EARLY AND LATE TOXICITY

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Introduction: Breast conservation surgery (BCS) followed by whole breast radiotherapy (WBRT) represents the standard of care for early- stage breast cancer. Large randomized trials have shown that fewer larger fractions (hypofractionation), to a total dose < than 45 Gy, may be as efficacious as "conventional" treatment without increased toxicity. The aim of this study is to evaluate results and to determine both acute and late toxicity profile of hypofractionated adjuvant WBRT in a mono-institutional series.

Materials and Methods: From April 2007 to April 2012 , 227 women treated with BCS for early stage breast cancer (pathological stage pTis, pT1 or pT2, pN0-N1) underwent WBRT with hypofractionated radiation regimen. Median age was 61 years (range 36-86). One hundred and twenty (53%) patients (pts) had right side cancer, 102 (45%) pts left side, 5/227 (2%) pts underwent bilateral WBRT. Sequential chemotherapy and hormone therapy given concomitantly to radiotherapy were given in 11/227 (5%) pts, while 154 /227 (68%) pts received hormone therapy alone and 7/227 (3%) pts had trastuzumab concomitant to irradiation. WBRT consisted of 16 total treatments given as five treatments per week, 2.65-2.66 Gray per fraction to a total dose of 42.5-42.56 Gray, and was delivered with two opposed tangential fields by using 6 MV photon in 222/227 (98%) pts and 60CO in 5/227 (2 %) pts. Boost irradiation to the tumor bed was administered in 35/227 (15%) pts. Acute radiation reactions were evaluated at the end of the radiotherapy course and a month later and scored according to the RTOG toxicity grading system. Late toxicity was assessed in pts achieved at least 6 months' follow-up according to the LENT SOMA system.

Results: With a median follow up of 17 months (range 1-59): no pt had local relapse, 3 (1%) pts experienced disease recurrence (all with systemic spread). Two hundred and nineteen (96%) pts are alive without breast cancer disease, 4 pts died (1 of progression of disease), 2 pts are alive with metastatic disease, 2 pts are lost. Compliance to therapy was excellent: no pts showed severe acute toxicity requiring interruptions. Forteen /227 (6%) pts developed no toxic effect, 126/227 (55,6%) pts had grade1 acute toxicity, 86/227 (38 %) pts grade 2. Major toxicity (grade 3) was detected only in 1/227 (0,4%) pt. A month after the end of the radiotherapy course 41/227 (18%) pts had residual toxicity (G1 and G2). Late radiation toxicity was evaluated in 182 /205 pts with at least 6 months' follow up: no late toxicity was observed in about 60 % of pts, high grade late effect was detected only in 1/182 (0.5%) pt. The most common late reaction was breast oedema, shown in 55/182 (30%) pts: grade 1 in 51 pts and grade 2 in 4 pts. Forty/182 (22%) pts developed pigmentation change: G1 in 38/40 (95%) pts and G2 in 2/40 (5%) pts. Seven /182 (4%) pts showed telangiectasia: G3 only in 1 pt, with large size breast an treated with 60CO. Three/182 (2%) pts had radiation fibrosis, G1 in 3 pts, G2 in 1 pt. Poor cosmetic outcome due to late toxicity was found in 3/182 (2%) pts. No worse results either in acute or in late toxicity were observed in pts treated with boost.

Conclusions: WBRT is well tolerated and represents a good alternative to the standard regimen; our findings support its implementation in clinical practice.

C070

HYPO-FRACTIONATED RADIATION THERAPY WITH OR WITHOUT SYSTEMIC TREATMENT COMPARED TO STANDARD TREATMENT REGIMEN FOR GLIOBLASTOMA MULTIFORME: LOCAL CONTROL AND TOXICITY

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Backgrounds: Glioblastoma (GBM) is the most common malignant primary brain tumour in adults. The standard treatment today is maximal surgical resection followed by concomitant chemo-radiation therapy followed by adjuvant TMZ according to Stupp protocol, with median overall survival of 14.6 months and 2-year survival rate of 26.5%. Despite the progress in neurosurgery, radiotherapy and oncology, the prognosis still result poor.

Purpose: In order to reduce the long time of standard treatment, maintaining or improving the clinical results, in our institute we investigated the effects of hypofractionated radiation therapy for patients with GBM. For comparison, a group of 25 patients with similar characteristics and treated with concomitant conventional radiation therapy and TMZ followed by adjuvant TMZ according to Stupp protocol was retrospectively selected.

Materials and Methods: 67 patients affected by GBM underwent surgical resection (total, subtotal or biopsy) were treated between October 2005 and December 2011 with hypo-fractionated radiation therapy followed or not by adjuvant chemotherapy with temozolomide (6-12 cycles). The most important eligibility criteria were: biopsy-proven GBM, KPS>60, age>18 years, not previous brain irradiation, informed consensus. Hypo-fractionated radiation therapy (5 Gy/fraction/day) was delivered to a total dose of 25 Gy in 5 fractions, dose prescribed at the

70% isodose. All patients were immobilized using a standard helmet mask system. All patients received a non-contrast CT scan and MRI for treatment planning. After image fusion, the target volume was defined by the contrast-enhanced tumour edges on axial T1 and FLAIR sequences by consensus agreement of the neurosurgeon, neuroradiologist, and radiation oncologist. Treatment planning was performed to cover the 100% of planning target volume by 25 Gy, with maximum dose of 35.7 Gy. For treatment delivery, all patients received an portal image prior to each treatment fraction. Sex, age, type of surgery, Karnofsky performance status, Recursive Partitioning Analysis (RPA) classification, time between surgery and initiation of radiotherapy were analyzed as potential prognostic factors for survival using the univariate log-rank method.

Results: All patients have completed the treatment protocol. Median age was 64,5 years (range 41-82 yrs) with 31 females (46%) and 36 males (54%). Median KPS at time of treatment was 80. The surgery was gross total in 38 patients and subtotal in 14 patients; 15 patients underwent only biopsy. The patients characteristics of the two groups of patients are similar. With mean follow-up of 14.9 months (range 3-62 months), the median overall survival and median progression- free survival were 12.43 and 6.9 months, respectively. No grade 3-4 acute or late neurotoxicity was observed. Post-treatment median KPS was 90 (range 70-100). The overall tolerance of patients to hypo fractionated RT was not different from that for conventional radiotherapy. Not statistically significant difference in terms of overall survival between hypofractionated RT group and Stupp protocol group was reported (p 0.12).

Conclusions: The hypo fractionated radiation therapy can be used for patients with GBM , resulting in favourable overall survival, low rates of toxicity and satisfying QoL. Future investigations are needed to determine the optimal fractionation for GBM.

C071

LATE TOXICITY FOR FORWARD PLANNED INTENSITY MODULATED WHOLE BREAST HYPOFRACTIONATED RADIOTHERAPY

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Purpose: START A and START B studies have demonstrated a similar toxicity obtained by hypofractionation and standard fractionation in whole breast adjuvant radiotherapy. The aim of this study is the evaluation of hypofractionation effect on toxicity in our breast cancer patients.

Materials and Methods: From 02/2009 to 01/2012 500 patients were treated with hypofractionated whole breast radiotherapy, 40 Gy/15 fractions, delivered in 3 weeks, in our institution. Five patients had bilateral treatment. Each breast was countead separately (= 505 patients). The median patient age was 62 years (28-91 years). One hundred twenty five pts (25%) had neoadjuvant, adjuvant or concomitant chemotherapy. A median number of 4 segments was used (2-12) within a tangential two field irradiation technique. 357 (70,69%) of breasts needed more than 4 segments to obtain a homogeneous dose. To report the acute toxicity (6 months follow up included), the RTOG/EORTC scale was used, while for late toxicity the SOMA LENT scale was used.

Results: The median follow-up of this group of patients was 11 months (1-37 months). One patient was dead at the last follow up, with distant metastases and 7 pts presented progressive disease: 5 distant, 1 local and 1 infrapectoral. The toxicities were: see Table 1: breast hypofractionation toxicity. No patient nedeed treatment interruption for toxicity caused by radiation therapy. Twenty-one of 505 pts (4,16%) presented delayed acute toxicity, 5-30 days after the end of radiotherapy. Toxicity was intended as skin discoloration, oedema and fibrosis. No lung or heart toxicity were recorded.

Conclusions: The hypofractionated FIMRT regimen (2,67 Gy/fr) used for WBRT in our institution allowed us to obtain a good acute and late toxicity, better than historical standard fractionation results, with no treatment interruptions.

Table 1.

Toxicity grade	End of R (505 pts)	At 6 mts (420 pts)	At 12 mts (232 pts)	At ≥24 mts (54 pts)
G0	119 (23,56%)	327 (77,85%)	203 (87,50%)	52 (96,29%)
G1	327 (64,75%)	92 (21,90%)	28 (12,06%)	2 (3,7%)
G2	55 (10,89%)	1 (0,23%)	1 (0,43%)	1 (1,85%)
G3	4 (0,79%)	0	0	0

C072

LATE TOXICITY USING 3D EXTERNAL HYPOFRACTIONATED RADIOTHERAPY TO THE WHOLE BREAST WITH CONCOMITANT TUMOR BED BOOST

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Purpose: to evaluate the late reactions in breast cancer patients treated with hypofractionated radiotherapy and concomitant boost in breast cancer adjuvant setting.

Materials and Methods: between May 2003 and October 2005, 270 patients who presented T1-T3, irrespective of nodal involvement, were treated with conservative surgery and hypofractionated whole breast radiotherapy.

The schedule consisted of 2.25 Gy/day whole breast irradiation with a daily concomitant photon tumor bed boost of 0.25 Gy in 20 fractions. Late toxicity was evaluated based on the Subjective Objective Management Analytic Late Effect of Normal Tissue (SOMA/LENT) criteria, six months after the end of radiotherapy and every twelve months afterwards. Subjective toxicities was recorded using the Numeric Rating Scale (NRS) for itch, pain, and burning at each visit.

Results: Subjective and objective late toxicity data is available for 247 patients with a median follow-up time of 75.5 months (range 10.1 - 102.4 months). 21% of patients experienced pain as late treatment toxicity according to the SOMA/LENT scale, but it was limited to grade 1 and grade 2. Grade 3 pain was reported in 0.8% patients. Nineteen patients (7.7%) reported a very slight and occasional hithching as a late consequence of treatment. Five patients (2%) complained of burning sensation to the skin. According to the NRS scoring system, the intensity of pain was intense in 2.4%. One patient suffered from G2 breast edema (0.4%). G2 breast fibrosis was observe din 2.4% of the patients. Patient's opinion on the cosmetic result according to Harvard scale was rated excellent or good in approximately 67% of cases. 65.6% of the patients were satisfied of the overall treatment course. No-one experienced clinicial sign of radiation pneumonitis o cardiac side effects.

Conclusions: This hypofractionated Rt scheme resulted in acceptable objective and subjective late toxicity and support the feasibility of incorporating boost to the tumor bed inside the whole breast treatment using a 3D conformal technique, without the need of advanced forms of radiotherapy.

C073

IMPACT OF A NON CONVENTIONAL SCHEDULA ON NEUROCOGNITIVE FUNCTIONS IN HIGH GRADE GLIOMAS: A LONG TERM ANALYSES OF A PROSPECTIVE PHASE II STUDY

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Purpose: The aim of this analysis is to evaluate the neurological functions (NF) in 2 groups of patients (pts) affected by High Grade Glioma: pts receiving standard treatment according to Stupp' schedule (Group A) and pts enrolled in a phase II study of 3D-Conformal Radiation Therapy (3D-CRT) plus Fractionated Stereotactic Conformal Radiation Therapy (FSCRT).

Materials and Methods: Group A: pts underwent to 3D-CRT with conventional fractionation of 180 cGy/die to tumour bed plus margins, delivered until a total dose of 59.4 cGy. Group B: pts (≥18 yrs) with CTV≤8 cm underwent to 3D-CRT (180 cGy/die) plus concomitant FSCRT boost (10 fractions of 90 cGy) and/or sequential FSCRT boost (4 fractions of 250 cGy/die) until a total dose was 69,4 Gy. Concomitant and adjuvant TMZ was administered in both of groups according to Stupp'schedula. NF were evaluated in pts with an overall survival (OS) better than Stupp's study (14,6 months); they received the Mini-Mental-State-Examination (MMSE) (total score-TS =30) during the follow-up (FUP) and several skills were analyzed: space-time orientation (TS=10), short-term memory (TS=3), attention and ability to calculate (TS=5), memory (TS=3), language (TS=8) and construction skills (TS=1).

Results: Group A: 37 pts were eligible to a neurological evaluation: 21 male and 16 female with a median age of 48 aa (range 19-77). Median FUP was 35 months (range 14-113); we observed a mean TS of 28.7: mean score (MS) of space-time orientation was 9.6; mean short-term memory and memory score were 2.9 and 2.5 respectively; MS of attention-calculation and language skills were 4.8 and 7.8 respectively; only 4/37 pts presented difficulties in construction skills (MS:0.8). Group B: 11 pts were eligible: 8 male and 3 female with a median age of 53aa (range 32-70). Median FUP was 96 months (range 50-103); we observed a mean TS of 27,9: short-term memory and language functions were completely preserved in all pts, while the attention and calculation skills were the more damaged functions (mean TS of 4,1), but it may be correlated to the scolarity level; MS of space-time orientation and memory were 9,6 (4 pts obtained 9/10) and 2,2 respectively and only 1 patient presented difficulties in construction skills. Late neurological toxicity included 2 radio-necrosis histologically proved (at 14 and 24 months).

Conclusions: FSCRT boost associated to 3D-CRT and TMZ is well tolerated with a good preservation of neurological functions.

C074

ACUTE TOXICITY IN PROSTATE CANCER PATIENTS TREATED WITH HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY

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Purpose: To evaluate acute toxicity resulting from hypofractionated intensity-modulated radiotherapy (IMRT) in prostate cancer patients.

Materials and Methods: Between May 2009 and December 2011, 96 patients with prostate cancer underwent IMRT. The patients' characteristics were as follows: median age 73 years (range 58-83); stage T1N0 in 18 patients (18,75 %), T2bN0 in 8 (8,33 %), T2a N0 in 9 (9,37%), T2cN0 in 45 (46,87 %), T3a N0 in 2 (2,08%), T3bN0 in 13 (13,54 %) and T4N0 in 1 (1,04 %); Gleason score 2- 6 in 56 patients (58,33 %), 7 in 29 (30,21 %) and 8-10 in 11 (11,46 %). The median basal PSA was 8 ng/ml (range 3,51-36,13). The median pre RT and post RT PSA levels were 8,175 ng/ml (range 0.005 – 22,83) and 1,2 ng/ml (range 0.08 – 10,35l) respectively; 34/96 (35,42%) received hormonal therapy (LHRH analogue and/or

antiandrogen) because of high risk features. IMRT was delivered with 15 MV photons using a five-fields technique.The target volume included the prostate in 53 (62,16 %) patients , prostate and seminal vesicles (SV) in 43 (37,83%) on the basis of the risk or direct involvement of SV. Planning target volume (PTV) consisted of CTV plus 1 cm in all directions except than the prostate fossa-rectal interface where 0.5 cm margin was added. The prescribed dose to prostate ± SV was 74.25 Gy in 33 fractions at 2.25 Gy/fraction, equivalent to 78 Gy in 2-Gy fractions; SV received 62 Gy in 33 fraction at 1,879 Gy/fraction using a simultaneous integrated boost (SIB-IMRT) when the risk of involvement was >15%. The median prostate volume was 44,26 cm3 (range 16,72-121,60 cm3). Acute toxicity was scored using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 criteria. Biochemical failure was defined according to the Phoenix definition (increase of ≥ 2 g/L greater than the prostate-specific antigen nadir after RT).

Results: Median follow-up time was 11,5 months (range: 6 - 33 months). Distant metastasis developed in 3 patients (8.1%) at a median of 7,9 months (range 6,7-10,9). When data were analysed 93/96 patients (96,87 %) were alive without disease, 3 patients (3,12 %) were alive with distant metastases. Acute gastrointestinal (GI) toxicity, mainly consisting in proctitis, was observed in 27 (28,12%) patients: G1 in 16 (16.66%), G2 in 7 patients (7.29 %) , G3 in 4 patients (14,16%).There was no G4 acute toxicity. Acute genitourinary (GU), mainly nicturia, dysuria, urgency and frequency of urination, were observed in 62 (64.58 %) patients: G1 in 37 (38.54 %), G2 in 14 (14,16 %), G3 in 14 (8,33 %), G4 in 3 (3,12 %). Patients with larger prostates (>50 cm3) had a (prostatic volumes >50 cm3 were associated with a) higher rate of acute Grade 3 genitourinary toxicity. Late GU and GI toxicities occurred in 4 (4,16%) and 8 (8,33%) patients respectively.

Conclusions: Our data confirm that acute obstructive urinary symptoms are the most frequently reported side effects; IMRT is associated with overall acceptable acute GI and GU toxicity rates. A larger series is necessary to corroborate our data on acute toxicity and a longer follow-up to evaluate late toxicity and biochemical response rates.

C075

HYPOFRACTIONATED RADIOTHERAPY *VS.* STANDARD FRACTIONATION FOR ELDERLY BREAST CANCER PATIENTS: PRELIMINARY RESULTS OF ACUTE AND LATE TOXICITIES

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Introduction: To compare Hypofractionation regimens of Radiotherapy (HRT) *vs*. Conventional Radioterapy (CRT) in elderly patients (pts) with right breast cancer and evaluate acute and late toxicity.

Materials and Methods: Between January 2009 and March 2012, 42 patients with non-metastatic right breast tumors were treated with surgery and adjuvant RT. 34 patients were evaluable. Twenty patients, median age 75 yrs (64-88) were treated with HRT. Two HRT schedules were used: 42.4 Gy in 16 daily fraction (2.65 Gy/fx) and 40 Gy in 16 daily fraction (2.5 Gy/fx). The clinical stage distribution was as follows: pTis 5%, pT1a 5%, pT1b 25%, pT1c 50% and pT2 15%. Axillary lymph nodes were positive in 30 % of pts. Three pts received boost (10 Gy, 2Gy/fx) on tumour bed by electrons. No patients received neoadjuvant chemotherapy. Adjuvant hormonal therapy was given in 75% of pts. 3 pts received adjuvant chemotherapy. The median follow-up was 14 months (3-28). Fourteen patients were treated with CRT (50 Gy in 25 daily fraction; 2 Gy/fx). The clinical stage distribution was as follows: pT1c 36%, pT2 57% and pTy0 7%. Axillary lymph nodes were positive in 50% of pts. Twelve pts received boost (10 Gy, 2Gy/fx) on tumour bed by electrons. Adjuvant hormonal therapy was given in 71% of pts. Three pts received neoadjuvant chemotherapy, 4 pts received adjuvant chemoterapy. The median follow-up was 17 months (3-31). Acute and late cutaneous and pulmonary toxicities were scored according to the Radiation Therapy Oncology Group criteria (RTOG).

Results: At the time of the analysis all patients were surviving and any breast relapse or nodal recurrence (supraclavicular, axillary and internal mammary nodes) occurred.

Conclusions: Although with a short time of follow-up, in both groups we observed a prevalence of G1 and G2 acute and late toxicity while none severe (G3-G4) acute and late toxicity occurred. Therefore it seems that hypofractionated and conventional RT can be either safety useful.

HYPOFRACTIONATED RT					
ACUTE TOXICITY	**G0**	**G1**	**G2**	**G3**	**G4**
SKIN	6 (30%)	4 (20%)	10 (50%)	0	0

CONVENTIONAL RT					
ACUTE TOXICITY	**G0**	**G1**	**G2**	**G3**	**G4**
SKIN	1 (7%)	0	13 (93%)	0	0

HYPOFRACTIONATED RT					
LATE TOXICITY	**G0**	**G1**	**G2**	**G3**	**G4**
SKIN	17 (85%)	2 (10%)	1 (5%)	0	0
SUBCUTANEUS	16 (80%)	4 (20%)	0	0	0
PULMONARY	0	0	0	0	0

CONVENTIONAL RT					
LATE TOXICITY	**G0**	**G1**	**G2**	**G3**	**G4**
SKIN	3 (21%)	11 (79%)	0	0	0
SUBCUTANEUS	9 (65%)	4 (28%)	1 (7%)	0	0
PULMONARY	13 (93%)	1 (7%)	0	0	0

C076

EFFICACY AND TOLERANCE OF HYPOFRACTIONATED RE-IRRADIATION IN CARCINOMA OF THE RECTUM PREVIOUSLY TREATED WITH RADIOTHERAPY

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Aims: Although historically considered dangerous, the re-treatment with pelvic radiotherapy may be used in selected cases with local recurrence of rectal cancer already irradiated, for pain and rectal bleeding to achieve symptomatic relief. Some literature data show that, even in the re-treatment of recurrent rectal cancer, radiation therapy performed with a few fractions and high dose per fraction, has the greatest effect in terms of subjective response. Purpose of this study is to evaluate the toxicity and local control after treatment with hypofractionated radiotherapy for recurrent rectal cancer in patients previously irradiated on the pelvis.

Materials and Methods: From January 2009 to December 2011, ten previously irradiated rectal cancer patients were re-treated in our centre with radiotherapy for symptomatic pelvic recurrence. Five of them were females and 5 males. The mean age was 63.7 years (range 33-94), with two nineties patients; the performance status was more than 70 at least, painful symptoms were present in all cases, worthy of treatment with anti-inflammatory drugs and, in 3 cases, with opioids. Rectal bleeding was associated with pain in 6 of them. The median time to recurrence of 13 months (range 6-23). Seven patients underwent external beam radiation therapy (ERT) and 3 intra-operative treatment (IORT) with a single dose of 12 Gy on the site of adhesion/infiltration. ERT was performed with a total dose of 24 Gy/8 fractions in 5 cases and 20 Gy/5 fractions in two patients who had received the previous irradiation over one year before. The target included the macroscopic disease (CTV) with a radial safety margin of 2 cm (PTV). All patients were followed for evaluating the therapeutic effect and tolerance

Results: The median follow-up was 21.7 months (range 11-32). All patients completed the planned treatment without interruption and presented an immediate benefit within the first 2 weeks after the end of it, with subjective improvement of symptoms and objective reduction in bleeding and pain (2 patients discontinued analgesic therapy, all the others reduced it, with opiates interruption in two patients). The average duration of pain relief was 6.2 months (range 3-12), with median survival of 11.2 months (range 6-15) and four patients died of disease. The re-treatment was well tolerated without grade ≥ 3 toxicity (4 patients presented symptoms of acute proctitis grade 2 WHO) with a significant impact on quality of life. Age did not seem to influence toxicity neither the treatment effectiveness.

Conclusions: Preliminary results of this experience show the efficacy and safety of pelvic hypofractionated re-irradiation in rectal cancer already treated with radiotherapy. Despite the high cumulative doses, relevant worsening in toxicity was not found and a significant improvement in quality of life of re-treated patients was observed.

C077

CAN TREATMENT VOLUME, DOSIMETRIC AND CLINIC PARAMETERS BE RELATED TO THE OCCURRENCE OF RILI (RADIATION-INDUCED LUNG INJURY) AFTER THORACIC RADIOTHERAPY?

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Purpose: The radiological finding of RILI (radiation-induced lung injury) is common after radiation therapy for lung cancer, even if not always it is associated with the clinical manifestation of pneumonitis, nor it correlates with a decrease of patient's pulmonary function.

Materials and Methods: The predictive value of dosimetric parameters and Pulmonary Function Tests (PFTs) and their correlation with the incidence of RILI were the object of this study. Data of patients submitted to radiotherapy on lung and/or mediastinum, in our Institution were analysed. Eligibility criteria were: presence of visible tumor on a diagnostic chest CT scan, availability of CT scans before irradiation and at 3–6 months follow-up, baseline PFTs, with at least forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), total lung capacity (TLC), functional residual capacity (FRC) and vital capacity (VC) at 2–4 months follow-up. The worsening of pulmonary function was evaluated comparing PFTs performed before and after radiotherapy.

Results: From 2005 to 2010, 64 cancer patients (NSCLC:60 SCLC:3, thymoma:1) received 3D conformal radiotherapy on lungs and/or mediastinum via Linear Accelerator. In particular: 49 patients were delivered 50.4Gy/1.8 Gy; 9 patients received hypofractionated stereotactic body radiotherapy (SBRT) at a total dose of 50Gy/10 Gy or 42Gy/14 Gy (in both cases the EQD2 was >100 Gy); 6 patients received low-dose of radiotherapy (6,4 Gy or 4,8 Gy delivered in fractions of 0,4 Gy, twice daily) as a chemopotentiator of chemotherapy regimen. The majority of the patients were male, and their median age was 69 years, median CTV was 94.21cc (range 18.8-243). During a median follow-up period of 25 months (range 3-72), 32 patients (50%) developed radiation-induced changes in lung tissue. The volume of CT*Vs* was no significant factor for occurrence of RILI. Logistic regression was performed to verify whether the commonly used lung dosimetric constraints could be predictive of RILI. MLD was found to be the strongest predictor of RILI (Odds Ratio: 1.20; 95% CI: 1.04 – 1.39; p: 0.012). No worsening of PFTs resulted in clinically significant decrease of patient's respiratory performance.

Conclusions: In our study, occurrence of RILI was not significantly influenced by the lung irradiated volume and not necessarily correlated with a worsening of the patient's respiratory performance. Despite this, our data

confirmed the important role of dosimetric parameters for the prediction of lung toxicity.

C078

IMPACT OF CONE-BEAM COMPUTED TOMOGRAPHY IN THE DEFINITION MARGINS IN LOCALLY ADVANCED LUNG CANCER

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Purpose: The use of image guidance in the delivery of radiotherapy has become increasingly popular. One of most important device is the cone-beam computed tomography (CBCT). The benefit of on-board CT-base image guidance is the increased positioning accuracy of the target volume, which enables to use smaller margins, decreasing dose to normal tissue. Purpose of our study was to evaluate set-up error (systematic ∑ - random error) using CBCT in order to obtain therapy PTV margins for weekly CBCT/Image Guide Radiation Therapy in locally advanced non-small cell lung cancer radiation.

Methods: From May 2010 to April 2011 35 patients with a diagnosis of locally advanced lung cancer, were treated in our Institution. Two different scenarios of set up control were analyzed: In A) scenario patients were located using skin tattoo with no image guidance. The daily setup error that would have occurred with this scenario was simply the shift obtained from daily CBCT. In B) scenario patients were located using the mean shifts calculated from imaging during the first 5 fractions, and then set up control was evaluated with weekly CBCT imaging. 817 CBCT scans were coregistered to the planning scan and 2451 measures were obtained in all directions (Antero-Posterior AP- Cranio-Caudal CC- Latero-Lateral LL). Set-up margins were calculated using the population-based van Herk formula: 2.5 ∑+0.7.

Results: The set up error data for each imaging scenario was described in Table 1 and Table 2. Population's set up margins obtained by using van Herk margin formula are described in Table 3.

Table 1.

A	LL	CC	AP
∑	2.9	3.5	5.3
σ	2.9	2.8	4.1

Table 2.

B	LL	CC	AP
∑	1.7	2.5	3.1
σ	2.5	2.9	4.2

Table 3.

Margin	LL	SI	AP
A	9.4 mm	10.8 mm	16.2 mm
B	6.2 mm	8.5 mm	10.9 mm
Daily CBCT (literature)	3 mm	3 mm	4 mm

Conclusions: The use of CBCT image guided in lung cancer radiotherapy treatment is very important to reduce set- up margins; however the imaging frequency can change these values. Daily CBCT is the optimal scenario to evaluate set-up error and then to permit a maximum margin reduction in PTV definition. Another option is to image daily for the first 5 fractions, and then weekly. In this case, appropriate imaging can be added following the indication of the present study. This option may reduce additional radiation doses, time delivery and costs despite a slight increase of set up margin.

C079

A TWO-STEPS IRRADIATION TECHNIQUE FOR SMALL CELLS LUNG CANCER PATIENTS

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Aims: In order to elaborate an optimal radiation therapy treatment planning in bronchogenic cancer, it is necessary to assure an adequate dose delivering to targets (GTV-CTV) and, at the same time, pay attention to organs at risk (OAR) such as spinal cord and lungs. In recent decades, technological improvement and better understanding of physical and clinical aspects, have led to the definition of new techniques an methods of irradiation of patients with lung cancer. The purpose of our work is to describe a 3D-conformal radiotherapy tecnique for the irradiation of small cells lung cancer patients.

Materials and Methods: For small cells lung cancer patients undergoing radiotherapy treatment, a specific irradiation technique in two steps has been developed in our Institution. It consists of the following phases: patient is set-up on a dedicated carbon-fiber oblique table with handles above the head for a correct chest immobilization; a CT scanning with 0.5 cm slice thickness combined with a virtual simulation software for the identification of the final treatment isocenter is acquired; OAR (spinal cord, lungs, heart) and a large PTV counturing is performed (the contoured volume ranges from 950 to 1000 cm3). The "two steps irradiation technique" consists in: First phase - PTV is irradiated with two opposed anterior-posterior beams, with a percent weight at the isocenter of 60% in anterior and 40% in posterior. Through this step, a first dose of 30 Gy fractioned in 15 sessions is prescribed to the isocenter. Second phase - An angular beams setup (gantry angles of 0°, 40% weighted, 120° and a 240°, each 30% weighted) has been chosen, conformed to the same PTV, for a total dose of 20 Gy fractioned in 10 sessions, prescribed to the isocenter. The complete dose delivered by the two treatment steps is 50 Gy/25 fractions, prescribed to the isocenter.

Results: The efficacy of this radiotherapy technique in terms of DVH evaluation for doses distribution to PTV and OAR is satisfactory and no major toxicities were detected in the immediate follow-up. Moreover a CT scan examination performed two months after the completion of treatment shows good results in terms of tolerability, while the evaluation of responses is still to be defined.

Conclusions: The irradiation technique divided in two

steps allows some advantages: as regards the organs at risk, the first phase permits to spare the two lung volumes, while the second one permits to protect the spinal cord. As result, the sum of the two phases allows both the compliance of the tolerance levels of all organs at risk and a local control of PTV in terms of total dose (50 Gy fractioned in 25 sessions, prescribed to the isocenter).

C080

THE ROLE OF THE PET-TC FOR EVALUATING THE RESPONSE OF NON SMALL CELL LUNG CANCER (NSCLC), STAGE III, INOPERABLE, AFTER THE COMPLETION OF CHEMO-RADIOTHERAPY

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Backgrounds: The objective of this study was to identify role of the PET-TC for evaluating the response of non small cell lung cancer (NSCLC), stage III, inoperable, after the completion of chemo-radiotherapy, its predictive value in identifying patients for surgery. We also analyzed correlation of PET TC results and histological results.

Methods: Between March 2010 and December 2012, 6 patients received chemo-radiation (CRT) for stage III NSCLC. For the stage of disease in the first instance had been ruled out surgery. Five of 6 patients were men (83%) and 1 woman, and the median age was 64 years (range 57-71 years). Five patients (83%) was stage IIIA NSCLC, and 1 patients had stage IIIB NSCLC. Radiotherapy (RT) was given after chemotherapy to all patients; all the patients underwent to surgery after 2 months. The median RT dose was 64 Gy (range, 60-70.4 Gy). Five patients performed 4 D PET TC recording phases of respiratory cycle after using immobilization system device, and so we define the target volume. 1 patients were planned with Volumetric modulated arc therapy (VMAT), and 5 performed 3DCRT.

Results: All the patients underwent a whole body 18F-FDG-PET/CT scan, 45 days after the end of radiotherapy, before surgery. A complete pathological response (CR) was achieved in 3 patients, and the histopathology was ypT0N0. In the other 3 we have partial response (PR, >30%), with histopathology ypT2N0 in 2 patients and ypT1N0 in one. Actually all patient are alive and no one developed toxicity.

Conclusions: This evaluation has become increasingly important with the advent of neoadjuvant therapy before surgery. Our study confirm the role of TC PET and its correlation with pathologic response and the good result of RTCT treatment for NSCLC.

C081

NUMBER OF NODAL STATIONS AS PROGNOSTIC FACTOR FOR LOCALLY ADVANCED NSCLC AFTER MULTIMODALITY TREATMENT: OUR EXPERIENCE

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Purpose: Lung cancer is the most common cause of cancer-related death for men and women in the world. The most common tumour is non-small cell lung carcinoma (NSCLC) with a 5 year survival rate of 67% (stage IA) to <5% (stage IV). Currently the most important prognostic factor of lung cancer is the stage (TNM). We evaluated the number of nodal stations and the tumour size as prognostic factors for locally advanced NSCLC after multimodality treatment.

Materials and Methods: We retrospectively reviewed 80 patients affected by NSCLC from January 2005 to December 2011 at the "Sapienza" - University of Rome, Policlinico Umberto I, Department of Radiation Oncology (follow up range 24-84 months). Sixty patients were male (75%) and 20 female (25%). The mean age was 66.4 years (range 29- 86). Fifty-nine patients (74%) were classified as IIIA stage and 21 patients (26%) as IIIB, according to TNM classification. All patients were divided in three groups based on tumour size (20-50mm, 50-70mm and >70mm) and on number of nodal stations (2-3, 4-6 and 7 or more). Using Log-Rank Test we analysed disease response for each group according to T and N stage. Histology evidenced squamous cell carcinoma in 27 patients (66%), adenocarcinoma in 53 patients (34%). All patients underwent surgery and sequential radio-chemotherapy. RT was delivered with a range of dose between 50-70 Gy with a daily fraction of 180/200cGy, with a 6 MV linear accelerator, using a three-dimensional external conformal radiotherapy (3D-ECRT) technique.

Results: A log-rank test did not show a significant effect of the tumour size (T) on the response rate to the treatment ($p=0.75$); instead it evidenced a significant effect of the number of nodal stations (N) on the response rate to the treatment ($p < 0.001$), with longer survival time for patients with 2-3 nodal stations than patients with 4-6 ($p < 0.001$) and 7 or more ($p < 0.001$) nodal stations.

Conclusions: Our study demonstrated that the number of lymph nodal stations involved appeared to have an important impact on OS: patients with few nodes examined have a better response. Tumour size has no effect on OS.

C082

MANAGEMENT OF VULVAR CANCER: RETROSPECTIVE EXPERIENCE OF THE RADIATION ONCOLOGY UNIT OF FLORENCE FROM 1983 TO 2010

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Purpose: We retrospectively analyzed our experience with patients affected by vulvar cancer (VC), focusing on radiotherapy intent, technical radiotherapy aspects (volumes, doses, use of brachitherapy (BRT) and external radiation therapy (EBRT) and outcomes.

Patients and Methods: From 1983 to 2010 a total of 200 patients were initially evaluated for our analysis; a total of 87 patients were elegible to be enroled in our study. 37 were treated with adjuvant intent, 22 were treated with radical intent and 28 were treated with salvage intention at the time of local relapse. Median age was 72 years; 86 patients were affected by invasive squamouscell carcinoma of the vulva, 1 patients was affected by Paget's intraepithelial disease. In adjuvant setting radiotherapy volumes were the following: vulvar region+inguinal region+pelvis (14 patients), inguinal region+pelvis (8), vulvar region+inguinal region (5), vulvar region+pelvis (2 patients), inguinal region (2), vulvar region (2). Mean dose for EBRT was 52.7 Gy for vulvar region (range 46-64); 53 Gy for inguinal region (range 22-66) and 49.6Gy for pelvis (range 38-58).4 patients were treated in adjuvant setting with exclusive BRT with a mean dose of 53 Gy. In radical and salvage setting radiotherapy volumes were the following: vulvar region (15), vulvar region+inguinal region (3), vulvar region+inguinal region+pelvis (9), inguinal region (3), inguinal region+pelvis (3). Mean dose for EBRT in radical setting was 54 Gy for vulvar region (range 30-66); 52.7 Gy for inguinal region (range 36-64) and 48 Gy for pelvis (range 36-54). 17 patients were treated in radical and salvage setting with brachitherapy with a mean dose of 57 Gy. Overall 49 patients were treated using 2D technique (+/- electrons), 20 with 3DCRT.

Results: Median DFS in this series was 9.3 months: in adjuvant setting (13 patients) was 15 months, in radical setting (12 patients) was 6 months and in salvage setting was 7 months. Local control of disease was achieved in 51 (58%) patients: 24 (47%) in adjuvant setting and 27 (53%) in radical and salvage setting. 3-year and 5-year OS was 40.2 and 29.8% respectively.

Conclusions: Radiotherapy confirms to be a well tolerated treatment in VC. Postoperative RT showed a better local control than the treatment at the time of relapse. RT could be an alternative treatment when surgery is not feasible, in fact radiotherapy guaranteed a local control in more than a half patients.

C083

GYNECOLOGICAL CANCER TREATED BY HDR BRACHYTHERAPY ± EBRT:10 YEARS EXPERIENCE

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Backgrounds: Therapeutic options for patients with gynecological cancer are surgery, external-beam radiation therapy (EBRT), high dose rate brachytherapy (HDR), and chemotherapy. Aim of this study is to evaluate our results in HDR ± EBRT of gynecological cancer.

Materials and Methods: From 2001 to 2011 186 women (mean age 57 years, range: 25-82) with endometrial (62%), cervical (33%) and vaginal (5%) cancer were treated by HDR±EBRT. Histology was: endometrial carcinoma (72%), SCC (20%), sarcoma and others. 79% of patients underwent surgery. 82% of patients present negative surgical margins, 14% positive and 4% close. The FIGO stage was: IB (16%), IC (20%), IIA (12%), IIB (19%), IIIA (13%), IIIB (11%), IIIC (6%), IVA (3%). Histological grades were G1 in 9%, G2 in 42% and G3 in 49%. 162 women (87%) received HDR+EBRT, where HDR was administered sequentially or during EBRT. 9% pts received HDR alone,4% EBRT alone. Prescribed doses for HDR were: 7 Gy in single fraction (6% cases), 10 Gy/2 frs (25%), 12 Gy/3 frs (3%), 15 Gy/3 frs (8%), 16 Gy/4 frs (53%) and 22 Gy/4 frs (5%). Doses for bladder and rectum were respectively ≤110% and ≤100% of the prescribed doses. EBRT was administered with 3D-CRT until 2008 in conventional fractionation; from 2009 with IMRT-SIB and from 2010 with IMRT-IGRT-SIB with Tomotherapy (moderate hypofractionation). 30% of cases also received chemotherapy. Acute and late toxicity were evaluated according to the RTOG-EORTC scale.

Results: Mean follow up was 5.4 years (1-11 y). Acute gastro-intestinal (GI) toxicity was: G1 34%, G2 20% and G3 1.6%. Acute genitourinary (GU) toxicity: G1 32% and G2 9%. Late GI and GU toxicity were respectively 7% and 11% (for G1); 4% and 5% (for G2). Two cases of GI G4 late toxicity were observed, both receiving HDR doses ≥16 Gy. Regarding HDR the maximum dose received by bladder and rectum was in mean respectively 80% and 92%. At 5y disease-free survival was 88%. Vaginal recurrences occurred in 5%, locoregional recurrences in 3%, distant metastases in 12%; 2% of patients dead.

Conclusions: In our experience toxicity and outcome were in agreement with literature data. HDR+EBRT is effective and safe with a low rate of recurrences and late complications. The two cases of GI G4, requiring surgery resection, occurred in patients treated in 2001, during early experience of 3D-CRT+HDR, with total dose ≥70 Gy. This is one of reason why from 2010 this treatment is done with 10 Gy/2 fr HDR+50-54 Gy with IMRT-IGRT-Tomotherapy.

C084

INTENSITY-MODULATED ARC THERAPY WITH THE USE OF FDG-PET/CT GUIDED FOR RADIOTHERAPY CERVICAL CANCER

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Purpose: to evaluate the role of FDG-PET/CT guided for radiotherapy treatment planning (intensity modulated radiotherapy with simoultaneous integrated boost (IMRT-SIB)) based on volumetric intensity modulated arc delivery.

Materials and Methods: From June 2010 to December 2011, 42 patients (pts) were treated for definitive cervical cancer with RapidArc-IMRT-SIB. All pts received concomitant chemotherapy (agents: CDDP or CDDP plus Paxlitaxel). CT scan was integrated either with CT/FDG-PET and MRI for gross tumour volume (GTV) delineation. The GTV-T(PET) and GTV-N (PET+), identified as focal areas of increased activity, were contoured by a nuclear medicine as the gross tumour volumes (GTV-PET) on the PET/CT images. Clinical target volume (CTV-T) and CTV-N were created by manual clinical margin and adding 7 mm margin to GTV-T/ GTV-T (PET) and GTV-N/ GTV-N (PET+), respectively. Margins of 15 mm and 5 mm were then added to create PTV-T (planning target volume) and PTV-N from CTV-T and CTV-N, respectively. Simultaneous integrated boost (SIB) technique was employed: 45-50.4 Gy (1.8 Gy/fraction) was prescribed to the T, N0 pelvic and/or para-aortic lymph nodes and 55 Gy (2.2 Gy/fraction) to the positive lymph nodes. For all pts the radiation treatment schedule included also a boost of 25-30 Gy to be delivered with high or pulsated dose rate brachytherapy (HDR or PDR). Cone beam CT (CBCT) was performed and any variation of set-up was applied.

Results: The FDG-PET/CT leads to a better volume definition and has the potential of showing lymph-nodes metastasis and T-tumour area. With RapidArc-IMRT we have obtained an excellent target coverage and low dose to organ at risk (OAR). In addition, RapidArc-IMRT reduced significantly the treatment time per fraction. In consequence, this treatment can have a clinical impact on single patient in terms of comfort, immobility and minimisation of internal organ's displacement due to intra-fraction organ motion.

Conclusions: Results from DVHs analysis showed an excellent reduction in OAR exposure maintaining high target coverage and conformality.With FDG-PET/CT it was possible also to definite better GTV. The impact of FDG-PET/CT findings on long-term survival and the study of other PET tracers which as biomarkers of tumour hypoxia and for an "adaptive radiotherapy" will be a subject of our future studies.

C085

VOLUMETRIC MODULATED ARC THERAPY WITH SIMULTANEOUS INTEGRATED BOOST FOR HIGH RISK ENDOMETRIAL CANCER VERSUS 3D-CONFORMAL RADIOTHERAPY: A DOSIMETRIC COMPARISON

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Purpose: To quantify differences in treatment dosimetry between 3-dimensional conformal radiotherapy (3D-CRT) and volumetric modulated arc therapy (VMAT) for high risk endometrial cancer treatment.

Materials and Methods: Twenty endometrial cancer patients treated with 3D-CRT and 20 with simultaneous integrated boost VMAT (SIB-VMAT) were selected for this planning study. Pelvic elective nodal irradiation (45 Gy, 1.8 Gy/fraction) plus concomitant boost to the vaginal vault (55 Gy, 2.2 Gy/fraction) was the treatment of choice. PTV2 was defined as the clinical target volume (CTV2) plus 8 mm margin. The CTV2 was defined as upper two-thirds of the vagina (if not involved) or the whole vagina (if involved at pathologic evaluation), obturator lymph nodes, external iliac nodes, internal iliac nodes, and presacral nodes (cranial to S2–S3 vertebrae). The boost volume (PTV1) consisted of the upper two-thirds of vagina plus resection lines in the parametria (CTV1) as delineated on the planning CT scan with an 8 mm margin. Target coverage, dose homogeneity, and sparing of organs at risk (OAR) were compared across techniques.

Results: The mean PTV1 and PTV2 volumes were 152.4 cc (SD+58.87) and 994.3 cc (SD+259.9), respectively. All techniques met the prescription goal for planning target volume coverage as shown in Table 1.

Table 1: Target coverage (mean±SD).

	3D-CRT	SIB-VMAT	P
PTV1			
Dmean (cGy)	5504±64.0	5614±54.9	**0.000**
D2 (cGy)	5621±96.1	5818±73.8	**0.000**
D98 (cGy)	5363±104.5	5305±73.4	**0.040**
V95 (%)	99.31±1.3	99.13±0.9	ns
HI_1	0.046±0.1	0.091±0.1	**0.000**
CI_1	3.04±0.8	1.99±0.5	**0.000**
PTV2			
Dmean (cGy)	4871±99.9	4899±78.5	ns
D98 (cGy)	4373±89.0	4367±152.6	ns
V95 (%)	99.40±1.4	98.28±1.8	ns
HI_2	0.249±0.0	0.279±0.1	**0.002**
CI_2	0.434±0.1	0.320±0.1	**0.011**

HI: Homogeneity Index
CI: Conformity Index

The SIB-VMAT technique produced more inhomogeneous plans than 3D-CRT, but showed significantly better conformity index (CIs) for both PTVs. SIB-VMAT was associated with significant reduction in the irradiated small bowel volume compared with 3D-CRT for the majority of dose/volume constraints analyzed. Moreover, significant differences were found with respect to OARs Dmean by SIB-VMAT technique as reported in Table 2.

Table 2: OARs sparing (mean±SD).

	3D-CRT	SIB-VMAT	p
Small bowel			
Dmean (cGy)	1316±917.4	1247±556.3	ns
D2 (cGy)	4844±404.0	4915±276.0	ns
V5 (cc)	417±250.2	434±188.0	ns
V10 (cc)	328±212.1	275±127.1	ns
V15 (cc)	277.7±189.9	159.1±82.1	**0.010**
V20 (cc)	249±181.2	120±59.6	**0.004**
V25 (cc)	206±166.2	96±43.7	**0.006**
V30 (cc)	147±146.9	75±34.8	**0.036**
V35 (cc)	111±121.1	57±28.1	**0.053**
V40 (cc)	91±107.8	40±21.5	**0.037**
V45 (cc)	63±91.8	12±12.5	**0.016**
V50 (cc)	6.5±18.4	1.1±4.7	ns
Bladder			
Dmean (cGy)	4952±302.3	4506±393.9	**0.000**
Rectum			
Dmean (cGy)	4828±386.0	4478±417.1	**0.006**
Right Femoral Head			
Dmean (cGy)	2858±564.4	2510±633.8	**0.062**
Left Femoral Head			
Dmean(cGy)	2895±583.0.9	2376±514.0	**0.003**

Conclusions: In postoperative radiotherapy for endometrial cancer, SIB-VMAT significantly improves the dose conformity and sparing of bowel, rectum, and bladder compared with 3D-CRT.

C086

EVALUATION OF TREATMENT VOLUME IN VULVAR CANCER THERAPY IN RADICAL AND ADJUVANT TREATMENT BY INTENSITY MODULATED RADIATION: A SINGLE INSTITUTION EXPERIENCE

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Purpose: The purpose of this study was to determine whether intensity modulated radiation therapy (IMRT) reduce the radiation dose to organ at risk (OAR) and investigate the use of simultaneous integrated boost (SIB IMRT) in vulvar cancer treatment.

Materials and Methods: From November 2010 to April 2012 we treated 15 patients with vulvar cancer, 5 underwent to adjuvant radiation therapy (RT) and 10 to definitive intent RT; 2/5 and 5/10 pts received concomitant chemotherapy (CDDP and 5FU) for the post operative group (POG) and for definitive group (DG), respectively. All pts underwent to CT scan from L4 to middle third of femur with slices separation of 2.5 mm and immobilisation system for legs (COMBIFIX) previous bladder filling with iodinated contrast by catheterization, rectal landmark and small bowel opacification by gastrographin®; in selection cases we used ev iodinated contrast for CT scan.We used step and shoot IMRT(6-15MV) in 13/15 pts and dynamic IMRT with tomotherapy in 2/15 pts.For POG the schedule was 50.4Gy/28 fx/ 5 weeks (LQED2 49.6Gy considering /ß=10 for efficacy -BED10 59.5Gy- and /ß=3 for late effects BED3 80.6Gy) for whole pelvic irradiation, in 2/5 pts we planned SIB 61.6Gy/28fx/5 weeks (LQED2 62.6Gy-BED10 75.2Gy- BED3 106.8Gy) (1 for positive urethral margin and 1 for Pet positive node).For DG the schedule was 45-50.4Gy/25-28fx/ 5weeks (LQED2 44.3-49.6 Gy- BED10 53.1-59.5 Gy and BED3 72-80.6 Gy) for whole pelvic irradiation with SIB 53.7-64.4 Gy (LQED2 58.9-66 Gy- BED10 70.7-79.2 Gy- BED3 101.6-113 Gy) for CTV T and 46.2-61.6 Gy (LQED2 44.9-62.6 Gy- BED10 53.8-75.2 Gy- BED3 71.6-106.8 Gy) for CTV N; 2/10 pts performed HDR-brachytherapy (HDR_BRT 18Gy/3fx) after EBRT for vaginal involved.

Results: In POG median age was 74.4 yrs (range 65-80), 4/5 pts had SCC and 1 adenocarcinoma, TNM stage was pT1b-G1/2-N1a/N2c; whole pelvic PTV95 was 95%-99% (median 95.5%), inguinal PTV95 was 95-99% (median 96.3%), for bladder and rectal we evaluated V50,V40,V30,V20 and for small bowel V20 (Table 1).

Table 1.

	Rectal median dose				Bladder median dose				Small bowel
	V50	**V40**	**V30**	**V20**	**V50**	**V40**	**V30**	**V20**	**V20**
POG	0.55%	19%	53%	86.7%	3.85%	33.4%	73%	96.3%	53%
	V50	**V40**	**V30**	**V20**	**V60**	**V50**	**V40**	**V30**	**V20**
DG	1.1%	10.4%	34%	67%	1.02%	5.9%	43.5%	64.5%	31%

Acute toxicity was erithema (G1-2) and GU (G1-2) following RTOG scale, none pts had rectal toxicity.In DG median age was 72.7 yrs (range 52-90), all pts had SCC, TNM stage was cT2/T4-N0/N1; 1/10 pts underwent to surgery and interstitial BRT after EBRT and 1 pts received additional boost by interstitial BRT. Whole pelvic PTV95 was 94-99% (median 97.5%), inguinal PTV 95 was 80-98% (median 96.5%), for bladder and rectal we evaluated V60, V50, V40, V30, V20 and for small bowel V20 (v table 1). Acute toxicity was erithema (G2) in all pts, GU (G1-2) in 6 pts and rectal toxicity (G1-2) in 3 pts; for bowel/haematologic toxicity in 1 pts RT was interrupted for a week. 5/10 pts had RC.

Conclusions: IMRT reduces the dose to OAR and improves the coverage nodal involved without compromising coverage of the target volume; in our experience IMRT with SIB is well tolerated and feasibility even if a further dose escalation study with an adequate number of patients and a longer follow-up may be useful.

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BOOST SIMULTANEO INTEGRATO (SIB): IMPLICAZIONI RADIOBIOLOGICHE E CLINICHE

P001

MODERATE HYPOFRACTIONATION AND SIMULTANEOUS INTEGRATED BOOST WITH VOLUMETRIC MODULATED ARC THERAPY BY RAPIDARC FOR PROSTATE CANCER: REPORT OF FEASIBILITY AND ACUTE TOXICITY

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Objectives: To report about acute toxicity profile for prostate cancer patients treated with simultaneous integrated boost (SIB) with Volumetric Modulated Arcs in a hypofractionated regime.

Materials and Methods: Seventy patients treated with RapidArc between May 2010 and September 2011 were retrospectively evaluated. According to NCCN classification, patients were stratified in low (36%), intermediate (49%) and high-risk (16%) groups. Clinical Target Volumes [expanded anisotropically 0.8 in all direction and 1 in craniocaudal to define the planning volumes (PTV)] were: CTV1=prostate, CTV2=CTV1+seminal vescicles, CTV3=CTV2+pelvic nodes. Low-risk patients received 71.4Gy to PTV1; intermediate-risk 74.2Gy to PTV1 and 61.6 or 65.5Gy to PTV2; high-risk 74.2Gy to PTV1, 61.6 or 65.5Gy to PTV2 and 51.8Gy to PTV3. All treatments were performed in 28 fractions. The acute rectal, gastro-intestinal (GI) and genito-urinary (GU) toxicities were scored according to EORTC/RTOG scales. Univariate and multivariate analyses were performed with patients and treatment data.

Results: Median age and Gleason score were 75 years and 7. The median follow-up was 330 days (115-690). Acute toxicities were: for GU G0=31/70 (44%); G1=22/70 (31%); G2=16/70 (23%); G3=1/70 (1%). For rectum: G0=46/70 (66%); G1=12/70 (17%); G2=12/70 (17%); no G3. For GI: G0=54/69 (77%); G1=11/69 (16%); G2=4/69 (6%); no G3. Median time to rectal, GU and GI toxicities were 27, 30 and 33 days. Only the GI toxicity correlated with stage and pelvic irradiation. Univariate analysis presented significant correlations between GI toxicity and intestinal irradiation (V50Gy and V60Gy). In the multivariate analysis, the only significant dosimetric variable was V50Gy for intestinal cavity.

Conclusions: Moderate hypofractionation with SIB and RapidArc showed to be safe, with acceptable acute toxicity. Longer follow-up is needed to assess late toxicity and clinical outcome.

P002

ACUTE MUCOSAL TOXICITY OF PLATINUM-BASED CHEMORADIATION WITH INTENSITY MODULATION (IMRT) AND SIMULTANEOUS INTEGRATED BOOST (IMRT-SIB) *VS.* IMRT SEQUENTIAL BOOST (IMRT-SEQ) IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMAS (HNSCC): A RETROSPECTIVE ANALYSIS OF THE EXPERIENCE AT OSPEDALE DI CIRCOLO DI VARESE

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Purpose: To investigate acute mucosal toxicity in a retrospective series of patients (pts) radically treated with platinum-based chemoradiation and IMRT-SIB *vs*. IMRT-SEQ for locally advanced HNSCC.

Materials and Methods: Between March 2009 and

February 2012, at the Radiotherapy Department of Varese University Hospital, 118 pts received radical definitive IMRT with/without concomitant platinum-based chemotherapy (CHT) for locally advanced HNSCC. During the study period the radiotherapy treatment policy has changed: pts were initially treated with IMRT-SEQ (24 pts) and thereafter with IMRT-SIB (94 pts). The IMRT-SEQ schedule delivered 50 Gy in 25 fractions (2 Gy/fract) to PTV2 (elective volume) and 20 Gy boost in 10 fractions (2 Gy/fract) to PTV1 (primary site and nodal metastases) up to 70 Gy ICRU total dose in 35 fractions. The IMRT-SIB delivered 54 Gy (1.8 Gy/fract) and 66 Gy (2.2 Gy/fract) in 30 fractions to PTV2 and PTV1, respectively. For the purpose of this analysis we retrospectively reviewed our database and established the following selection criteria in order to compare acute mucosal toxicity of both IMRT schedules in pts receiving concomitant platinum-based CHT: pts treated for nasal cavity and paranasal sinus cancer and pts who did not receive concomitant platinum-based CHT were excluded from both groups. Sixteen pts resulted eligible in the IMRT-SEQ group, thus we checked the mean dose range to mucosae in these pts (40-66 Gy, on the sum plan) and we used it to select the pts in the IMRT-SIB series which resulted in 18 eligible pts. All pts had histologically confirmed HNSCC. In the IMRT-SEQ, 8/16 pts (50%) had received also neoadjuvant CHT; 5/16 pts (31.25%) received concomitant CHT with CDDP 100 mg/m2 every 3 wks, while 11/16 pts (68.75%) were treated with a concomitant weekly schedule of CDDP 40 mg/m2. In the IMRT-SIB, 6/18 pts (33%) had received neoadjuvant CHT and all 18 pts (100%) received the concomitant CDDP 3-wk schedule. In the IMRT-SEQ the primary site distribution was: 44% nasopharynx, 50% oropharynx, 6% oral cavity; in the IMRT-SIB: 11% nasopharynx, 22% hypopharynx, 67% oropharynx. UICC stage of the IMRT-SEQ was: stage II in 3 pts, stage III in 3 pts, stage IVa in 8 pts, stage IVb in 1 patient; in the IMRT-SIB the stage was: stage II in 1 patient, stage III in 2 pts, stage IVa in 15 pts. Univariate comparison between groups was performed by the Pearson's X2 test and the Fisher's exact test, with p value of ≤0.05 considered statistically significant.

Results: Maximum grade (RTOG/EORTC) of acute mucosal reactions was G2 in 12/16 pts (75%) and in 11/18 pts (61%) and G3 in 4/16 pts (25%) and 7/18 pts (39%) in the IMRT-SEQ and IMRT-SIB group, respectively (p=ns). Acute G2 mucosal reaction started at 20-54.4 Gy and 22-66 Gy in each group, respectively (p=ns); acute G3 mucosal reaction developed at 20-38 Gy and 28.6-57.2 Gy in each group, respectively (p=ns). Duration of acute G2 mucosal reaction was 10-28 dd in the IMRT-SEQ and 7-30 dd in IMRT-SIB (p=ns); duration of acute G3 mucosal reaction was 20-31 dd and 7-30 dd in the IMRT-SEQ and IMRT-SIB, respectively (p=ns).

Conclusions: This retrospective analysis showed no statistical significant differences in maximum grade amount, onset time and duration of G2 and G3 acute mucosal reactions between IMRT-SEQ and IMRT-SIB pts, thus it confirms our IMRT-SIB schedule as a well-tolerated IMRT regimen even in conjunction with concomitant platinum-based CHT.

P003

OUR EXPERIENCE WITH IMRT-SIB IN PATIENTS WITH LOCALLY ADVANCED CANCER

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Purpose: To assess compliance and tolerance in radiochemotherapy treatments using SIB-IMRT technique (Simoultaneous Integrated Boost) in patients with cancer of the head and neck or pelvic.

Materials and Methods: From October 2009 to April 2012 in our center a total of 152 patients, 97 men and 55 women, were treated with RT SIB-IMRT technique at a total dose between 54 and 72.6 Gy. The treatment sites were in 82 cases pelvis (gastro-intestinal and genito-urinary tract) and in 70 cases head and neck. All patients presented locally advanced disease. Most of all received concomitant chemotherapy. For patients with pelvic diseases boost doses were of 2,25-2.40 Gy per fraction, for patients with diseases of the head and neck from 2.1 to 2.40 Gy per fraction.

Results: The encountered acute effects, grade G1-G2 according to the scale RTOG, were less than or equal to those in the literature for fractionations of conventional type. Only two patients had to stop treatment for a period exceeding 7 days. A patient with Ca of the Rectum, chemo-radio treated, had diarrhea G3 and was necessary to stop RT for one week and another one patient with Oropharynx cancer has lost more than 10% of body weight and was therefore admitted to perform parenteral nutrition interrupting radiotherapy for a week.

Conclusions: The SIB-IMRT technique allows alteration of the standard dose fractionation differentiating the dose on differents volumes of interest. The results in terms of acute effects are encouraging, sometimes appearing improvement compared to those observed with standard dose of 2.0 Gy per fraction, also there were no significant suspension of treatment. This altered fractionation reduces the duration of treatment with obvious advantages for patient compliance.

P004

SIMULTANEOUS INTEGRATED BOOST RADIOTHERAPY IN HIGH RISK PROSTATE CANCER WITH IGRT: RESULTS OF ACUTE TOXICITY

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Backgrounds: Hypofractionated "dose escalation" intensity modulated radiotherapy (IMRT) might be able to improve locoregional control in prostate cancer without an increase in OAR toxicity. Image guidance is a widely accepted approach to increase the therapeutic ratio in external radiotherapy (IGRT). If IGRT and IMRT are

combined it is even possible to use SIB approach in order to reduce the number of fractions and therefore the treatment time length.

Materials and Methods: Between December 2009 and January 2012 in our institution we treated 57 patients with high risk prostate carcinoma (≥T3 or Gleason score ≥ 8or PSA ≥ 20 ng/ml). The median age was 73 years (range 61–88). All patients underwent a neoadjuvant, concomitant and adjuvant hormonal therapy with antiandrogen (bicalutamide 150 mg) in 19 patients (33.3%) and LHRH analogous in the other 38 patients (66.7%) for a total of 2 years overall starting 3 months before radiotherapy. Stage was cT1c in 2 patients (3.5%), cT2a in 4 patients (7%), cT2b in 9 patients (15.8%), and cT2c in 5 patients (8.8%), cT3a in 17 patients (29.8%), cT3b in 18 patients (31.6%) and cT4 in 2 patients (3.5%). Gleason score was 5 in 2 patients (3.5%), Gleason 6 in 14 patients (24.5%), Gleason 7 in 18 patients (31.6%), Gleason 8 in 16 patients (28.1%) and Gleason score 9 in 7 cases (12.3%). All patients performed a simulation CT scan with 2,5 mm slice thickness to execute 3D conformal planning IMRT (intensity modulated radiation therapy) developed with Eclipse System. They were immobilized with a footlocker in supine position. All patients underwent proper rectal and bladder preparation. MR imaging were fused with planning CT for to help clinical target volume (CTV) delineation. The CTV1 included the pelvis, CTV2 included the seminal vesicles and CTV 3 only the prostate. The margins for the planning target volume (PTV) were 5 mm in all directions. The total dose to PTV1 was 45 Gy in 25 fractions (1.8 Gy each fraction), the total dose to PTV2 was 55 Gy (2.2 Gy each fraction) and the total dose to PTV3 was 68.75 Gy in 25 fractions (2.75 Gy each fraction), 5 days for week. Patients were controlled during treatment with Cone-Beam (ChiloVoltage) CT. Follow-up evaluations were performed at 1, 3, 6, 9 and 12 months after treatment, and every 6 months thereafter. Acute side effects were evaluated according to the RTOG/EORTC late morbidity Scoring Scale.

Results: Median follow-up was 14 months (range 2-28 months). The acute toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity in 7 patients (12.3%), grade 1-2 genitourinary (GU) toxicity in 15 patients (26.3%); grade 3 GU toxicity in 1 patient (1.7%). The toxicities 1 month after the end of the treatment were grade 1-2 GI in 1 patient (1.7%), grade 1-2 GU in 10 patients (14%). The toxicities 3 months after the end of the treatment were grade 1-2 GI in 1 patient (1.7%), grade 1-2 GU in 4 patients (7%). The median PSA at diagnosis was 10.1 (range 2.92-45.4) and that at the last follow-up was 0.06 ng/ml (range 0-1.1 ng/ml).

Conclusions: Technological progress enables the implementation of new technologies such as intensity modulated radiation therapy (IMRT) and image guided radiotherapy (IGRT). IMRT allows to minimize the volume of normal tissue irradiated and allowed an excellent acute toxicity in all patients.

P005

SIB-IMRT IN LOCALLY ADVANCED HEAD AND NECK CANCER

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Aims: IMRT allows dose escalation improving tumour control probability without arising dose to spine and at least one parotid gland and, conseguently, probability of side effects, which are particularly dose-limiting. The aim of this paper is to describe SIB-IMRT in head and neck cancer radiation therapy using three dose levels prescribed to three different volumes.

Methods: Since November 2008 to May 2012, 58 patients affected by locally advanced head and neck cancer received simultaneous integrated boost using a rotational IMRT with dynamic MLC (15 pts with Serial Tomotherapy and 43 pts with VMAT®). Radiation doses were 69.9/2.33 Gy to primary and metastatic lymph nodes (PTV1), 60/2Gy to lymph nodes at high risk of subclinical invasion (PTV2) and 54/1.8 Gy to lymph nodes at low risk of subclinical invasion (PTV3). Overall treatment time was 6 weeks. Concomitant weekly CDDP (30 mg/m2) was performed in 46 pts, 31 of them received also induction chemotherapy. Doses to spine and parotid glands, evaluated on DVH, were used as toxicity predictors. Biological Equivalent Dose (BED) was calculated using Linear Quadratic Formula: BED= D(/ +d)/ (/ +2).

Results: BED on primary and OARs are shown in Table 1, with relative/ratio present in literarure. In our series, we reported oesophageal toxicity G1-2 in 23 pts and G3 in 4 pts, skin toxicity G1-2 in 50 pts and G3 in 13 pts, mucositis G2 in 44 pts. In 1 pt a G3 mucositis requiring radiation course interruption was observed after sixteen fraction. Salivary toxicity G1 was observed in 37 pts. One patient died during treatment, after 29 radiation fractions. In 43 patients with follow-up exceeding one year, was observed G1 late skin toxicity in 5 pts, G1-2 late salivary toxicity in 5 pts and G4 mucositis in 1 pt after 8 months from treatment completion.

Table 1. BED in different H&N tumors and normal tissue.

Tissue	α/β ratio	Prescribed dose/constraint (Gy)	BED (Gy)
Larynx	14.5	69.9/2.33/30fz	71.3
Oropharynx	16	69.9/2.33/30fz	71.2
Buccal mucosa	6.6	69.9/2.33/30fz	72.6
Tonsil	7.2	69.9/2.33/30fz	72.4
Nasopharynx	16	69.9/2.33/30fz	71.2
Early responders			
Skin	8.5	Max: prescription dose	72.1
Oesophagus	10		71.8
Late responders			
Spine	2.25*	Max 45/30fz	39.7
Salivary glands	3	Mean 30/30fz	24

**average of different velutes reported in literature (range 1.5-3).*

Conclusions: Hypofractionation provides to dose-escalation in particular in tumors with lower/ratio. In Head and Neck cancer this advantage is less evident in

respect, for example, to prostate cancer. Moreover, due to location of early reaction tissue such as skin and oesophagus very close to primary, we expect an increase in acute toxicity. Because toxicity is proportional to volume of irradiated tissue, perhaps this attended result can be limited using IMRT, which could spare a greater volume of skin and oesophagus than 3DCRT. Due to low constraints of late responders tissues, we don't expect an increase of late toxicity. However IMRT allows sparing of at least 1 salivary gland. SIB-IMRT allows treatment of negative nodes with two different dose levels, according to their risk of microscopic involvement, calculated on the basis of primary site and its T-N stage. The real radiobiological advantage in hypofractionation with SIB-IMRT in H&N cancer is probably the shortening of overall treatment time (from 7 weeks with conventional fractionation to 6 weeks). This could be particularly useful in this type of cancer, because of its short time of repopulation.

P006
HYPOFRACTIONATED TREATMENT: TECHNOLOGICAL INNOVATION AND APPLICATION IN GYNAECOLOGICAL ONCOLOGY

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Purpose: Hypofractionated treatment with intensity modulated radiotherapy (IMRT), arc therapy, stereotactic body radiotherapy (SBRT) and Cyberknife is a valid conservative alternative in exclusive or recurrent gynaecological cancer when brachytherapy is not feasible.

Materials and Methods: In our "Advanced Radiotherapy Center" the majority of patients (pts) affected by gynaecological cancer were treated with conventional or hypofractionated radiotherapy +/- brachytherapy boost. From June 2010 to May 2012 162 pts were treated. When brachytherapy is inadequate or not feasible, hypofractionated schedule with external beams is a very good solution (virtual brachytherapy). The introduction of new technologies such as IMRT, Rapid-arc therapy, SBRT, Cyberknife and the application of image guidance and adaptive planning techniques makes easier to spare critical organs at risk (OAR) in order to minimize late toxicity, that is a concern because of the closeness among OAR and target. In order to compare the different fractionation schedules, 2 Gy equivalent total doses (EQD2) were calculated using the linear quadratic model with/ratios of 3 Gy for late normal tissue effects and 10 Gy for the tumor.

Results: All patients received Rapid arc radiotherapy with simultaneous integrated boost (SIB) :45-50.4 Gy (1.8 Gy/fraction (fr)) were prescribed to the T, N0 pelvic and/or para-aortic lymph nodes and 55 Gy (2.2 Gy/fraction) to the positive lymph nodes. The dose for the hypofractionated boost schedule is 5 Gy/fr for 3 fr = 15 Gy , EQD2=18.8 Gy (PTV 65%) isocenter EQD2=83 Gy or 5 Gy/fr x 4 fr : 20 Gy EQD2 = 25 Gy. For the pts who received the hypofractionated treatment alone the doses for IMRT or SBRT was: 6 Gy /fr x 5 fr= 30 Gy (isodose 95%)= EQD2=40 Gy, 5 Gy /fr x 5 fr = 25 Gy (isodose 95%) EQD2=30 Gy , and for Cyberknife the dose was :10 Gy/fr x 3 fr (isodose 73%) EQD2= 45 Gy , 15 Gy/fr x3 fr (isodose 87%) EQD2= 45 Gy.

Conclusions: The possibility to hypofractionate the treatment offers a new approach for a minimally invasive treatment in the management of cancer when current surgical approach and other conventional radiotherapy techniques are unsuitable.

P007
CLINICAL RESULTS OF SIMULTANEOUS INTEGRATED BOOST IN IMRT FOR HEAD AND NECK CANCER: ANALYSIS OF 54 RADICAL TREATMENTS

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Purpose: To evaluate the efficacy and the toxicity of the intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) in 54 patients with head-and-neck squamous cell carcinoma.

Materials and Methods: From March 2008 to April 2012, 54 consecutive patients, with stages II-IV (12 II stage, 14 stage III and 28 stage IV) head-and-neck squamous cell carcinoma (28 oropharynx, 6 hypopharynx, 6 larynx, 11 nasopharynx and 1 oral cavity) were treated with radical IMRT-SIB concomitant to systemic treatment in 48 patients (45 platinum based chemotherapy and 3 cetuximab). The median doses for radiotherapy were: 69.09 Gy (range, 68.8-70.4 Gy) in fractions (fx) of 2 Gy (range, 2.0-2.26 Gy) to the planning target volume 1 (PTV1) (primary tumour and metastatic cervical lymph nodes), 62.0 Gy (range, 58.0-66.0 Gy) in fx of 2 Gy (range1.94-2.16) to the PTV2 (high risk node), and 53.8 Gy in fx of 1.8 Gy (range, 1.65-2.0 Gy) to the PTV3 (low risk node). All patients underwent computed tomography imaging after 20 RT sessions to assess tumour regression and possibly adapt RT. Replanning was performed in 5 patients. Patients were assessed for acute and late toxicities according to the Radiation Therapy Oncology Group (RTOG) criteria.

Results: Of the 54 patients, 98.9% completed radiation treatment as prescribed. One patient died during the treatment for aspiration pneumonia. The median treatment duration was 50 days (range, 38–54 days). No patients interrupted RT more than 5 working days. The complete response rate assessed by clinical evaluation and post-treatment imaging was 94%. The median follow-up was 11 months (range,6–48.1 months). One-year local control was 90.4%. At the end of the treatment, grade 3 mucositis, dermatitis, and dysphagia occurred in 26 (48.1%), 21 (38.9%), and 3 patients (5.5%) respectively. No patients experienced grade 3 xerostomia, while grade 2 xerostomia occurred in 8 patients (14.8%). Grade 3 late dysphagia occurred in 1 patient and 100% of patients was feeding tube free at 6 months after therapy.

No patients experienced other grade 3 late toxicities. Grade 2 soft-tissue fibrosis, xerostomia, occurred in 3 patients (5.7%), 13 patients (25%), respectively.

Conclusions: Our results show that acute and late toxicities were tolerable and acceptable. Intensive supportive care strategies should be defined to better manage radiation-induced toxic effects. Longer follow-up is required to determine the incidence of late radiation toxicity and the rate of tumor control.

P008

MULTIPLE BRAIN METASTASES TREATED WITH INTENSITY MODULATED RADIOTHERAPY AND SIMULTANEOUS INTEGRATED BOOST: A CASE REPORT

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Aims. The treatment of patients with multiple metastases is based on whole brain palliative radiotherapy, especially in patients with more than 3 metastatic lesions. In this report we refer to the case of a young breast cancer patient with 7 brain metastases who underwent to an intensity modulated radiotherapy (IMRT) treatment on the brain.

Patients and Methods: A 37 years old female patient underwent neoadjuvant chemotherapy and mastectomy for infiltrating ductal breast carcinoma. Two years after diagnosis, brain recurrence was diagnosed with MRI, that documented the presence of 7 sub-centimeter lesions. Given the young age and excellent performance status (ECOG: 0) an IMRT radiotherapy treatment with curative intent was proposed. Whole brain was defined as clinical target volume 2 (CTV2) and the related planning target volume 2 (PTV2) was obtained by adding a 5 mm margin. The prescribed dose to PTV2 was 40 Gy (2 Gy/fraction). Furthermore, a simultaneous integrated boost concomitant boost was prescribed on each single metastasis, with 5 mm margin to macroscopic lesion to define each CTV1. The prescribed dose to the 7 different PTV1s (defined by adding a margin of 5 mm to CTV1s) was 50 Gy (2.5 Gy/fraction). Concurrent temozolomide was administered during irradiation (130 mg/day, 5 days/week).

Results: During radiotherapy the patient presented mild headache and dizziness. After 3 months a MRI examination showed the complete disappearance of most of the lesions. Only two millimetres areas of impregnation of the contrast medium were still evident. Subsequent MRIs performed every 3 months have documented only two pinpoint areas, in the more voluminous metastases site. Two year after treatment MRI controls documented the absence of disease in the brain. The patient's neurological examination is normal remaining only alopecia. The patient denied visual disturbances, headache or drowsiness, and plays a normal family and work activities.

Conclusions: To the best of our knowledge this is the first case where such a large number of brain metastases received a concurrent boost radiotherapy. The patient, after 2 years of treatment, is free from disease progression and enjoys good conditions, in the absence of neurological symptoms.

P009

HEAD AND NECK INTENSITY MODULATED RADIOTHERAPY AND SIMULTANEOUS INTEGRATED BOOST: TIME OF RE-PLANNING FOR PAROTID GLANDS

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Aims: To investigate the correct time point for replanning, evaluating parotid glands (PGs) dosimetric changes during Intensity Modulated Radiotherapy (IMRT) Simultaneous Integrated Boost (SIB) for head and neck cancer patients.

Materials and Methods: Patients with head and neck cancer treated by IMRT-SIB were enrolled. Total doses consisted of: 70-72Gy to macroscopic disease clinical target volume (Clinical Target Volume, CTV1); 60-66Gy to microscopic high-risk disease (CTV2) and 54-58Gy to microscopic low-risk disease (CTV3)for 5 days/week. During treatment all patients underwent kilovolt Cone Beam Computed Tomography (CBCT) scans to verify set-up positioning. CBCT scans at treatment days 10, 15, 20 and 25 were used to transfer the original plan (CBCTplan I, II, III, IV, respectively) using a rigid registration between the two. PGs were retrospectively contoured and evaluated with the Dose Volume Histogram. The mean dose, the dose to 50% of volume, the percentage of volume that received 30Gy and 50Gy were evaluated for each PGs. The Wilcoxon sing ranked test was used to evaluate the effects of dosimetric variations and a significant value less than 0.05 was assumed.

Results: From February to June 2011, 10 patients were analyzed and, for each patient, five IMRT-SIB plans were evaluated. All the dosimetric end points increased throughout the course of treatment. However, this increase was statistically significant at day treatment 10 and 15 (CBCTplan I, II; p=0.02, p=0.03, respectively).

Conclusions: Our data showed that during IMRT-SIB, CBCT is a feasible method to assess the dosimetric variations of the parotid glands. Perhaps an adaptive radiotherapy could be indicated during the third week of treatment.

P010

PARMA CLINICAL EXPERIENCE CONCERNING ACUTE TOXICITY IN HEAD AND NECK CANCER PATIENT MANAGEMENT WITH VOLUMETRIC MODULATED ARC THERAPY AND SIMULTANEOUS INTEGRATED BOOST (SIB)

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Backgrounds: Technical advances in radiotherapy like volumetric intensity modulated arc therapy (VMAT) have helped to spare the normal tissues, while delivering a curative dose to the tumour tissues. We analysed data of acute toxicity (mucositis, dysphagia, xerostomia and dermatitis following RTOG Criteria) during radiation treatment with RapidArc technology in patients with head and neck local advanced disease.

Methods: From 2009 to 2012, 26 patients (18 males and 8 females, median age 60 years) were treated at Radiation Therapy Department of Parma with RapidArc. Patients have a different anatomical localization of head and neck cancer (8 oropharynx, 7 oral cavity, 4 nasopharynx, 2 salivary glands, 2 ipopharynx and 2 larynx and 1 was metastatic laterocervical adenopathy of occult disease) Of these, 12 received concomitant chemotherapy, 1 cetuximab and 1 cetuximab plus chemotherapy. 7 patients were treated as postoperative curative intent and 19 were treated as exclusive curative intent. The mean dose was prescribed at Planning Target Volumes (PTV=CTV +3mm) with simultaneous integrated boost technique (SIB) at the first target (PTV-Tumor): 60 Gy in 30 fractions (2 Gy/fr) in the group of postoperative patients; 66 Gy in 30 fractions (2.2 Gy/fr) or 70 Gy in 33 fractions (2.12 Gy/fr) in the group of exclusive curative intent. Daily check of patient positioning was performed for all patients by means of kV-cone beam CT (CBCT) system integrated in the machine (IGRT – image guidated radiation therapy).

Results: Most of patient experienced G2 dermatitis (50%). Only one had G3 dermatitis related to concomitant cetuximab-radiotherapy treatment. 54% of patient had G2 mucositis and only 3/26 patients presented ulceration and/or hemorrhage of mucous membrane. 70% of patients had no change of salivary gland function and 58% of patients had G2 dysphagia. Moreover, the highest acute toxicity is related with concomitant chemo-radiation therapy treatment.

Conclusions: These preliminary results show that RapidArc radiation treatment presents an acceptable acute toxicity with the opportunity to deliver a greater dose to the target compared to classical 3D conformational radiation technique.

P011

CRITICAL APPRAISAL TO WHOLE BRAIN RADIOTHERAPY (WBRT) WITH SIMULTANEOUS INTEGRATED BOOST (SIB) FOR METASTATIC BRAIN PATIENTS WITH 1-3 LESIONS

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Purpose: to assess the feasibility of simultaneous integrated boost (SIB) with volumetric modulated arc therapy (V-MAT) for patients with one to three brain metastases.

Materials and Methods: a sample of ten consecutive patients (pts) treated since November 2010 till May 2012 has been considered for this mono-institutional review. All pts had a personalized immobilization device. All pts were stratified according to RPA classes. Three patients were in RPA class I, six pts in class two and a patient in class III. Three patients were treated for a single lesion, six pts had two lesions while only one patient had three lesions. The whole brain prescription was 30 Gy in ten consecutive fractions, while the lesions received 40 Gy in 10 fractions with SIB technique. Patients were evaluated for acute, intermediate and late side effects, and for clinical outcome also. A cone beam CT was performed before each fraction to check the accuracy of set-up. Response to the treatment was assessed with a brain MRI, performed three months after the end of the treatment.

Results: No significant acute side effect is reported for the whole series. With a median follow up of 12 months, six pts (with at least 6 months follow up) out of ten are evaluable for late toxicity. No relevant late side effect was seen among the six patients with an adequate follow up. Nine pts out of ten are alive; the patient who died was the one in RPA class III. Concerning clinical outcome, two patients assessed complete remission of the lesions, five pts a near complete remission, two patients achieved partial remission while one patient is not evaluable for late complications and response. The integral dose to the body for "WBRT with SIB" was the same as for "WBRT alone".

Conclusions: VMAT was able to achieve adequate whole brain coverage, performing SIB. This technique can provide a shortening in overall treatment time (two weeks *vs* three weeks), with an improvement of radiobiological effect, in terms of healing possibility. The absence of organ motion can guarantee there is no risk of target missing, while the "non tumour complication probability"(NTCP) can be minimized thanks to the daily cone beam CT that allows "image guided radiotherapy"(IGRT). Finally, this study shows that RPA classes are the strongest prognostic factor for brain metastatic patients. Adequate follow up and number of patients are needed to evaluate the impact of WBRT with SIB in brain metastatic patients with 1-3 lesions.

P012

SIMULTANEOUS INTEGRATED BOOST (SIB) IN THE TREATMENT OF HEAD AND NECK CANCER: ACUTE TOXICITY EVALUATION AND EARLY RESULTS

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Introduction: Radiotherapy (RT) plays an essential role in the management of head and neck cancer both in the curative and in the postoperative setting. RT treatment planning in head and neck region is complicated due to the critical structures which are necessary to spare. Metanalysis show that RT with altered fractionation schedules, such as hyperfractionation or accelerated radiotherapy, allows a better outcome than conventional RT. Intensity modulated Radiation Therapy (IMRT)allows highly conformal dose distributions around tumor targets and sparing of the critical organs involved, but also the possibility of dose escalation and altered fractionation schedule through the Simultaneous Integrated Boost (SIB) technique.

Methods: Between February 2010 and March 2012, 15 patients with histologically confirmed head and neck cancer (T1-4, N0-3, M0) were evaluated in the Center of Barletta. Each patient was evaluated by a multidisciplinary team composed by Radiation Oncologist, Oncologist and Otorhynolaryngologist. A PET-CT in the treatment position was acquired and a SIB plan was calculated for each patient. The prescribed doses were 66-69.96 Gy (2.2/2.12 Gy/fraction) for the high-dose volume, 60-59.4 Gy (2-1.8 Gy/fraction) for the intermediate –dose volume, 54Gy (1.8-1.6 Gy/fraction) for the low-dose volume. The planned number of fractions were 30 or 33. Planning parameters were assessed according to the RTOG IMRT parameters. All patients received concomitant chemotherapy with CDDP (30 mg/mq, q7 or 100 mg/mq, q21) or Cetuximab. Acute toxicity was evaluated weekly according the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 scale for skin, mucous membrane, salivary glands, pharynx and blood count. Late toxicity was evaluated according to the RTOG-EORTC toxicity scale.

Results: 12 (80%) patients completed the therapy. 9 patients (60%) completed the therapy without interruption due to acute toxicity of radiotherapy. The mean OTT (Overall Treatment Time) was 48 days (range 40-82); the mean of interruption time was 4 days (range 0-30). Only 1 patient (6,7%) had G4 hematologic toxicity. No other G4 toxicities were recorded. 46.7% showed G1 acute salivary toxicity, no patient had >G1 acute salivary toxicity. All patients had G1-G2 acute skin toxicity. Almost all patients had acute mucosal toxicity (60% G2, 33.3% G3)and dysphagia (93.3% G2). At a median follow-up of 10.2 months (range 0-21)no patient showed >G2 late xerostomia (46.6% G1, 13.3% G2).One patient showed late dysphagia (6.7%). 2 patients (13.3%) showed persistent disease at after radiation therapy and underwent salvage surgery. One of them had subsequently distant metastases to the lung. Actual overall survival is 87.5%. 2 patients died for cause not cancer-related. 2 patients (13.3%) had second malignancies (1 synchronous thyroid cancer and 1 metachronous esophageal cancer, outside the irradiation fields).

Conclusions: The results confirm that the irradiation with a SIB-IMRT protocol is a therapy with acceptable acute toxicity, even if associated with concomitant chemotherapy. The majority of patients carried out the entire course of radiation without interruption. No severe late toxicity was detected. Overall survival and locoregional disease control incidence appears to be comparable with other reports. Nevertheless, a longer follow up and a larger number of patients are needed to confirm these early findings.

P013

PRELIMINARY EXPERIENCE OF SIMULTANEOUS INTEGRATED BOOST INTENSITY MODULATED RADIOTHERAPY (SIB-IMRT) IN THE TREATMENT OF HEAD AND NECK CANCER (HNC) PATIENTS AT THE ONCOLOGYCAL CANCER CENTER A. BUSINCO OF CAGLIARI

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Purpose: In the radiotherapy (RT) of HNC patients (pts), the prescribed dose of radiation should be administered over a specific time. In fact, the overall treatment time (OTT) is an independent prognostic factor in main of the HNC treatments. Hence, at the Sardinian Oncological Cancer Center, SIB-IMRT has been introduced to reduce the OTT, to improve the dose-coverage to the target volumes, to reduce the irradiation to the organs at risk (OARs), hence the acute and late toxicity.

Materials and Methods: From August 2011 to May 2012 38 pts affected with HNC was treated with "Step and Shoot" SIB IMRT. The setting was radical (RS) in 21 pts, adjuvant (AS) in 17 more other ones. All pts treated with RS and 16 pts treated in AS were staged as III or IV, 1 patient (pt) treated in AS were in staged II, according to AJCC TNM 2010. Three pts had positive margins in AS. Neoadjuvant and/or concomitant chemotherapy was often administered. Dose prescriptions was 56,1 Gy, 1,7 Gy/fr to the low risk volume, 69,3 Gy to the high risk volume, 2,1 Gy/fr, with SIB technique in the RS; 54 Gy in 1,8 Gy/fr to the low risk volume, 60 or 63 Gy in 2 or 2,1 Gy/fr to the high risk volume, according to the presence of high risk TNM and/or histological features, with SIB technique in the AS. Cord, brain stem, oral cavity, larynx, thyroid, superior constrictor muscle, mandibula, parotid glands, optic apparatus,

cochleas and brachial plexus if requested, were contoured. Every patient was visited and weighted at the simulation time, then weekly during the RT. Acute toxicity was recorded each visit.

Results: Median duration of RT period was 47 days (from 45 to 66 for RS, from 43 to 65 for AS) for both groups. In RS, 1 pt affected with nasopharyngeal cancer and 1 pt with oropharyngeal cancer died during the treatment period due to a progression of the disease. One pt treated with exclusive RT, died for not-treatment related causes. 18/21 pts were evaluated for toxicity in RS: 2 pts had G3 mucosal toxicity; 10 G2 and 6 G1 mucosal and/or skin toxicity; 5 G2 and 13 G1 weight loss toxicity; 1 patient required nutritional support. 15/17 pts were evaluated for toxicity in AS: 2 pts experienced G3 mucosal toxicity, 1 pt had G3 odynophagia; in the remaining pts 3 G1 and 9 G2 were recorded; 6 G2, 8 G1 and 1 G0 weight loss were recorded.

Conclusions: SIB-IMRT schedules evaluated in HNC patients are safe. More follow-up and patients are needed to further prospective studies.

P014
PRELIMINARY DOSIMETRIC EVALUATION OF VIRTUALCT IN HEAD-AND-NECK ADAPTIVE RADIATION THERAPY

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Purpose: The purpose of this work is to verify dose distribution of on-line virtualCT scans for Adaptive Radiotherapy (ART) in Head and Neck (HN) cancer treatment.

Methods: In our previous work, we proposed an approach to generate virtualCT scans by means of non-rigid registration of simulation Computed Tomography (CTsim) and Cone-Beam CT images (CBCTs), acquired for patient setup and proposed to use these for planning adaptation instead of acquiring a conventional re-planning CT (CTrepl). In this work, we study the fast update technique in terms of dose distribution. We retrospectively analysed twenty patients, treated at European Institute of Oncology with Intensity Modulated Radiation Therapy (IMRT), for a HN malignancy, according to the image guided conventional protocol (IMRT + SIB). Different anatomical structures were considered: mandible, parotid glands and Planning Target Volume (PTV). The dose was re-calculated using an in-house Monte Carlo (MC) simulation engine. We first of all verify the agreement bewteen MC and commercial planning software (Eclipse, Varian, CA). Besides recalculating at CTsim and CTrepl, we simulate the dose distribution on virtualCT using the original plan at CTsim and structures adapted by means of the deformation estimated by deformable registration. We compare the Dose Histogram Volumes (DVH) of PTV 56.1 Gy, 66Gy, 69.9Gy and of mandible and parotids at CTsim, CTrepl and virtualCT, both qualitatively and quantitatively (average, min, max dose).

Results: Preliminary results show the absence of significant difference between clinical dose distributions and MC simulation both at CTsim and CTrepl. The DVHs simulated on virtualCT showed good agreement with both CTsim and CTrepl. Differences in average dose between CTsim and virtualCT were around 1Gy for PTVs and mandible, 7Gy for the parotid gland ipsi-lateral to the tumor volume and 2Gy for the contra-lateral parotid gland. Between virtualCT and CTrepl, difference in average dose were all below 1Gy, besides for the ipsi-lateral parotid whose mean dose step up of 6Gy. Maximum dose differences also reflected these values.

Conclusions: The promising preliminary analysis suggests that the virtualCT approach may contribute significantly in reducing the need of full CT-based replanning in head-neck radiotherapy, reinforcing the already provided geometric validation of the approach.

P015
SIMULTANEOUS INTEGRATED BOOST IN IMRT FOR HEAD AND NECK CANCER: ANALYSIS OF 54 POSTOPERATIVE TREATMENTS

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Purpose: The aim of the present prospective study is to evaluate the toxicity and efficacy of the adjuvant intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) in 54 patients head-and-neck squamous cell carcinoma.

Materials and Methods: From November 2008 to April 2012, 54 consecutive patients, with pathological stage I-IV (4 stage I with positive surgical margins, 10 stage II, 14 stage III and 26 stage IV) head-and-neck squamous cell carcinoma (8 oral cavity, 9 oropharynx, 7 hypopharynx, 6 salivary glands, 18 larynx and 6 unknown primary) were treated with adjuvant IMRT-SIB concomitant to platinum-based chemotherapy in 19 patients. The median doses for radiotherapy were: 66.0 Gy (range 60.0-66.0 Gy) with fractions of 2 Gy (range 2.0-2.16 Gy) to the planning target volume 1 (PTV1) (primary tumour bed, positive surgical margins and extracapsular extension), and 54.0 Gy with fractions of 1.8 Gy (1.75-2.0 Gy) to the PTV2 (low risk lymph nodes). Patients were assessed for acute and late toxicities according to the Radiation Therapy Oncology Group (RTOG) criteria.

Results: Of the patients, 100% completed radiation treatment as prescribed. The median treatment duration was 47 days (range, 37-52 days). No patients interrupted

RT more than 5 working days. At the end of the treatment, grade 3 mucositis and dermatitis occurred in 16 (29.6%) and 18 patients (33.4%), respectively. No patients experienced grade 3 xerostomia. Grade 2 xerostomia occurred in 4 patients (7.4%). The median follow-up was 12.1 months (range,6–30.1 months). One-year local control was 89.9%.Grade 3 late dysphagia occurred in 4 patients (7.4%). No patients experienced other grade 3 late toxicities. Grade 2 soft-tissue fibrosis, xerostomia occurred in 7 (12.9%), and 6 patients (11.1%), respectively.

Conclusions: Our results show that acute and late toxicities were tolerable and with an acceptable toxicity rate. This schedule of moderate hypofractionation allowed a reduction of overall treatment time. Longer follow-up is required to determine the incidence of late radiation toxicity and the definitive tumor control rate.

P016

ANALYSIS OF CLINICAL RESULTS AND TOLERANCE AFTER INTENSITY-MODULATED RADIATION THERAPY WITH SIMULTANEOUS INTEGRATED BOOST TECHNIQUE AND CONCOMITANT CHEMOTHERAPY FOR LOCO-REGIONALLY ADVANCED HEAD AND NECK CANCER

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Purpose: The aim of this work was the evaluation of the feasibility and efficacy of intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost (SIB) and concomitant chemotherapy for loco-regionally advanced head and neck cancer (HNSCC).

Materials and Methods: Between October 2010 and November 2011, in our institute, were treated 26 patients(pts) (21 male and 5 female; mean age 64 years) affected by locally advanced HNSCC. The tumor site was nasopharynx in 3 pts, oropharynx in 18 pts, hypopharynx in 4 pts and larynx in 1 patient. 8 pts (30%) had stage III and 18 pts (70%) had stage IVA.16 pts received 2-3 cicles of neoadjuvant chemotherapy (NCT) with the following regimens:5-fluorouracil(5FU) and cisplatin(CDDP) in 7 pts and TPF(docetaxel, CDDP and 5FU) in 9 pts. After NCT,1 patient had a Tumor Complete Response(CR),6 pts had a Tumor Partial Response(PR)≥ 50%,4 pts had a Nodal PR≥50% and 5 pts had both Primary and Nodal PR≥50%. All 26 pts underwent concomitant radio-chemotherapy(RTCT). Dose prescription of IMRT was as follows:69 Gy at 2.3 Gy/fraction(fz) to Gross Tumor Volume(GTV),66 Gy at 2.2 Gy/fz to Clinical Target Volume of tumor and positive nodes(CTV T-N) and 54 Gy at 1.8 Gy/fz to elective neck(EN). Parotid glands were delineated in all planes. Mean dose of main volume was: 69.3 Gy to GTV(range 67.6-72.79),67.3 Gy(range 66.61-69.35) to CTV T-N, 56.44 Gy to EN(range 54.6-58.1) and 21.12 Gy (range 4.06-33.55) to parotid glands. CT schedules were: CDDP 75-100 mg/m2/die q28 in 17 pts and Cetuximab 400 mg/m2 of induction+250 mg/m2/weekly for 8 weeks in 2 pts.

Results: The mean time of total treatment was 43 days(range 42-49). Acute toxicity consisted of: mucositis G2(52%)-G3(26%);dysphagia G3(35%);dermatitis G2-G3(47%) and xerostomia G2(60%). None G4 event was observed. Late effects were: Xerostomia G1-G2(27%) and dysgeusia(30%). Local complete response was achieved in 25 pts(96%), only one patient had residual nodal disease and underwent to a modified radical neck dissection. Loco-regional failure was observed in 3 pts, one at tumor site and 2 at nodal regional site. With a mean follow-up of 12 months(range 6-20) 22 pts(85%) are alive free of disease, 2 pts(7.5%) are alive with loco-regional disease and 2 pts(7.5%) are alive with systemic disease.

Conclusions: In our preliminary experience RTCT with IMRT-SIB in the definitive treatment of loco-regionally advanced HNSCC was feasible, well-tolerated and ensured a good local control.

P017

PROPHYLACTIC NODAL IRRADIATION USING SIMULTANEOUS INTEGRATED BOOST WITH IMRT IN HIGH RISK PROSTATE CANCER TREATMENT: A MONOISTITUTIONAL PRELIMINARY EXPERIENCE

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Aims: Prostate cancer (PC) local control requires high radiation doses (70-80 Gy with conventional fractionation). Prophylactic nodal irradiation (PNI) was discussed because of uncertain utility and potential toxicity increase. From RTOG 9413, it is recommended only in high risk patients with GS=7-10 and PSA<30ng/ml or GS<7 and PSA>30ng/ml. The aim of this paper is to describe dosimetric and early clinical results of simultaneous integrated boost (SIB) using a rotational dynamic IMRT technique in prostate cancer requiring PNI.

Methods: Since May 2008 to May 2011, 7 patients affected by PC eligible for PNI underwent to SIB-IMRT (2 pts with Serial Tomotherapy and 5 pts with VMAT). All pts received neoadjuvant hormonetherapy(HT) for 3-6 months and adjuvant HT for two years. In every patient on CT scan were delined CTV1, including prostate and seminal vescicles, and CTV2, including pelvic nodes. An additional margin of 0.6cm posteriorly and 1cm in the other directions was added to CTV1 to obtain PTV1, while CTV2 was expanded with 0,5cm to obtain PTV2. Organs at risk (OARs) were bladder, rectum, femoral heads and penile bulb. Prescription doses were 70 Gy to PTV1 and 56 Gy to PTV2 delivered in 28 fractions. Constraints to OARs were these suggested by QUANTEC. (Figure 1) Acute toxicity was classified according to RTOG Acute Radiation Morbidity Scoring Criteria. PSA was evaluated every three months in the first year after treatment and then every six months.

Resuts: In all treatment plans PTVs were encluded totally within 90% isodose and 95% of volume received 95% of prescribed dose. Mean dose average was 71Gy for PTV1 and 56.7Gy for PTV2. Mean dose maximum was 75.5Gy in PTV1 and 64.8Gy in PTV2. OARs constraints were always respected. Toxicity pattern was 1 G3 diarrhoea and 2 G2 cystitis. In all pts at RT start PSA was suppressed by HT. Only 2 pts were evaluable after the end of HT: one presented stable PSA values <1ng/ml at 1 year after hormone suspension and one presented rising PSA and bone metastasis after 14 months.

Conclusions: Prophylactic nodal irradiation with SIB-IMRT is quite feasible without increase in side effects although higher prophylactic doses (56 Gy) prescribed in consideration of high doses necessary for tumor control in PC. This aim can be achieved using IMRT, because the small bowel can be spared by concave isodoses. Using LQ model and considering/1.5, BED to PTV1 was 80 Gy. Due to the assumed low/of prostate cancer (PC), the use of hypofractionation will widen the therapeutic window since the ratio for PC might be lower than that of OARs. In particular, considering rectal/=3, BED70Gy will be 77Gy, with theoretic reduction in toxicity in comparison with high dose conventional treatment (*e.g.* 80Gy in 40 fz). Moreover, reduction in fraction number and, consequently, in accelerators occupation is an important result in a Radiotherapy Unit.

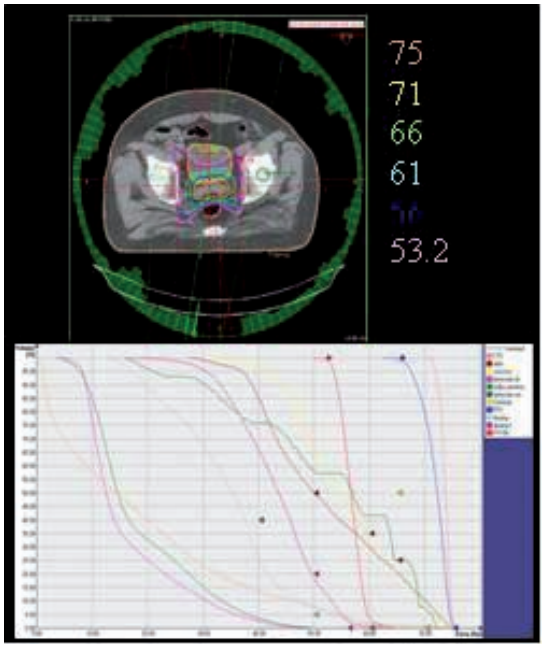

Figure 1. Example of treatment plan and DVH.

P018

DOSE DISTRIBUTION AND COMPLIANCE IN NASOPHARYNX CARCINOMA (NPC) TREATED BY HELICAL TOMOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST (SIB) COMBINED WITH CHEMOTHERAPY (CT): A MONO-INSTITUTIONAL EXPERIENCE

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Purpose: To evaluate our initial experience in the treatment of nasopharyngeal carcinomas with chemotherapy combined with intensity-modulated radiation therapy with Simultaneous Integrated Boost (SIB) delivered by Helical Tomotherapy (HT). This novel technique could result in a better dose distribution and improve normal tissue tolerance.

Table 1.

Volume	Prescription	Mean	D99%	D95%
D5%	D1%	Critical	Mean	Critical
Max				
	Dose (Gy)	Dose	(Gy)	(Gy)
(Gy)	(Gy)	StructuresDose (Gy)		
Structures	Dose (Gy)			
PTV1	66	65.8	60.6	62.9
67.2	67.8	Parotid glands	29.5	Mandible
62.5				
		(range		
		16.7-54)		
PTV2	60	62	54.9	57,8
63.2	64.2	Cochlea	30.65	Spinal Cord
33.2				
PTV3	54	55.2	51.7	52.6
56.1	57.5	Oral Cavity	35.1	

Materials and Methods: Between March 2009 and January 2012 24 patients, median age 50.5 years, with stage II (7 pts), III (8 pts), IVa (7 pts), IVb (2 pts) were treated with CTRT. Induction CT (TPF or CDDP and Epidoxorubicin) before combining CTRT was given to 15 pts with bulky local or regional disease; 13 pts underwent 3 courses of 5 FU and CDDP (week 1-4-7) alternated with 3 courses of radiation (weeks 2-3,5-6,8-9) and 11 pts received concurrent CDDP on days 1-21 and 43. Radiotherapy was delivered by HT with SIB technique. The prescribed doses were 66 Gy to CTV1 (primary tumor and pathologic nodes), 60 Gy to CTV2 (high risk disease) 54 Gy to CTV3 (low risk subclinical disease) delivered in 30 fractions. Dose constraints to minimize the dose to OARs were prescribed. Megavoltage CT scans were obtained for patient alignment before each treatment. PTV doses were accorded to the following: at

least 95% of the volume should be covered by the 95% of the dose; at least 99% of the volume should be covered by the 90% of the dose and at least no more than 1% should receive more than 7% of the prescription dose. The clinical status during RT was analyzed through the evaluation of supportive care type defined by analgesic need, need for nutritional support.

Results: For all pts dose distribution results for PTVs and some of the critical structures are reported in Table 1. The median follow-up is 17 months (range 3-35). The most significant severe acute toxicities reported at treatment end were grade 2 (29%) and grade 3 (5%) mucositis. 5 (21%) pts required short term nasogastric feeding or parenteral nutrition and 6 (25%) needed analgesic support (tramadol, codeine or major opioids). At a minimum FU of 6 months, with 18 pts evaluable, no grade 3 and 4 late toxicities have been observed. Grade 2 xerostomia was reported in 6 pts (35%). The severity of grade 2 xerostomia changed into grade 1 or less in 5 patients within two years. Response rate at 5 months after treatment (24 patients evaluable) were 16 CR (67%) and 6 PR (25%), evaluated with MRI. One patient had evidence of local relapse, after initial CR, at 36 months from the end of RT. One patient died for cancer non-related causes.

Conclusions: HT achieves great homogeneity in the dose distribution and a significantly good sparing of the organs at risk. IMRT-SIB combined with CT (both in neoadjuvant and concomitant regimens) is very satisfactory in terms of toxicity and local control.

APPROCCI INTEGRATI NELLE NEOPLASIE LOCALMENTE AVANZATE DEL TORACE

P019

SEQUENTIAL *VS* CONCURRENT CHEMO-RADIOTHERAPY IN STAGE III INOPERABLE NSCLC: RETROSPECTIVE ANALYSIS OF OUR INSTITUTIONAL DATA

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Aims of the Study: We report our institutional data of multimodality approach to stage III inoperable NSCLC.

Materials and Methods: From 2006 to 2010, 46 patients with stage III NSCLC were treated with a combination of chemotherapy and radiotherapy in our Institution: 26 patients were stage IIIA and 20 patients were stage IIIB, mean age was 65 years (range 44-82 years), 39 were male, 7 female.

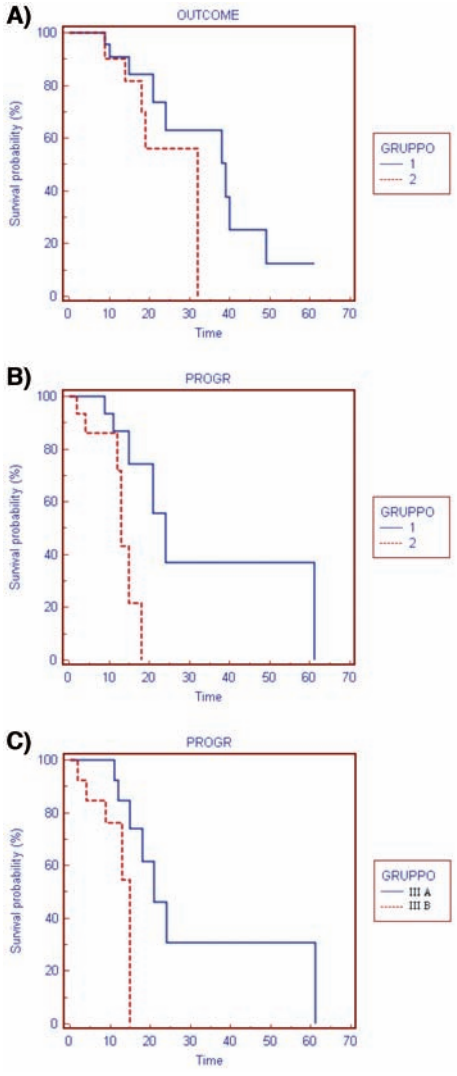

Figure 1.

They all received a combination of chemotherapy and radiotherapy: 24 patients received concomitant chemo-radiation (CDDP alone during radiotherapy or CDDP alone during radiotherapy followed by platinum-based couple): 10 in stage IIIA and 14 in stage IIIB. Twenty-two patients received sequential therapy (a platinum-based couple or mono-chemotherapy followed by radiotherapy alone): 16 in stage IIIA and 6 in stage IIIB. All patients received 3DCRT: dose prescribed varied between 50 and 66 Gy with conventional fractionation, mean dose was 58.6 Gy. Overall survival (OS) and progression-free survival (PFS) curves were calculated with the Kaplan-Meier method.

Results: OS was 39 months for the sequential group (Group 1) and 32 months for the concomitant group (Group 2) (ns) (see Figure 1A). PFS was 24 months for the sequential group and 13 months for the concomitant group ($p<0.007$) (see Figure 1B). PFS was 21 months for the IIIA and 15 months for the IIIB group ($p<0.026$) (see

Figure 1C). No difference in OS was observed between chemo-radiation alone and chemo-radiation following induction chemotherapy.

Conclusions: The appropriate combination of chemotherapy and radiotherapy in the treatment of locally advanced inoperable NSCLC is a matter of debate. According with our institutional data concomitant chemo-radiation or sequential chemo-radiotherapy are comparable in terms of OS. Sequential chemo-radiotherapy seems better than concomitant chemo-radiation in terms of PFS, probably due to the higher proportion of stage IIIA patients in this group.

P020

THERMAL ABLATION FOLLOWED BY CONVENTIONAL RADIOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: FEASIBILITY, EFFICACY AND TOLLERANCE

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Purpose: To evaluate the feasibility, efficacy and tollerance of pulmonary thermal ablation (PTA) followed by external radiotherapy (ERT) in the treatment of patients with locally advanced NSCLC.

Materials and Methods: Between April 2008 and May 2012, 5 patients with locally advanced NSCLC with good performance status (PS 0 or 1) (all men, mean age in the time of the treatment 66.6 years, age range 58-76 years) received one of three modalities of CT-guided pulmonary thermal ablation, namely radiofrequency (RF) ablation, microwave (MW) ablation, and cryoablation, followed by radiotherapy. One patient underwent two sessions of PTA due to a secondary lung tumor.Staging work-up including a contrast enhanced CT scan of the thorax and a 18FDG-PET scan. Two patients underwent CT-guided percutaneous MW ablation, one patient was subjected to two CT-guided percutaneous RF ablation session, and two patients underwent cryoablation, one of which intraoperatively. Before radiation treatment, the prescribed dose was variable between 30 and 60 Gy with conventional fractionation (1.8-2 Gy), and the treatment technique was preferentially the three-dimensional conformal radiotherapy.

Results: All five patients were eligible for analysis. The histologic subtypes were: adenocarcinoma (40%); squamous cell carcinoma (40%); and adenocarcinoma plus epidermoid cancer (20%). Two patients presents a stage III A disease, two stage IIIB disease, and one patient had stage IV. No procedural deaths occurred and there were no grade 3/4 toxicity. Procedural complications during thermal ablation were one pneumothorace resolved after drainage, and two cases of limited hemoptysis. During RT two of 5 patients experienced grade 2 esophagitis, and an isolated grade 2 pneumonitis was recorded.Responses after PTA treatment were as follows: total necrosis was noted in 3 lesions and partial necrosis was achieved in 3 lesions. Radiotherapy was administered in the primary tumor and thoracic nodes, and globally after treatment was observed objective responses in four of 5 patients; one patient showed progressive disease.

Conclusions: the potential role of combination of PTA with ERT appears to be a reasonable and clearly feasible option as a palliative treatment in more advanced disease. Procedural complication rates are low, and no additional major toxicities were seen despite the addition of PTA to ERT.

P021

SURVIVAL AFTER HIGH DOSE RADIATION THERAPY DELIVERED WITH TOMOTHERAPY TO THE INTACT LUNG FOR MALIGNANT PLEURAL MESOTHELIOMA PATIENTS TREATED WITH RADICAL PLEURECTOMY/DECORTICATION

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Purpose: To asses the efficacy and morbidity of radical radiation therapy to the intact lung delivered with Tomotherapy in patients affected by malignant pleural mesothelioma (MPM) who underwent radical pleurectomy/decortication (P/D).

Materials and Methods: This prospective study was conducted with the approval of our Institutional Review Board. Between October 2008 and February 2011, 20 MPM patients were enrolled in this prospective study and underwent radical radiation therapy with Tomotherapy after radical P/D. The clinical target volume was defined as the entire hemithorax, including chest wall incisions and drain sites, and excluding the intact lung. The dose prescribed to the planning target volume was 50 Gy delivered in 25 fractions. All patients underwent FDG-PET for staging after surgery. Any FDG-avid areas or regions of particular concern for residual disease were given a simultaneous boost of radiotherapy to 60 Gy. Nineteen patients received pre-operative and/or post-operative platinum-based chemotherapy; radiation was delivered after completion of chemotherapy. Toxicity was graded using the modified Common Toxicity Criteria v3.0. The pattern of relapse was reported. Kaplan-Meier analysis was used to calculate rates of progression-free survival (PFS) and overall survival (OS).

Results: The median follow-up was of 21 months (range, 9-37 months) from the time of surgery. The median OS and PFS were 33 and 29 months, respectively. The Kaplan-Meier estimates of OS at 1 and 2 years were 90% and 67%, respectively. The estimates of PFS at 1 and 2 years were 80% and 57%, respectively. Nine (45%) patients finally relapsed; 6 developed distant metastases as the first site of failure, whereas 3 failed loco-regionally. Five of the 20 patients (25%) experienced severe respiratory symptoms within 5 months after the completion of RT, corresponding to Grade 2 pneumonitis in 2 cases, and Grade 3 pneumonitis in 3 cases. No fatal respiratory toxicity was reported. One patient experienced a Grade 3 pain

to the chest wall, and one developed a Grade 3 piastrinopenia. There were no cases of Grade 3 esophagitis.

Conclusions: Tomotherapy allows the safe delivery of high dose of radiation to the hemithorax of MPM patients with intact lung, leading to promising PFS and OS results. This approach might be considered an alternative treatment option to those patients who can not tolerate extrapleural pneumonectomy.

VOLUMI CLINICI NELL'IRRADIAZIONE DELLE NEOPLASIE GINECOLOGICHE

P022

PRELIMINARY RESULTS OF DEFINITIVE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER WITH INTENSITY-MODULATED RADIOTHERAPY (IMRT) SIB ASSOCIATED TO CONCURRENT CHEMOTHERAPY

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Backgrounds: Concurrent chemoradiation is the standard treatment for advanced cervical cancer. Limited data are available regarding gynecological malignancies treated with Intensity-Modulated Radiotherapy (IMRT) used to reduce RT-related toxicity rates. We evaluated treatment feasibility and tolerance of 3 enrolled patients with locally advanced cervical cancer treated with curative IMRT-SIB and concurrent chemotherapy followed by vaginal brachytherapy (VBT).

Materials and Methods: We enrolled 3 patients with locally advanced cervical cancer. Mean age was 49 years (range: 38-55 years). All patients presented with clinical stage IVA according to FIGO. Tumor histology was as follows: adenocarcinoma 1 patient, squamous cell carcinoma 2 patients. All women underwent prior chemotherapy with iphosphamide - cisplatin - paclitaxel regimen for 3-4 courses. All patients underwent Image-guided radiotherapy (IGRT) with concurrent single-agent weekly cisplatin at 40mg/m2. Radiation therapy was based on FDG-PET /TC and MRI treatment planning. RT was delivered using 6 MV photons. Patients received 50.4 Gy in 28 daily fractions of 1.8 Gy/each on the pelvis e prophylactic lumbo-aortic nodes, 61.6 in 28 fractions of 2.2 Gy/each on the GTV (tumor and positive lymph nodes). Patients received high dose-rate VBT with Iridium 192. Brachytherapy was delivered to a total dose of 21 Gy in 3 fractions of 7 Gy/ each 3 times a week. Constrains for OAR was as following: for the bladder a dose < 80% delivered to a volume of 5cc, and for the rectum a dose < 75% delivered to a volume of 2 cc for each fraction. Toxicity was recorded according to CTCEA v3.0 scale.

Results: Two patients completed programmed treatment at the full dose prescribed. One patient interrupted chemotherapy and RT after 26 delivered fractions. Constrains have been met on dose-volume histograms. Acute toxicities occurred as follows: one patient presented grade 3 hematological toxicities (leukopenia, anemia and thrombocytopenia); one patient developed grade 1 anemia and leucopenia, grade 1 cystitis and grade 1 diarrhea; the other patient developed grade 2 cystitis, grade 1 low serum magnesium levels and grade 1 lymphopenia.

Conclusions: Curative IMRT-SIB associated to concurrent platinum-based chemotherapy for locally advanced cervical cancer is a feasible and well-tolerated treatment. Long-term follow up is needed to observe late toxicities, response and survival benefits.

P023

SURVIVAL AND TOXICITY OF RADICAL RADIOTHERAPY (WITH OR WITHOUT BRACHYTHERAPY) FOR FIGO STAGE I AND II CERVICAL CANCER: A MONO-INSTITUTIONAL ANALYSIS

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Purpose: To assess the efficacy and toxicity of radical radiotherapy (RT) for FIGO Stage I and II cervical cancer and to verify the advantage given by the addition of brachytherapy (BRA) to external-beam radiotherapy (EBRT).

Materials and Methods: 240 patients affected by cervical cancer (FIGO Stage I and II, any N) were treated with radical RT between 1990 and 2009 at "Istituto del Radio O. Alberti" of Brescia. 32 of them received EBRT alone, 189 EBRT+BRA, 19 BRA alone (early stages and/or very old women). BRA was delivered with low dose rate (LDR, 64%) till 2003 and then with high dose rate (HDR, 36%). The percentage of FIGO IIb stages, such as the percentage of pts presenting with pathological lymphnodes, was significantly higher in the second decade with respect to the first decade (respectively, 34.4 *vs* 59.9% for IIb stages and 5.4% *vs* 19% for N+ stages). Concomitant chemotherapy (CHT), mainly weekly cisplatin 40mg/m2, was administred mostly after 2000; the delivered radiation doses too were higher in this period if compared to the first decade ones.

Results: Five years overall survival (OS) was 65%, and disease specific survival (DSS) was 77%. Regardless of stage of disease, better DSS was evident in women treated with the combined modality (EBRT+BRA) compared with those treated with EBRT alone (82% and 58% respectively, p:0.005); similarly, women treated with concomitant CHT (dose intensity >=50%) and with high radiotherapy doses (RT cumulative dose EQD2 >= 75Gy) obtained better DSS. Among patients treated with EBRT and BRA, 172 pts (92.5%) obtained a complete response of the disease, that was maintained for 80.8% of them: for most of the remaining cases (9.9%), the first relapse was a distant metastasis. When BRA was used, OS and DSS were not statistically related with the different dose rate. Older patients had better outcomes than younger ones

regardless of stage of disease. Chronic G3/G4 toxicity (CTCAE criteria v 4.0) was evident respectively in 11.2% and 7% of pts, especially in the intestinal/rectal tract. Total dose and association with concomitant CHT were not related significantly with the serious chronic sequelae.

Conclusions: Our mono-institutional analysis confirms the efficacy of radical radiotherapy for the treatment of cervical cancer and provides more support to the role of brachytherapy both in the early stages and in the locally advanced ones with a G3 and G4 chronic toxicity acceptable and only partially influenced by the dose rate.

P024

INTRAVAGINAL PULSED DOSE RATE BRACHYTHERAPY FOR STAGE I (FIGO STAGING SYSTEM) ENDOMETRIAL CANCER: OUTCOME AND TOXICITY IN OUR EXPERIENCE

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Purpose:The overall prognosis for patients with endometrial cancer is excellent, particularly for stage I. Despite the excellent outcome in this groups of patients, the optimal treatment remains unclear. Some Authors recommend observation instead of adjuvant radiotherapy and others recommend Pelvic RT. We evaluated the outcome and related toxicity after multimodality treatment comprehending surgery, followed by External Beam Radiotherapy (EBRT) and Intravaginal Brachyterapy. (BRT).

Materials and Methods: We retrospectively reviewed 39 patients affected by Endometrial Carcinoma from January 2006 to March 2011 at the "Sapienza" - University of Rome, Policlinico Umberto I, Department of Radiation Oncology (follow up range 13 - 89 months). The average age was 68 years. All patients were classified as I stage according to FIGO Staging System; Thirtyfive patients (90%) were classified as Stage FIGO IB, and 4 patients (10%) were classified as Stage FIGO IA. All patient underwent surgery and all the tumors were classified as adenocarcinoma. After surgery all patient underwent pelvic EBRT with a range of dose between 45 –50,4 Gy with a daily fraction of 180/200 cGy, with a 6-MV linear accelerator, using a 3D conformal radiotherapy technique. For all patients EBRT was followed by a boost delivered with intravaginal BRT, using a Pulse Dose Rate technique (PDR) for a total dose of 15 Gy with fraction of 500 cGy delivered once a week for 3 weeks.

Results: During the follow up all 39 patients had no recurrence of disease. Median disease free survival (DFS) was 36 months. The tolerance to the RT was good and 26 patients (67 %) have no significant side effects during EBRT, while we observed gastrointestinal toxicity (G1-G2 RTOG), in 9 patients (23%), and skin toxicity (G1-G2 RTOG) in 4 patients (10%). After BRT no patient had any side effect and the tolerance was excellent.

Conclusions: According to our experience, adjuvant EBRT followed by BRT provides excellent outcome and acceptable morbidity. The results about DSF were particularly encouraging. Particularly BRT showed excellent outcomes and acceptable morbidity with absence of early and late toxicity.

P025

THE ROLE OF 18FDG-PET/CT IN STAGING AND TREATMENT PLANNING FOR VOLUMETRIC MODULATED RAPIDARCTM RADIOTHERAPY (RA-IMRT) IN CERVICAL CANCER: EXPERIENCE OF THE EUROPEAN INSTITUTE OF ONCOLOGY, MILAN

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Purpose: to evaluate the role of 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) integrated to computer tomography (CT) scan (18FDG-PET/CT) in the staging and target volume definition in RA-IMRT in cervical cancer.

Materials and Methods: From June 2010 to December 2011, 66 patients (pts) affected by cervical cancer were treated with RA-IMRT. After standard staging with CT and magnetic resonance imaging (MRI), all pts underwent 18FDG-PET/CT in order to exclude distant metastases and to define gross tumour volume (GTV). 40 and 26 pts received exclusive and adjuvant radiotherapy, respectively. RA-IMRT with simultaneous integrated boost (SIB) to the positive disease technique was employed.

Results: In our experience 18FDG-PET/CT has changed the stage in 25 % and 7.7 %, compared to conventional MRI and CT scan staging, and the radiotherapy treatment planning in 22.5 % and 7.7 % of patients that received exclusive and adjuvant radiotherapy, respectively. In particular, 18FDG-PET/CT imaging showed metabolically active tumour in para-aortic lymph nodes and iliac nodes, therefore the stage and the treatment planning changed for these pts. In 2/26 pts (post-operative treatment) 18FDG-PET/CT showed the persistent of disease after surgery in para-aortic nodes (1 pt) and in T area (1 pt) confirmed by biopsy.

Conclusions: Our preliminary results indicate that the 18FDG-PET/CT leads to a better staging of disease and to a better volume definition and has the potential of showing lymph-node metastasis not only within the pelvis but also in the para-aortic area. In addition, 18FDG-PET/CT is useful for better definition of the target volume and to produce a "dose painted" treatment especially if combined with IMRT. This might also open the space for the escalation dose regimens.

P026

EVALUATION OF DOSE VOLUME HISTOGRAMS (DVH) COMPARING THE IMRT RAPIDARC AND THE 3D CONFORMAL RADIOTHERAPY IN SEVEN PATIENTS WITH GYNECOLOGICAL CANCER TREATED WITH EXCLUSIVE RADIOTHERAPY WITH CURATIVE INTENT

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Purpose: IMRT has many intrinsic advantages if compared to the traditional 3D conformal especially on organ at risk (OAR) sparing, target coverage, implementation of dose escalation and simultaneous integrated boost (SIB) and re-irradiation considering that the major concern has always been the dose the OAR have already received in previews treatments. We report our preliminary experience in gynecological cancer.

Materials and Methods: we evaluated the Dose Volume Histograms (DVH) comparing IMRT RapidArc and the 3D conformal radiotherapy in seven patients with gynecological cancer treated with exclusive radiotherapy and curative intent. Constrains were applied to OAR. Patients were treated with IMRT but on the same CT scan we calculated a 3D plan for comparison. Definition of IMRT volumes: the Gross Tumor Volume (GTV) was defined as the gross extent of tumor shown by imaging matching In some cases the MRI images. Also FDG-PET/TC was used in the delineation of GTV. The Clinical Target (CTV) was drawn by clinical criteria and was defined as GTV plus a margin for microscopic spread to the ovaries, parameters, the upper part of the vagina and the pelvic lymph nodes. A margin for Planning Target Volume (PTV) was generated by expanding the CTV by 15 mm in all directions except 10 mm in the cranio-caudal direction for the T and by 0,5 cm for lymph nodes. Ovaries were considered as part of GTV. The 3D fields' definition has been made using standard criteria.

Results: The analysis of DVH demonstrates that RapidArc treatment spares rectum, bladder and the bowel better than what 3D does. Considering the bladder, in fact, although the dose constraints aren't fulfilled, the RapidArc DVHs are lower. Collaterally treatment time is a lot shorter with IMRT than the average box plan time.

Conclusions: The dosimetric comparison with 3D conformal plans was, as expected, favourable to IMRT RapidArc.

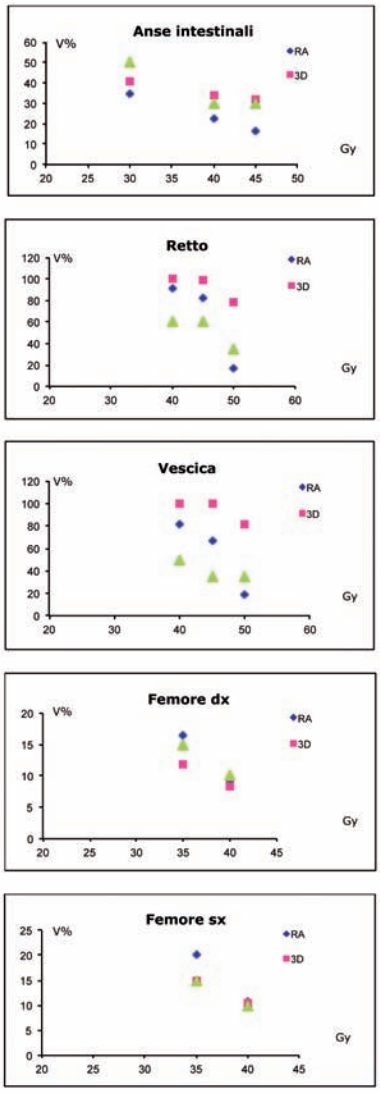

Figure 1. Graphics comparing avarage DVH for each organ at risk using an IMRT RA tecnique or a 3D. The green triangle rapresents the constraints.

P027

EVALUATION OF DOSE VOLUME HISTOGRAMS (DVH) COMPARING THE IMRT RAPIDARC AND THE 3D CONFORMAL RADIOTHERAPY IN NINE PATIENTS WITH GYNECOLOGICAL CANCER TREATED ON THE LOMBO-AORTIC TRACT

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Purpose: Radiotherapy on the lomboaortic tract although often necessary in gynecological cancer patients, has always been a concern for the radiation oncologist for the proximity of the spine cord which limits the dose delivery as well as for the complexity of the plan whenever a higher dose than 45Gy is needed.

Materials and Methods: we evaluated the Dose Volume Histograms (DVH) comparing the IMRT RapidArc and the 3D conformal radiotherapy in nine patients with gynecological cancer patients treated on the lombo-aortic tract (as well as on the pelvis). CTV has been drawn manually by the following criteria: cranially right below the diaphragm pillars, caudally to the root of the common iliac vessels, laterally drawing a sickle around the vertebral body, including the aorta, the cava, the interaortocaval space and the renal arteries. The PTV has been created by adding a 0.5 cm around the CTV in all directions but the anterior, that's been expanded by 0.7 cm. Dose range varied from 45 Gy to 55Gy. In patients with positive lombo-aortic lymph nodes, if doses higher than 45Gy were needed, we delivered 50 Gy on all lombo-aortic axe and up to 55Gy in the bulky nodes with simultaneous integrated boost (SIB). Same doses were used in the 3D plans developing two consecutive plans up to the prescript dose. The 3D fields' definition has been made using standard criteria.

Results: DVH analysis demonstrates that RapidArc treatment is more conservative on bowel, rectum and bladder. Also in those patients in which the dose constrains on bladder and rectum aren't met RapidArc DVHs are lower. The kidney and the liver receive a higher dose due to the dose bath.

Conclusions: The DVH dosimetric comparison between IMRT and 3D conformal plans is favorable to IMRT RapidArc. The possibility to deliver SIB allows dose escalation for a better local control.

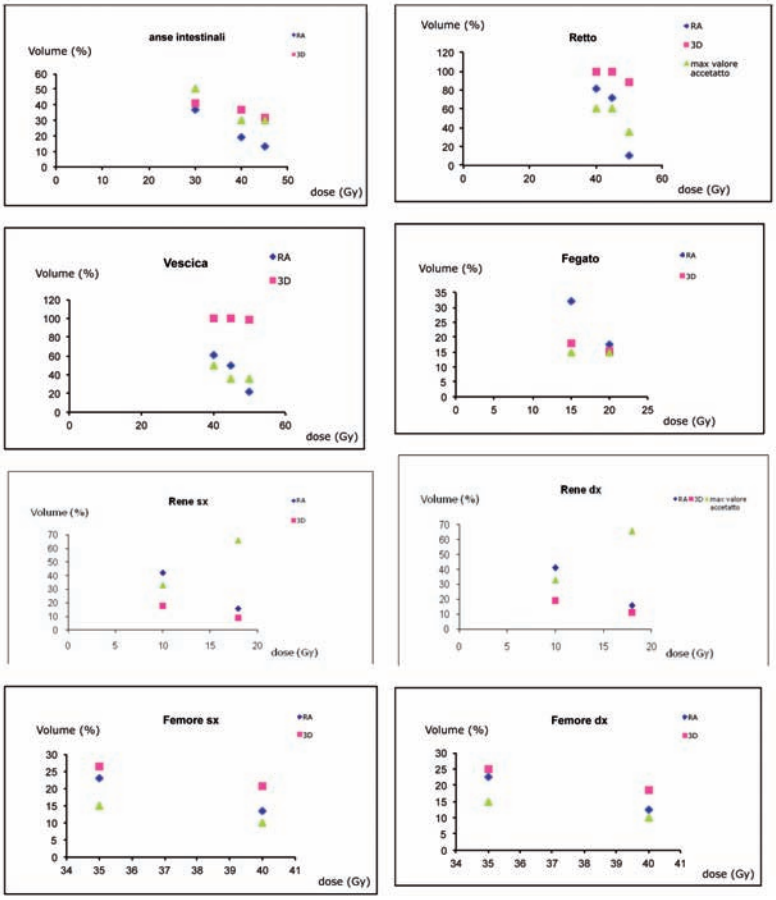

Figure 1. Graphics comparing avarage DVH for each organ at risk using an IMRT RA tecnique or a 3D. The green triangle rapresents the constraints.

P028

ACUTE AND LATE TOXICITY WITH 3DCRT *VS* IMRT-LINAC BASED *VS* TOMOTHERAPY IN PATIENTS TREATED FOR CERVICAL CANCER

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Backgrounds: Goal of this study was to evaluate toxicity in three consecutive group of patients (pts) with cervical carcinoma, irradiated on pelvic ± lumbar-aortic (LA) volumes by different techniques (3D-CRT, IMRT and IMRT-IGRT-SIB Tomotherapy-Tomo), associated or not to High Dose Rate brachytherapy(HDR).

Materials and Methods: From 2001 to 2011, 62 women with cervical cancer were treated with External Beam Radiotherapy (EBRT): 85% pts received also HDR, 15% EBRT alone, 67% received surgery and 48% chemotherapy. Histology were SCC (85%) and adenocarcinoma (15%). Between 2001 and 2009, 55% pts underwent 3D-CRT with 41% also CT. From 2010, 32% received IMRT with 55% also CT and 13% received Tomo with 60% also CT. 3D-CRT was performed with 4-field box technique with18-MV photons, on pelvic region with 50.4 Gy (1.8 Gy/fr); a boost HDR of 16 Gy (4 Gy/fr) was used for adjuvant and of 19.5 Gy (6.5 Gy/fr) for radical treatment. A 7/8-field technique IMRT, with 6-MV photons, on pelvic volume with 54 Gy (1.8 Gy/fr) +concomitant boost on N+ to 66 Gy (2.2 Gy/fr) and a boost HDR 16 Gy for adjuvant treatment. In radical treatment a further boost on T+ and N+ and/or parametrial+ to 66 Gy with HDR boost 14 Gy (7 Gy/fr) was used. For Tomo pelvis and LA nodes received 50.4 Gy +concomitant boost on N+ to 66 Gy +boost HDR 16 Gy for adjuvant intent. For radical 54 Gy on pelvis +concomitant boost on LA nodes to 51 Gy (1.7 Gy/fr)+concomitant boost on T+ and N+ and/or parametrial+ to 66 Gy+boost HDR 14 Gy.

Results: Acute GI toxicities were respectively G1: 26% for 3D-CRT, 11% for IMRT and 5% for Tomo; G2: 16%, 6% and 3%; G3:1,6% for 3D-CRT and for IMRT (each 1 pt); while G4 resulted only for 3D-CRT in 1 pt (1.5%). Acute GU toxicities were respectively: G1 18% for 3D-CRT, 8% for IMRT and 5% for Tomo; G2: 13%, 6% and 3%; G3: 3% for 3D-CRT and 1.5% for IMRT. Late GI toxicities G1 were: 11% for 3D-CRT, 1.5% for IMRT and 0% for Tomo. G2 8% and 1.5% for both IMRT and Tomo. Late GU toxicities were: G1 18% for 3D-CRT, 1.5% for both IMRT and Tomo; G2 was 8% for 3D-CRT, 1.5% for IMRT 0% for Tomo.

Discussion: Our results show that IMRT and Tomo lead to a significant reduction in acute GI and GU toxicities compared with the 3D-CRT, despite largest treatment volumes. The global rate of G2-G3 acute toxicities are respectively 35% and 23% for 3D-CRT and for IMRT-Tomo; similarly the rate of late toxicities are 16% and 4.5%; the superiority of IMRT by Tomo in terms of global toxicity is evident.

P029

THREE-DIMENSIONAL HIGH DOSE RATE BRACHYTHERAPY BOOST FOR ENDOMETRIAL CARCINOMA

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Introduction and Aims: Endometrial carcinoma is the most common gynecologic malignancy in Italy. Fortunately disease is often confined to the uterus in most patients but women with high-risk features or extrauterine disease require adjuvant radiotherapy. Most of these patients receive intracavitary brachytherapy as a part of their treatment. Bladder and rectum are important dose-limiting structures during gynaecological brachytherapy because of their close location to the target. The goal of brachytherapy is to achieve as low a radiation dose as possible to the normal tissue while delivering the highest homogeneous dose within the target. This study aims to evaluate efficacy and toxicity of adjuvant HDR-BT boost by using Computed Tomography (CT)-based tridimensional conformal brachitherapy for endometrial cancer patients.

Materials and Methods: Between January 2010 and December 2011, thirty-one patients with endometrioid endometrial cancer were treated at Radiotherapy Department in Foggia with ERT followed by vaginal boost of HDR-BT. Mean age was 64 years (range between 52 and 80 years) and all patients were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pathological stage was I FIGO for 35%, II FIGO for 35% and III FIGO for 30% of patients while 48% of them received also adjuvant chemotherapy. Pelvic external radiotherapy was administered 4-6 weeks after surgery with a total dose of 50.4 Gy (1.8 Gy/die) and delivered by a linear accelerator with 10-18 MV energy. HDR iridium-192 intravaginal brachytherapy was administered from one to three weeks after the end of ERT with a total dose of 10-12 Gy (5-6 Gy per fraction) using Fletcher ovoids. CT scans of the pelvis in supine position with empty rectum and full bladder with catheterization, were obtained in order to contour Clinical Target Volume (one-half to two-thirds of the length of the vagina), Planning Target Volume and organs at risk (bladder and rectum) for each obtained scan. We proceeded with plan optimization, DVH analysis and evaluation of the overdose index (OI) and homogeneity index (HI). Rate of local recurrence, metastasis and survival were evaluated. The late rectal and genitourinary (GU) toxicities were scored according to the EORTC/RTOG scales.

Results: Median follow-up was twenty-three months and last controls were performed in May 2012. GU acute toxicity was observed in 9.6% of patients (G1) while late GU toxicity was observed in 12.9% of patients (G1). No acute rectal toxicity was observed while late rectal toxicity (proctitis) was observed in 9.6% of patients. Median HI and OI were 0.60 and 0.15. No local recurrence was observed and two patients experienced distant metastases (liver and lungs) and died for their disease.

Conclusions: Our analysis showed that CT-based tri-

dimensional conformal brachitherapy should be used in order to reduce dose at organs at risk and improve target dose distribution with less toxicities. 3D adjuvant HDR-BT vaginal boost for high- and intermediate-risk patients with endometrial carcinoma provides excellent local control and survival with minimal genitourinary and rectal toxicity also after ERT.

P030

CORRELATION BETWEEN CONVENTIONALLY DEFINED CT VOLUMES AND GTV–PET IN BRACHYTHERAPY FOR CERVICAL CANCER

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Aims: Concomitant chemoradiation with cisplatinum and intracavitary brachytherapy (BT) is the standard of care in patient with locally advanced cervix cancer. Treatment planning for BT provides for the use of three dimensional imaging, such as CT scan or MRI. Positron Emission Tomography with [18F]FDG is an imaging modality that can aid in image-guided radiation treatment planning. The purpose of our feasibility study was to compare the tumour volume measurement during BT, including or not PET informations, in order to establish the benefit from [18F]FDG-PET in BT planning.

Materials and Methods: From June 2007 to May 2010, at Radiation Department of San Gerardo Hospital in Monza, thirteen women with advanced cervical carcinoma were enrolled into the study. All patients underwent external beam radiation therapy (EBRT) plus concomitant weekly chemotherapy (cisplatinum 40 mg/m2) and HDR brachytherapy performed weekly during the course of EBRT. The HDR brachytherapy fractions have been planned with CT scan and, for the first and the fourth fraction also FDG-PET/CT was employed. Two volumes (CTVs) were defined: the first one called CTVstandard, was based on clinical information and on CT scan; the second one,called CTVPET-influenced, was created with the additional information brought by PET scan.

Results: A paired t-test was used to determine the statistical significance for comparison the two series of volumes. We compared the dimension of the two volumes and the intersection of CTVstandard and CTVPET-influeced and we calculated the difference between the volumes. Linear regression was employed for the correlation of the two volumes. In our small patient population the reduction of GTVPET getting through pelvic EBRT and the BT fractions was unpredictable and with residual tracer uptake areas often located far from the applicator and very difficult, if not impossible, to be included in the BT planning. We found also some PET negative patients during brachytherapy, meaning, probably, good prognosis but useless for treatment planning

Conclusions: It is very difficult, in our experience, to identify the role of PET in cervix brachytherapy treatment plan.In some few cases we observed that GTVPET was totally included in CTVstandard. In the majority of patients GTVPET was not coherent with clinical plus CT information.

P031

USE OF PET-TC IN DEFINING TREATMENT VOLUMES IN GYNECOLOGIC CANCER. THE EXPERIENCE OF TWO RADIOTHERAPY DEPARTMENTS (MAURIZIANO HOSPITAL IN TURIN AND IRCC IN CANDIOLO)

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Purpose: The definitive treatment and prognosis for gynecological cancer is markedly affected by the extent of disease at the time of diagnosis. MRI/CT studies have been used widely in staging gynecological cancers. The aim of our study is to evaluate the impact of FDG-PET in staging,definition of treatment volumes and to reduce inter-observer variability in contouring.

Materials and Methods: Between January 2008 and March 2012 129 patients with gynecological cancer and candidated for RT (adjuvant , radical or palliative) referred to Mauriziano and IRCC RT Dept; 54 of them underwent a PET-CT scan before the definition of treatment program. Of the 54 patients 47 had cervical, 6 endometrial and 1 vaginal carcinoma; 8 underwent adjuvant RT after radical surgery CT-RT (RT dose 64-67 Gy, boost HDR 21 Gy/3 fr or 24 Gy/4 fr). 33 patients were treated with 3DCRT, 21 with IMRT sib technique. Treatment planning was performed according to the fusion between PET & simulation CT; the GTV was defined with semi quantitative method (cut-off value 2.5 SUV) in order to reduce inter-observer variability.

Results: Staging was modified by PET in 8 patients (15%): PET-CT revealed distant metastasis and changed therapeutic option (patients underwent chemotherapy or palliative RT). In 27 patients (50%) staging was confirmed in PET-CT, MRI and CT imaging so there was no change in therapeutic decisions, in contouring and in dose prescription. In the remaining 19 patients (35%) staging was increased: PET -CT showed abnormal LF in pelvis or lomboaortic chains not previously revealed by MRI and CT. PET-CT could identify nodal metastasis even in nodes seen of normal dimensions in CT/MRI. In these patients contouring was more precise thanks to PET-CT simulation fusion and we could give higher doses to PET positive areas. In the group of the postoperative RT in only 1 patient PET revealed pelvic nodal metastasis.

Conclusions: Our work confirmed the results of other papers about the clinical impact of PET-CT imaging in RT. The importance in selection of patients for different treatment options, in definition of target volumes and in contouring allows us to increase the dose to the tumor and, at the same time, to reduce toxicity. This procedure also improved accuracy in contouring and delivering higher doses to GTV PET , particularly in the IMRT group. About the pro-

blems of PET response evaluation and prognostic informations, further studies must be conducted.

P032

VOLUMETRIC IMRT WITH SIMULTANEOUS INTEGRATED BOOST IN LOCALLY ADVANCED CERVICAL CANCER: VOLUMES AND DOSES IN A PRELIMINARY EXPERIENCE

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Aims: To describe feasibility and safety of simultaneous integrated boost (SIB) for dose escalation in patients with cervical cancer using a rotational dynamic IMRT (VMAT®).

Methods: From May to December 2011, 10 patients with loco-regionally advanced, node negative, inoperable cervical cancer (FIGO stage: IIB-IV) underwent primary chemoradiation (CRT). Six pts received 3 cycles of platinum-based chemotherapy (CT) before revaluation for surgery. Because of still inoperable disease, they underwent to CRT. In all pts were delineated PTV1 (primary, cervix and parametria with a 1cm-margin); PTV2 (body of uterus with a 1cm-margin); PTV3 (pelvic nodes). PTV1 was defined using image fusion between CT-scan and RM or PET/CT. Treatment plans, calculated using a rotational dynamic IMRT system on Oncentra Masterplan® (VMAT®), consisted in a SIB. Radiation doses were 60/2Gy to PTV1 and PTV2 and 54/1.8Gy to PTV3. During last 3 weeks of external radiotherapy (ERT), pts underwent to 4 weekly ERT fraction and brachiterapy (BRT) on Friday (7Gy). Total treatment time was 45 days. In 4 pts not eligible for BRT because of inaccessible cervical canal, radiation doses were 69.9/2.33Gy to PTV1, 60/2Gy to PTV2 and 54/1.8Gy to PTV3 in 30 fractions. Total treatment time was 40 days (Fig. 1) Concomitant CT consisted of weekly cisplatin 40 mg/m2. Dose–volume histograms and acute gastrointestinal, genitourinary, and hematologic toxicity were evaluated. After 3 months from CRT, pts were revaluated with cytology.

Results: All constraints were respected in every treatment plan. Toxicity pattern was diarrhoea G2 (3 pts) and cystitis G2 (2 pts). In 3 pts, we observed a G2 anaemia which required erythropoietin. All pts concluded radiation without suspension. In pts treated with ERT and BRT, BED on primary was 90 Gy, assuming a tumor/ratio as 10. In pts treated with hypofractionation, BED on primary was 72 Gy. Citology demonstrated complete response (CR) in 3 pts in the ERT-BRT group and in 1 pts in ERT alone group. All other pts showed a partial response (PR) higher than75%.

Discussion: Guidelines suggest that curative BED in cervical cancer must to be at least 85 Gy. This dose level is easily achievable when combination between ERT and BRT is possible. In pts with inaccessible cervical canal, dose escalation is limited by toxicity. Prescribing different doses to cervix and body of uterus with SIB-IMRT could allow dose escalation on primary, without toxicity arising, because of small bowel sparing. Moreover, IMRT, allowing concave isodoses, could provide to bladder and rectum sparing within tolerance doses. In all our pts, total treatment time was less than 8 weeks, as recommended by literature to improve local control. After this preliminary experience of feasibility, in pts with inaccessible cervical canal we will go on dose escalation on PTV1 with the aim of delivering BED as near as possible to 85Gy.

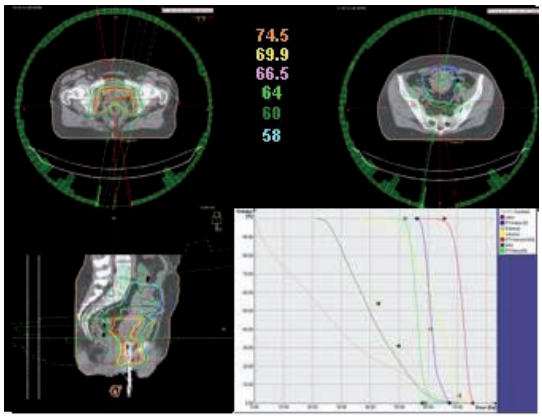

Figure 1. Example of treatment plan and DVH.

P033

COMPUTED TOMOGRAPHY IN COMPARISON TO THE ORTHOGONAL RADIOGRAPHY BASED TREATMENT PLANNING IN HIGH DOSE RATE VAGINAL CUFF BRACHYTHERAPY: AN INITIAL EXPERIENCE OF ASTI HOSPITAL

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Aims: To correlate and compare the informations obtained from the two approaches for high dose rate (HDR) brachytherapy (BRT) of vaginal cuff: the orthogonal conventional method and the computerized tomography (CT) three dimensions based calculation method in relation to the target and organ at risk (OAR).

Materials and Methods: From January 2012 we replaced the standard mode of calculation BRT treatment planning, Plato 2D, with a new BRT 3D treatment planning system, Oncentra Brachy. In six months we treated 10 patients with vaginal cuff HDR BRT by Microselectron. Cases included 7 adiuvant treatments (5 endometrial cancers and 2 cervical cancers) and 3 treatments for vaginal cuff's relapses by cervical cancers. In only one of these last 3 cases BRT was exclusive, in the other 2 cases BRT was combined with external beam radiotherapy (EBRT). Among the adiuvant treatments, BRT was delivered combined with EBRT in 5 cases, while it was exclusive in the other two patients. All patients had CT planning in the

first fraction with the vaginal applicator (single channel cylinder) and the Foley catheter inserted. On TC images we contoured the CTV, the PTV and the OAR. The generated plan was used in all the subsequent fractions without the Foley catheter inserted ; on the contrary in 3 cases we repeated TC planning in two or more sessions. In each fraction we carried out endorectal *in vivo* dosimetry. At the same time in each session we took two orthogonal radiographies, on which we specified rectum and bladder points according to ICRU 38 and we calculated dose to these points. Then we compared PTV and OAR doses obtained from the two different planning systems.

Results: The rectum D 0.1 cc in all sessions are higher than doses in the Plato-points, and the mean percentual deviation is 36%; the rectum D 1cc are still more important than the Plato's doses, but the mean difference is reduced to 18%; the rectum D 2cc are similar to Plato's doses, with a mean deviation of 6%. The bladder's doses show a similar trend. We verified in all cases a good agreement between *in vivo* rectal measured doses and calculated doses.

Conclusions: Three-dimensional CT-based planning for HDR vaginal cuff BRT helps to decrease dose to critical organs without compromising coverage of PTV by customizing the dosimetry according to individual patient anatomy; this advantage is more evident in cases in which BRT is a part of a curative setting for vaginal relapses after hysterectomy.

P034
USING ATLASES TO DELINEATE PELVIC OARS AND PRACTICAL IMPLICATIONS

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Introduction: To standardize OARs delineations is very important in radiotherapy planning. Recently one report provided the recommendations for the definition of the male and female pelvic normal tissue structures for radiotherapy planning. The deriving atlas is the result of a Radiation Therapy Oncology Group (RTOG) Consensus Panel. The purpose of our study is to estimate the application of this atlas in pelvic female contouring and to evaluate its impact on the reduction of inter-observer variability. We also compared delineation based on RTOG with delineation based on an atlas performed by our institution.

Materials and Methods: A planning CT of the pelvic district, free breathing, slice of 0.5 cm, was performed in a female patient with breast cancer to allow a definition of OARs in conditions of anatomo-morphological integrity. Organs surrounded were: rectum, bladder, femoral heads and ovaries. The delineation was made by two radiation oncologist. Two different delineations based both on RTOG atlas and our institutional atlas were performed by each radiation oncologist. Then the delineations were compared according to the Conformity Index (CI).

Results: On delineations performed in a blinded fashion by the two radiation oncologist (A and B) we have calculated CI in four comparison conditions: 1) CI based on RTOG atlas as reference tool= A *vs*. B; 2) CI based on our institutional atlas as reference tool= A *vs*. B; 3) RTOG *vs*. our atlas for observer A; 4) RTOG *vs*. our atlas for observer B. Comparing the delineations performed using the RTOG atlas CI was >0,7 (70%) for bladder and femoral heads while for rectum and ovaries CI were 0.5 (50%) for both of these OARs. When we compared the delineations based on our atlas we reached a similar acceptable conformity (CI: >0,7 [70%]) for the bladder and quite similar conformity for femoral heads (CI: >0.68 [68%]) while for rectum and ovaries CI were also in this case lower (CI: 0,63 [63%]). Analyzing for each observer the comparison between RTOG *vs*. our atlas, the bladder only continues to be correctly identified (CI: >0,7 [70%]).

Conclusions: From these data we conclude that the bladder is readily identifiable and therefore conformity is achieved independently of the anatomical landmarks. For the other organs both the anatomic landmarks and morphological characteristics can affect the results. Two important differences can be observed between the two atlases: a) femoral heads delineation because RTOG atlas includes the femoral neck; b) ovaries drawing, which are delineated including tubes. When CI is calculated comparing the two atlases, exactly emerge that they provide different landmarks for these organs except the bladder. The exception is the rectum for which it seems difficult to standardize contouring despite the same anatomical limits are indicated. Probably, the difficulty to identify the rectum-sigma junction is its main cause. In conclusion the OARs contouring, apparently simple, is in truth difficult for various reasons and despite the use of atlases. Nevertheless atlases and CT anatomic-radiological landmarks are necessary as is essential an appropriate imaging to provide a better identification of clinical volumes.

P034 bis
IMAGED BASED 3D TREATMENT PLANNING FOR VAGINAL CYLINDER BRACHITHERAPY: DOSIMETRIC EFFECTS ON OARS DUE TO PATIENTS POSITION DURING TREATMENT

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Purpose: Aim of this study was to evaluate dose distribution within Organs At Risk (OARs) and Planning Target Volume (PTV) based on three-dimensional treatment-planning (Nucletron Oncentra Brachy) according two different set-up positions, extended legs (Figure 1A) and gynecological position (Figure1B), in uterus carcinoma patients submitted to brachy radiotherapy on vaginal vault.

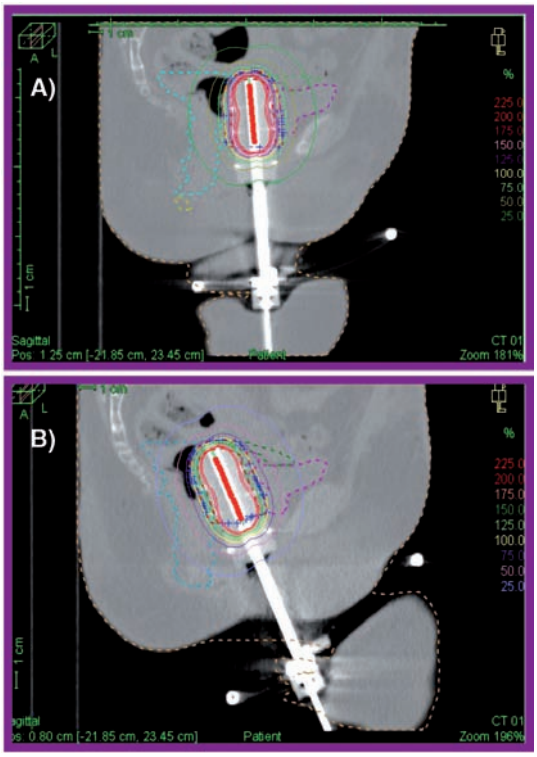

Figure 1. A) E.L., B) G.L.

Patients and Methods: 12 patients were prospectively investigated. For 3D Planning all patients underwent two consecutive pelvic CT-study with an indwelling catheter in place both in A and B position respectively; the CT scan was performed with 1,5 mm slice thickness to improve the image resolution for digitizing the source positions. All CT slices were transferred to the 3D treatment planning system, where 3D contouring of bladder, rectum and small bowel were performed; PTV was identified as applicator's surface with an isotropic 5mm margin expansion. For each patient, the external contours were delineated on each axial CT slice in the contouring workspace of the Oncentra Brachy treatment planning by use of sagittal and coronal views for assistance. To ensure consistency of structures between the scan set, contours for each patient were closely compared and verified on corresponding CT slices. Source positions inside the applicator were digitized and dwell times were optimized to generate the desired PTV prescription. Dose Volume Histograms (DVH) of OARs were calculated for each plan. For each OAR, the volume dose was definited by use of two different criteria: the dose value receiving in 2,0 cc and 1,0 cc volume.

Results: The analysis of results shows, for single fraction (5Gy), same coverage of PTV (POS A: min 94,81% - max 99,98%, POS B: min 94,90% - 100% max) and values of D1cc and D2cc obtained for rectum (POS A: D2cc Average 3,88Gy - D1cc Average 4,26Gy, POS B: D2cc Average 4,69 Gy - D1cc average 5,68 Gy), bladder (POS A: D2cc Average 4,43 Gy - D1cc Average 5,17 Gy, POS B: D2cc Average 4,56 Gy - D1cc average 5,22 Gy) and small bowel (POS A: D2cc Average 1,30 Gy - D1cc Average 1,91 Gy, POS B: D2cc Average 2,46 Gy - D1cc average 3,16 Gy) are small in setup A. In both cases D 2cc values are below the ICRU prescription.

Conclusions: In both position could be respected dose constraints but using A set-up it seems possible to reduce dose to OARs with the same PTV coverage with respect to B position.

VOLUMI CLINICI NELL'IRRADIAZIONE DELLE NEOPLASIE BRONCOGENE

P035

PATTERNS OF RECURRENCE IN NSCLC PATIENTS TREATED WITH PET-BASED INVOLVED FIELD 3D CRT

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Purpose: To analyze patterns of failure and disease control after PET-based involved-field (IF) radiotherapy in non-small cell lung cancer (NSCLC) patients (pts).

Patients and Methods: From 2007 to 2011, 116 NSCLC pts were treated with definitive radiotherapy (RT). A retrospective review of the 38/116 cases who underwent FDG-PET simulation scan and in-house follow-up was done. GTV was identified as FDG avid regions and elective nodal irradiation (ENI) was avoided. Response assessment was performed with CT and/or FDG-PET 4 months after the end of RT and subsequently every 4-6 months. Analysis and spatial comparison of the site of recurrences and the irradiated regions was performed. Intra-thoracic recurrences were considered in field (InF) when occurring inside the 90% isodose, marginal (M) when encompassed by the 50% isodose and out of field (OF) when outside the 50% isodose.

Results: Of 38 pts (20 squamous and 18 adenocarcinoma), 26 were staged IIIA (19 with N2) , 6 IIIB and 6 I- II. RT was administered with conventional fractionation (2 Gy/die) in 20/38 pts (Group A) to a median dose of 60 Gy (range 48-60 Gy) and with hypofractionation (2.5-3.0 Gy/die) in 18/38 pts (Group B) to a median dose of 42 Gy (range 39-60 Gy). All about 4 pts received neoadjuvant/adjuvant cisplatinum-based chemotherapy. Response to treatment at first CT scan was: 2 CR, 7 PR, 9 SD, 2 PD (Group A); 6 PR, 8 SD, 4 PD (Group B). Intra-thoracic disease failure occurred in 10/20 pts (50%) in Group A (mean time 8 months, range 3-16), and in 13/18 pts (72%) in Group B (mean time 7 months, range 3-29). In Group A, 5 InF only, 2 marginal and 3 both InF and OF were observed. In Group B, 5 InF, 2 marginal, 2 OF and 4 both InF and OF were detected. Only one OF recurrence could have been avoided by applying ENI irradiation. Distant failure occurred in 9 pts in Group A (mean time 6 months, range 1-19) and in 11 pts in group B (mean time 11 months, range 3-29). Severe lung toxicity (G3) was reported in 7 pts (18%)

who had received median dose of 50 Gy, 2 Gy/die, with the following dosimetrical parameters: V20 = 18 Gy, V20-omo= 38 Gy, MLD= 11 Gy. Three pts reported only radiological signs (G2) of lung fibrosis. No toxicity was registered in the 13 pts receiving hypofractionation (3 Gy/die).

Conclusions: In our experience, PET based involved field radiotherapy resulted a safe approach since only one recurrence occurred outside the treated volume. This approach allowed to reduce the irradiation of normal tissue. On the other hand more than half of pts recurred within the 90% isodose suggesting an insufficient tumour control.

P036

TUMOUR SHRINKAGE OF LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) TREATED WITH HELICAL TOMOTHERAPY (HT) DOES NOT IMPACT RADIOTHERAPY PLANNING

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Purpose: To retrospectively analyze whether shrinkage of tumour volume in locally advanced non-small-cell lung cancer (NSCLC) treated with helical tomotherapy (HT) may allow for treatment replanning.

Materials and Methods: Between March 2008 and March 2011, 48 NSCLC patients were treated with Helical Tomotherapy at the department of Radiotherapy of S.Camillo-Forlanini Hospital.According to AJCC-TNM classification, 22 patients were considered stage IIIa and 26 stage IIIb. Concurrent and sequential platinum– based chemotherapy was administered in 30 and 18 patients, respectively. The radiation treatment consisted of a moderately hypofractionated radiation course of 30 daily fractions of 2.25-2.28 Gy each up to a total dose of 67.5 -68.4 Gy to the PTV. Mega-voltage computed tomography (MVCT) scans were routinely obtained during RT course and co-registered with the simulation CT. The impact of tumour shrinkage on total dose of radiation received by organs at risk was calculated.

Results: Mean PTV shrinkage was 25%. When radiotherapy treatments were replanned on smaller tumour volumes, no significant differences was observed in the maximum dose received by spinal cord or esophagus, while the mean decrease in volume of lung receiving more than 20 Gy (V20) resulted no greater than 5%. After a median follow-up of 16 months (range, 6-36 months), no major (≥G3) toxicities were encountered. Grade2 acute treatment-related pneumonitis (TRP) occurred in 6% and 24% of patients, in the sequential and concomitant group respectively. In patients who received sequential chemo-radiotherapy, 6(20%) had complete local response, 4(13%) partial response, 4(13%) local progression and 8(27%) metastatic disease. In those whom received concurrent chemoradiotherapy 6 patients (33%) had complete response, 4(22%) partial response, 2(11%) local relapse and 4 patients (22%) progressive disease.

Conclusions: Our findings show that shrinkage of tumour volume in locally advanced non-small-cell lung cancer (NSCLC) treated with helical tomotherapy (HT) is modest and should not lead to treatment replanning. Since the expected benefits of targeting smaller volumes after replanning are small and counteracted by the risk of deliver unadequate dose to the tumour rind, where residual cancer clonogens may still be present, we do not recommend this strategy, given the low toxicity profiles and high rates of local control associated with helical tomotherapy (HT) in our series.

P037

INTER-OBSERVER VARIABILITY OF ORGANS-AT-RISK (OARS) DELINEATION IN ONE CASE OF NSCLC WITH AND WITHOUT A RADIATION THERAPY ONCOLOGY GROUP (RTOG) THORACIC OARS CONTOURING ATLAS

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Purpose: The radiation tolerance of OARs is a one of the main dose-limiting factors in radiotherapy planning, mostly in the lung cancer treatment planning. The 3D-CRT and new techniques as IMRT, IGRT and SBRT, are increasingly used in the treatment of lung cancer. The use of these techniques, which are able to give higher doses to the tumor with reduction of potential damage to OARs, requires more accurate definition of thoracic OARs. Aim of this study was to evaluate whether the use of RTOG thoracic OARs contouring atlas can reduce the inter-observer contouring variability of OARs in one case of NSCLC.

Materials and Methods: A treatment planning computed tomography (CT)(slice-thickness: 5mm)without intravenous contrast was acquired in one patient with NSCLC.The OARs was independently delineated on axial CT slices by 6 radiation oncologists of our institute, 3 senior (A-B-C) and 3 junior(D-E-F),with and without the RTOG thoracic OARs contouring atlas. The thoracic OARs contoured were: lungs, esophagus, proximal bronchial tree, heart, spinal cord and brachial plexus. The inter-observer variability in OARs delineating was assessed using Conformity Index(CI)as described from Struikmans et al. The CI of delineations was defined as the ratio of the overlapping volume and the encompassing total delineated volume. A CI of 1 indicates perfectly overlapping volumes. A CI of 0.5 indicates that the observers agree on 50% of the total delineated volume.We measured for each organ at risk the CI between all senior observers(A-B-C)and all junior observers(D-E-F)before(pre-atlas) and after(post-atlas) the use of RTOG atlas. Results: The results obtained were

Conclusions: The results showed that the CI pre-atlas and post-atlas of lungs, esophagus, spinal cord and heart were almost similar in both senior and junior groups. Lungs, esophagus, spinal cord and heart are visible in CT-simulation imaging and therefore your delineation

is quite easy. The CI pre-atlas of the proximal bronchial tree and of the brachial plexus was very low, but it slightly increased after the use of RTOG atlas. The delineation of these organs is very difficult because the brachial plexus is not visible in the CT imaging and the proximal bronchial tree required a good knowledge of thoracic CT imaging anatomy. Currently the OARs delineation is not standardized, therefore it is necessary that the radiation oncologists has an adequate knowledge of the CT imaging anatomy and also the possibility to consult contouring atlases to accurately and uniformly define OARs volumes and consequently generate more reliable and reproducible dosimetric data for delivery of more personalized treatments.

Table 1. The results obtained were

		Senior Group (A-B-C)	
OARs	**Observ**	**CI Pre-Atlas**	**CI Post- Atlas**
PROXIMAL BRONCHIAL TREE	A *vs* B	0.1	0.3
	A *vs* C	0.2	0.6
	B *vs* C	0.3	0.4
HEART	A *vs* B	0.6	0.8
	A *vs* C	0.6	0.9
	B *vs* C	0.6	0.8
ESOPHAGUS	A *vs* B	0.3	0.3
	A *vs* C	0.5	0.6
	B *vs* C	0.3	0.4
SPINAL CORD	A *vs* B	0.6	0.5
	A *vs* C	0.5	0.5
	B *vs* C	0.5	0.4
BRACHIAL PLEXUS	A *vs* B	0	0.3
	A *vs* C	0.03	0.1
	B *vs* C	0.09	0.2
LUNGS	A *vs* B	0.9	1
	A *vs* C	0.9	0.9
	B *vs* C	0.9	0.9
		Junior group (D-E-F)	
OARs	**Observ**	**CI Pre-Atlas**	**CI Post-Atlas**
PROXIMAL BRONCHIAL TREE	D *vs* E	0.4	0.5
	D *vs* F	0.4	0.4
	E *vs* F	0.3	0.4
HEART	D *vs* E	0.7	0.8
	D *vs* F	0.8	0.8
	E *vs* F	0.8	0.8
ESOPHAGUS	D *vs* E	0.5	0.6
	D *vs* F	0.5	0.6
	E *vs* F	0.5	0.6
SPINAL CORD	D *vs* E	0.5	0.5
	D *vs* F	0.6	0.6
	E *vs* F	0.6	0.7
BRACHIAL PLEXUS	D *vs* E	0	0.07
	D *vs* F	0	0.1
	E *vs* F	0	0.03
LUNGS	D *vs* E	1	1
	D *vs* F	1	1
	E *vs* F	1	1

P038

EVALUATION OF VMAT WITH MONTECARLO ALGORITHM FOR THE HYPOFRACTIONED TREATMENT OF LARGE AND IRREGULAR LUNG MALIGNANCIES: OUR EXPERIENCE ON 32 TREATED PATIENTS

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Purpose: The tumor volume and its irregularity represent a very important obstacle to treat with eradicative doses the locally advanced lung tumors due to difficulty to respect constraints to OAR (lung, great vessels, esophagus, spinal cord). The clinical implementations of VMAT and IGRT treatment delivery can offer a new possibility to overcome these difficulties. In this study, we explore the usefulness of VMAT in terms of local response of disease and toxicity.

Materials and Methods: From March 2011 to June 2012, 32 patients (M/F : 26/6) were treated; median age was 70,3 years (range 43/91); median performance status (ECOG scale) was 1. 4 patients had metastatic lung lesions (primary was pancreas, breast, colon and kidney) and 28 had primary lung lesions. Target mean volume was 113.2cc (range 11.9-603.1). The dose/fraction ranged between 4 and 8Gy (mean 7.6), total delivered dose to 70-80% isodose ranged between 28 and 56Gy (mean 39Gy). 24 out of 32 patients received surgery and chemotherapy before radiotherapy, while 8 patients received Radiotherapy as exclusive treatment. The stage of disease for 28 primary lung cancer patients was IIIA in 43,7% and IIIB in 47%. 9% of these patients showed also at least one metastatic site. The GTV and OAR were countered using contrast enhanced CT data set on 2 mm thickness slices. Breath hold technique both for planning CT acquisition and treatment delivery was used when necessary. VMAT plans were produced by MONACO TPS and dose distribution reoptimized by Montecarlo algorithm. The dose, prescribed to 80 or 70% isodose depending on GTV volume, was at mean value of 7,6Gy and total dose was of mean 39Gy in 4 to 8 fx. Treatment was delivered by 6Mv linac(Elekta Synergy S) and 40 leaf beam modulator (4 mm to isocenter) through multiple coplanar and no coplanar arc. Set-up of each patient and isocenter position were corrected before each fraction by cone-beam CT cofused with planning CT (XVI software). The local response was evaluated by contrast enhanced CT scan after 2 months and every four months successively. For local control evaluation sometime also CT-Pet scan was used. Toxicity was evaluated using CTCAE *VS* 2.

Results: Two months after the end of the treatment, 6,2% of patients showed SD, 28,1% P:R:, while 9% showed C.R. Acute toxicity of 1 to grade 2 was observed in 8 patients. Due to the short follow-up (median 4,2 months), any evaluation in terms of OS is impossible.

Conclusions: In our experience VMAT plans with Montecarlo dose correction, IGRT verifications by CBCT and correction of respiratory motion lead to the possibi-

lity of delivery high hypofractionated doses for chest malignancies also if large and irregular in shape, respecting dose constraints to OAR. In our experience this new technique of treatment delivery showed high rate of local response and low toxicity. The short time required for the treatment allows an easier association with chemotherapy regimens.

P039

IMPACT OF THE USE OF SIMULATION 18-FDG PET/CT ON TREATMENT VOLUMES AND DOSIMETRIC PARAMETERS IN THE TREATMENT OF LOCALLY ADVANCED NSCLC: PREDICTORS OF LUNG TOXICITY AND BASIS FOR DOSE ESCALATION?

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Purpose: Radiotherapy radical treatment of NSCLC still represents a challenge due to the high doses necessary to obtain a satisfactory local control; the latter is related to overall survival. Many approaches have been taken in account to obtain a safe dose escalation trying to respect lung tolerance. A debated matter is the best modality to contour target volumes in intrathoracic tumors with the availability of 18-FDG PET/CT.

Materials and Methods: Since 2009 simulation PET/CT is available in our institution; 50 patients affected by locally advanced NSCLC have been simulated with PET/CT. For the purpose of this preliminary analysis 10 patients have been contoured by the same physician using the following parameters: 1) automatic tumour delineation of primary lesion using a threshold of 40% of SUVmax (GTV-T-PET) and visual contouring of nodal areas positive on PET scan (GTV-N-PET); 2) contouring of primary lesion on simulation CT using a lung-preset (window 1601;level -300) (GTV-T-CT) and a thorax-preset (window 401;level 800) for nodal stations (CTV-N-CT). In the delineation of nodal areas on CT scan we considered all nodes with short axis >1cm and the corresponding nodal area with the aid of radiologic atlas. 1cm isotropic expansion was given both to GTV-T to obtain a PTV-T; 0.8cm isotropic expansion was given to GTV-N-PET and CTV-N-CT to obtain a PTV-N-PET and a PTV-N-CT respectively. PTV-PET and PTV-CT were then obtained by merging the corresponding PTV-T and PTV-N. 3DCRT was planned for a prescribed dose of 66 Gy in 2 Gy fractions to both PTV-PET and PTV-CT. Dosimetric parameters predictors of lung, oesophageal and spinal toxicity were compared in the two settings.

Results: GTV-PET-T were significantly smaller than GTV-T-CT volumes with a mean percentage difference of 43%. Even GTV-PET-N were smaller than CTV-N-CT volumes with a mean percentage difference of 64.5%. The difference between PTV-PET and PTV-CT was 25% (in favour of PTV-PET). Regarding V20 (calculated as the sum of both lungs volumes minus PTVs and in PET plans) we recorded a mean reduction of 8.4%. A mean reduction of 5.2% was experienced regarding V20 for affected lung. No significant differences were recorded in spinal Dmax and oesophageal V60.

Conclusions: Our preliminary results show a reduction of treatment volumes and dosimetric parameters predictors of lung toxicity. These findings are encouraging in the prospective of a safe dose-escalation to target volumes in NSCLC.

P040

STEREOTACTIC BODY RADIOTHERAPY (SBRT) USING REAL TIME TUMOUR TRACKING IN PATIENTS AGED ≥80 YEARS WITH STAGE I NON SMALL CELL LUNG CANCER (NSCLC): CLINICAL OUTCOMES

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Purpose: The best treatment for stage I lung cancer is surgery. Elderly patients (octagenarians) may be unfit for surgery because of comorbidity. The treatment of these patients (pts) is challenging. Stereotactic body radiation therapy (SBRT) for stage I NSCLC has led to an improvement in local control rate, with low high-grade toxicity in pts medically inoperable. However there has been less specific research regarding the tolerance and outcomes in pts aged ≥ 80 years. We report our experience in the treatment of inoperable octogenarians pts using SBRT with the real-time tumour tracking technique.

Materials and Methods: 29 pts aged ≥ 80 years (range 80-85) with stage I lung tumour were treated with SBRT. All pts were medically inoperable. The median Charlson score was 3 (range 1-7). Of the 29 pts 18 had T1 tumour, 10 T2a and 1 T1b. The median tumour diameter was 2.8 cm (range 1.2-5.5). All pts were treated using a CyberKinife System with Synchrony® Respiratory Tracking System (SRTS) device. Five pts were treated with a single fraction (f) of 26 Gy and 18 with 3 f of 17-18 Gy. A risk adaptive schedule of 32-48 Gy in 3-4 f was used for central tumours (6 pts). The dose was prescribed to the isodose line of 80%. Median FU was 23 months (range 7-60).

Results: 5 pts had local tumour progression 7,10,12,15,17 months after treatment. The actuarial tumour control rate at 3 years was 77.8%. Four of the 5 local recurrence occurred in pts treated with low doses (BED inferior 100 Gy10) resulting in an estimated local control rate at 3 years significantly better for pts treated with higth doses, 95% *vs* 43% (P=0.015).Overall, cause specific survival and disease free survival at 3 years were 65.5%, 70.8% and 69.9%, respectively. Treatment was well tolerated. Early side effects were: fatigue in 11 pts (38%) and local chest wall pain in 1 pts (3.4%). No clinically symptomatic pneumonitis was observed. Two pts

(7%) developed rib fracture. Subjective mild symptoms of increased dyspnoea during FU occurred in 3 pts (10%).Asymptomatic radiation induced lung fibrosis was detected in 10 pts (34%).

Conclusions: SBRT, with adequate doses, appears an effective therapy in terms of local control and likely survival in a population of frail elderly pts unfit for surgery. Aggressive treatment seems justified, the toxicity appears modest and does not affect the quality of life. However this latter consideration must be tested on more pts and with a longer FU.

P041

TC SIMULATION *VERSUS* TC/PET SIMULATION IN LUNG CANCER: GTV COMPARISON IN TWO CASES

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Aims: PET imaging plays an essential role in oncology not only in patient's diagnosis, staging and follow-up but also in radio-therapeutic planning. In association with CT, PET can help to correctly localize irradiation target volume, to respect dose constraints for organs at risk and to reduce gross tumour volume (GTV) determination. CT-PET with gated respiratory acquisition mode (4D) represents an important evolution. The possibility to correct motion artefacts improves spatial resolution and increases examination sensitivity. CT-PET 4D is useful in early diagnosis, staging and follow-up and in treatment planning especially for lesions located in motion involved anatomic areas (chest and abdomen).

Materials and Methods: A.O. SS Antonio e Biagio e C. Arrigo in Alessandria employs a 4D CT-PET scanner (GE Discovery 600). The equipment allows respiratory gating acquisition technique. CT/PET simulation for treatment planning is performed with the patient immobilized in the same positions applied during the following radiotherapy sessions. To ensure the reproducibility of the treatment, the same body supports and repositioning systems are employed. Nuclear medicine physician staff proceeds to identify tumour volume and to contour uptaking lesions on the CT-PET images (Advantage GE workstation). Images containing the defined gross tumor volume (GTV) are then sent to the treatment planning system (Oncentra MasterPlan), where radiotherapy physician staff completes the contouring of CTV (clinical tumor volume) and organs at risk on the CT images, to define the treatment planning.

Results: We analysed the case of two pulmonary cancer patients. CTV was defined by using CT window for parenchyma. PTV (planning target volume) was obtained adding one 10 mm margin in every direction but medially (5 mm), because both neoplasms were central and very near to the vertebral body. The radical treatment included a dose of 66 Gy with 3D conformal technique and 6 MV photons, generated by Linac equipped with multileaf collimator. A comparison was performed between GTV and PTV identified with CT images alone and GTV and PTV evaluated with CT-PET images. In both cases PET-defined GTVs resulted significantly smaller (31.6% and 48.7% respectively). PTVs were smaller too (22.7% and 42.6% respectively). It was possible to spare atelectasis regions that would have been diagnosed as neoplastic and treated accordingly, had only CT images been considered. In one case, a suspect secondary pleural lesion was excluded from radiation area: it was visible in the CT images but absent in the PET scans, because of its metabolic silence. We analysed dose-volume histograms for both cases: improvement in lung DVH is lower with PET/CT simulation, compared to reduction in GTV and PTV, the reason being that volume reduction is near the pulmonary apex and mediastinum, where parenchyma volume is more limited. Esophageal DVHs are instead better when CT/PET was employed in treatment planning.

Conclusions: CT-PET imaging was demonstrated to significantly modify the target volume if compared with CT imaging: volume was reduced by 32-49%. A smaller GTV allows smaller PTV and dose distributions sparing organs at risk of irradiation (lung, esophagus), reducing post irradiation complications.

P042

PATTERN OF FAILURE AND OUTCOME IN STAGE II AND III NON-SMALL CELL LUNG CANCER PATIENTS AFTER SURGERY AND ADJUVANT RADIATION THERAPY: A SINGLE ISTITUTION RETROSPECTIVE STUDY

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Purpose: To assess the pattern of failure and outcome in patients with stage II and stage III non-small cell lung cancer (NSCLC) treated with surgery and adjuvant radiation therapy (RT).

Materials and Methods: Thirty-six pathological stage IIA-IIIA NSCLC patients treated with surgery and adjuvant irradiation between 2001 and 2011 were analyzed. The pattern of failure was reported. Kaplan-Meier analysis was used to calculate rates of loco-regional control (LRC), disease-free survival (DFS), and overall survival (OS). Log-rank test was used to assess differences between strata variables.

Results: Median follow-up was of 33 months (range, 12-105 months). Pathologic stages were the following: stage II = 18 (T3N0 = 2, T1-2N1 = 16), stage III = 18 (T4N1 = 1, T2-3N2 = 17). Ten patients had FDG-PET/CT for staging before surgery. Twenty-seven patients underwent to lobectomy, and 7 to pneumectomy. Positive surgical margins were found in 7 patients. The median number of resected lymph-nodes was 13 (range, 0-47). Fifteen patients had adjuvant chemotherapy. Radiation treatment volume included the omolateral mediastinum. The median radiation dose was

54 Gy (range, 50-60 Gy). The 2- and 5-year LRC, DSF and OS were 90% and 80%, 51% and 31%, 71% and 34%, respectively. No difference in LRC, DFS and OS was noted between stage II and III patients. No risk factors between. Eight (22%) experienced a LRR, half of those were within the radiation therapy field ("in field" recurrence). No isolated loco-regional recurrences (LRR) were documented. At the univariate analyses no statistically significant prognostic factors predicting LRC, DFS and OS, including gender, performance status, PET/CT staging, histology, tumor grading, lymphovascular space invasion, T and N stage, number of resected lymph-nodes, number of positive lymph-nodes, positive interlobar *vs*. hilar *vs*. mediastinal nodes, margin status, and chemotherapy were noted.

Conclusions: The pattern of failure for stage II and III NSCLC patients treated with surgery and adjuvant radiation therapy is distant. No differences in survival and locoregional control were noted between stage II and III in our series.

P043

PATIENT SELECTION CRITERIA FOR USING 4D-CT IN THE RADIOTHERAPY OF LUNG CANCER

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Purpose: Imaging in the radiotherapy of lung cancer needs to account for tumor motion due to respiration. In the free-breathing irradiation, 4D-CT simulation has been applied to define the internal margins. However 4D-CT methods are time-consuming. The purpose of this study is to determine the criteria for using 4D-CT methods in the radiotherapy of lung cancer.

Materials and Methods: From January to May 2012, 5 patients with primitive lung cancer and cT1 staging were enrolled in the study. Patients were immobilized supine with the use of wing board with both arms above the head. A breathing training session was performed. A simulation CT was acquired in 4D mode, using a pressure sensor and a belt placed in the upper abdomen. A total scan time of 100s was required to scan whole lung volume. Three-dimensional CT were retrospectively reconstructed (slice thickness = 2 mm) at ten different amplitudes: 0%, 20% 40%, 60% 80%, 100% of the inspiration, and 80%, 60%, 40%, 20% of the expiration. For each patient, gross tumor volume (GTV) was delineated in the reconstructed set. A clinical target volume (CTV) was obtained expanding the GTV by 8 mm, to account for microscopic dissemination. An internal target volume (ITV) was constructed as the envelopment of CT*Vs*. The volumes of GTV and CTV in the 0% inspiration (GTV0, CTV0), and the ITV/CTV0 ratio were calculated for each patient. Finally, manual rigid-registration based on the GTV was performed and the maximal intra-fraction excursion (MIFE) measured along right-left (RL), antero-posterior (AP) and inferior-superior (IS) directions.

Table 1.

Patient number		#1	#2	#3	#4	#5
Tumor location (lobe)		right upper	right lower	left upper	right upper	right upper
VOLUMEs	GTV_0 (cc)	5.0	1.1	0.8	19.4	7.3
	CTV_0 (cc)	35.2	15.3	15.9	43.0	26.3
	ITV (cc)	43.1	22.2	19.2	45.2	29.0
	ITV/CTV_0	1.23	1.45	1.20	1.05	1.10
MIFEs (cm)	RL	0.1	0.1	0.1	0.0	0.1
	AP	0.2	0.2	0.1	0.0	0.0
	IS	0.2	0.4	0.2	0.0	0.1

Results: As shown in Table 1, the greater MIFE was measured in patient n = 2 (0.4 cm along IS direction) and a corresponding higher ITV/CTV0 was observed. In this patient the tumor was located in the lower lobe. In the other patients, with tumors located in the upper lobes, the MIFE displacements were comparable with CT slice-thickness and a small ITV/CTV0 was measured.

Conclusions: In the free-breathing irradiation of lung cancer respiratory management techniques has to be considered only if the range of motion is greater than 0.5 cm in any directions (AAPM NO.91). Moreover, the average amplitude of the tumor motion was greatest in IS direction for tumors located in the lower lobes (Seppenwoolde et al 2002). Our findings confirm that 4D-CT simulation can be recommended for the treatment of lung tumors located in the middle-lower lobe while a clinical decision is required in other site.

P044

NSCLC PATIENTS MANAGEMENT WITH VMAT: ACUTE TOXICITY RESULTS WITH OR WITHOUT ASSOCIATED CHEMOTHERAPY

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Backgrounds: VMAT is a technical solution in radiotherapy to spare the normal tissues, while delivering high dose to the tumour. We collected data of acute toxicity (skin, heart, lung, aesophagus, following RTOG Criteria) during radiation treatment with RapidArc technology in patients with NSCLC.

Methods: From May-2010 to May-2012, 19 patients (16 males and 3 females, median age 65 years) were treated at Radiation Therapy Department of Parma with RapidArc. Patients presented the following histology: 6 patients adenocarcinoma, 8 squamous, 5 NSCLC NAS, 9 patients had stage IIIB, 5 patients had stage IIIA, 2 patients had stage IIA, 1 patient had stage IB and 1 patient had stage IV. Most of patients received also chemotherapy (cis-platinum/carbon-platinum+gemcitabine/ taxol/alimta) and only two patients were subjected to adjuvant radiotherapy. The patients were treated with a dose range of 60-70 Gy (9

patients received 66 Gy, 6 patients 60 Gy, 1 patient 70 Gy, 2 patients 64 Gy, 1 patient 62 Gy). The patients with stage III and IV were treated with a conventional fractionation (2 Gy/day), whereas the patient with stage IB was treated with fractionation of 2.35 Gy/day and the patient with stage IIA received a fractionation of 2.2 Gy/day. Daily check of patient positioning was performed for all patients by compared KV-KV or cone beam CT (CBCT) system integrated in the machine (IGRT – image guidated radiation therapy). The mean dose was prescribed at Planning Target Volumes with simultaneous integrated boost technique (SIB) at the first target (PTV-Tumor).

Results: 2/19 patients did not develop acute lung-toxicity, 7/19 patients presented cough and dyspnea (Grade 1), persistent cough requiring antitussive agents occurred in 10 patients (Grade 2). No patients had acute heart-toxicity. 11/19 patients had not acute aesophagus-toxicity; G1(dysphagia) and G2(odynophagia and GERD) occurred in 5/19 and 3/19 patients respectively. 13/19 patients had not acute skin-toxicity, 5/19 presented erythema (Grade 1) whereas 1/19 patients had moist desquamatiom (Grade 3).

Conclusions: These preliminary results show that RapidArc radiation treatment presents an acceptable acute toxicity with the opportunity to deliver a greater dose to the target also in advanced stages and large tumors and also using concomitant chemiotherapy; the development of intensity modulated radiotherapy (IMRT) give maximum preservation of surrounding normal tissues.

P045

IMPACT OF 18FDG-PET ON GROSS TUMOR VOLUME (GTV) DELINEATION IN BRONCHIAL CARCINOMA

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Introduction and Aims: It has been demonstrated that Positron Emission Tomography (PET) can improve the accuracy of Gross Tumour Volume (GTV) delineation for radiotherapy planning. PET with 18FDG may facilitate dose escalation trying to deliver the highest dose to the tumour and the lowest dose to the normal tissues. This work delineates GTV in our experience thanks to knowledge of functional imaging methods. It has been also analyzed definition of radiotherapy volumes thanks to the evaluation of both Computed Tomography (CT) and PET interobserver variation and analyzing changes in interobserver variation with the use of coregistered CT/PET imaging.

Materials and Methods: Three patients (case A, case B and case C) with inoperable or unresectable bronchial carcinoma with or without mediastinal nodal metastasis were eligible for this analysis. They were referred for radical radiotherapy since they were not candidates for surgery. Patient age was 75, 71 and 58 years. Disease stage was IIIA for A and B cases and IIIB for C case. They all underwent a co-registered TC/PET before any form of treatment. Foci of abnormal FDG uptake with standardized uptake values of 2.5 or greater were considered tumour. Five experienced radiation oncologists independently outlined contours of the GTV-T and each observer defined two sets of volume. The first set volume was delineated using informations contained within the CT scans to obtain the GTV (CT-GTVT). The second set volume was delineated using CT/PET fusion image informations to obtain the GTV based on PET images (PET-GTVT). The CT-GTV volumes were defined without the knowledge of PET information. The CT-GTVT and the PET-GTVT volumes were compared by the concordance index, defined as the ratio of the intersection (A B) of the 2 volumes to their union (A B); that is, concordance index= (A B)/(A B). This index varied between 0 (complete disagreement) and 1 (perfect concordance). The inter-observer coefficient of variation (CV), defined as the standard deviation of the mean divided by the mean, was calculated. Moreover, for each case and each volume, the ratio of the largest to smallest volume was measured.

Results: Volumes expressed in cc, mean, ratio and CV are shown in the table below. For the three cases (A, B and C), the mean GTV-T volume based on CT (CT-GTVT) was 65.0 cc (range 57.4-78.8), 112.0 cc (range 100.5-128.5) and 10.0 cc (range 7.5-11.6), respectively. The mean GTV-T volume based on PET/CT (PET-GTVT) was 48.0 cc (range 31.0-58.4), 87.1 cc (range 85.6-87.8) and 16.5 cc (range 13.0-25.4), respectively (as shown in the Table 1). The mean value of concordance index for each pair of observers reached 0.80 for CT-GTVT and 0.79 for PET-GTVT.

Conclusions: Our experience showed that the PET-GTV volumes were smaller than CT-GTVTs for lung tumours. For 2/3 of lung cases, CT-GTVTs were reduced with the use of PET while for one case the PET/CT-GTVT was larger than the CT volume. The interobserver variability was similar with the use of CT/PET imaging or CT imaging alone. In conclusion, 18FDG-PET is desirable since it can improve the accuracy of GTV delineation reducing radiotherapy volumes and facilitating boost planning and dose escalation. It is also true that, despite the improvement derived from PET/CT, physician interpretation of the target still represents the largest source of uncertainty compared to other geometric uncertainties such as patient set-up and organ motion.

Table 1.

	obs.1	obs.2	obs.3	obs.4	obs.5	Mean	Ratio[a]	CV[b]
CT-GTVT								
A	63.0	57.4	59.1	66.8	78.8	65.0	1.36	0.13
B	112.1	108.9	128.5	100.5	110.2	112.0	1.28	0.09
C	7.5	11.6	8.7	11.0	11.4	10.0	1.55	0.18
PET-GTVT								
A	31.0	46.8	47.7	56.3	58.4	48.0	1.89	0.23
B	86.7	87.7	85.6	87.7	87.8	87.1	1.02	0.01
C	13.6	13.0	14.2	16.5	25.4	16.5	1.95	0.31

P046

IMPACT OF RESPIRATORY GATED 18F-FDG PET/CT ON RADIATION THERAPY VOLUME DELINEATION IN NON-SMALL-CELL LUNG CANCER

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Objectives: Different imaging techniques are used in radiation therapy for volume delineation and the informations are often merged to accurately identify volumes. In thoracic and abdominal regions, standard margins are added to the lesion volume to take into account for the lesion displacement due to patient's respiratory movements and to set-up errors. We have investigated the feasibility of applying different margins to each lesion volume according to the lesion movement recorded in respiratory gated (4D) PET/CT protocol. Preliminary results are presented.

Methods: Five patients (2 male and 3 female) with Non Small Cell Lung Cancer (NSCLC) were enrolled into the study. All patients were candidate for radiation therapy and underwent a (4D) PET/CT scan acquired with patient in radiation treatment set-up. Gating data were sorted retrospectively into six phases. Volumes were drown on PET and CT images in standard (ST) and gating (4D) conditions to obtain the corresponding Clinical Target Volumes (CTVST and CTV4D). PET volumes were created with an automatic contouring using a threshold of 42%. Such volumes were further expanded to obtain Planning Target Volume with a uniform margins of 1 cm in all directions in standard (PTVST) and adaptive margins of respectively 7 and 5 mm in CC direction and in the other directions in gated (PTV4D).

Results: A total displacement between 4 and 11 mm was recorded. CTVs range was (22.9 - 106.3 cm3) and (21 - 75.2 cm3) in standard and 4D situations respectively. CTV4D was smaller than the CTVST in 4/5 patients. CTV4D was larger than CTVST (1/5) for a lesion with the higher displacement during patient's breathing (11 mm). Planning target volume differences ranged from 6% to 54%. CTV4D was never completely included in standard planning target volumes in head-feet direction. Dose to 95% of the PTV was higher in 4D *vs* standard technique in 4/5 cases; little improvements were also recorded in organs at risk DVH4D *vs* DVHST.

Conclusions: Standard margins in NSCLC radiation treatment planning are often over-estimated although under-estimation in head-feet direction can be expected for lesions with large displacement during patient's breathing. 4D PET/CT images used for radiation therapy volume definition allow adaptive margins in each direction depending on lesion's movement and lead to a better dose distribution in target volumes.

P047

THE COMPARISON OF TWO ATLASES TO DELINEATE MEDIASTINAL LYMPH NODAL CTV AND PRACTICAL IMPLICATIONS

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Introduction: Variations in target volume delineation represent a significant hurdle in conformal radiotherapy implementation. In NSCLC, the delineation of treatment volumes for nodal contouring has been studied. Aim of our study is to compare Chapet published recommendations (University of Michigan Atlas 2005) *vs*. our institutional published recommendations ("A Guide for Delineation of Lymph Nodal Clinical Target Volume in Radiation Therapy" 2008) about the definition of the radiologic boundaries of Mountain and Dresler lymph node stations (LNS) on axial CT for mediastinal and hilar LNS.

Materials and Methods: Chapet and our contouring atlases were reviewed and compared. Regional lymph nodes were delineated as separate CTVs using the classification scheme proposed by Mountain and Dresler. We compared the two different modalities to describe and define lymph node localization and to provide differences between anatomical boundaries.

Results: The main differences are the following: Chapet combined stations 1 and 2 on the right and left side assuming that these often cover a short vertical distance and that station 2R is virtual in some patients. We chose to distinguish these stations and we proposed a separate description of the boundaries of stations 1R - 1L and 2R – 2L, following Mountain's classification (ed. 1997). Moreover, while Chapet indicated left subclavian artery and left common carotid artery as vessels that describe the anterior boundary of the combined volume station 1-2L, we considered them as posterior boundary of station 1L. This discrepancy between our and Chapet atlases may be explained by the different definition of the upper limit of station 1L. As a matter of fact, the upper limit of station 1L in our Atlas (thoracic inlet) is more cranial than the limit defined by Chapet (sternal notch) and for this reason we considered a longer segment of subclavian and common carotid arteries thus including their posterior course. Another difference regards cranial and caudal limits of station 3A. Our atlas identified a plane touching the top of sternal manubrium as cranial boundary and proposed a horizontal plane passing through line 2 as caudal boundary, with the prevascular and paraortic nodes lying respectively above and below line 2. Conversely, Chapet proposed the carina as the inferior limit of station 3A, and consequently, the inferior portion of station 3A and the upper portion of station 6 can be found on the same CT scan for several sections. Chapet located the origin of the right middle lobe bronchus in the inferior limit of station 7, whereas we chose the most inferior aspect of the right pulmonary artery. We proposed a horizontal plane passing through the auricle of right atrium as caudal limit of station 6 while Chapet located

this limit at the level of the lowest image where the right pulmonary artery is maximally visualized. Moreover, proposing the diaphragm as the caudal limit of station 8 we obtained the same result of Chapet who chose the gastroesophageal junction. Regarding the hilar lymph node stations (10-11R and 10-11L), we have focused on a less detailed description, while Chapet carefully identified all the limits.

Conclusions: Atlas should be adapted to the needs and RT planning techniques employed in the institution.

P048
CONTOURING OF OARS IN LUNG CANCER: DELINEATING BY ANATOMO-RADIOLOGICAL BOUNDARIES

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Introduction: The effect of organs at risks (OARs) delineation on the dosimetric parameters can be significant and could influence the treatment planning. The normal tissues within the thorax are often dose limiting during thoracic RT. Aims of this study are to provide anatomical boundaries for the correct identification and contouring of OARs in thoracic district.

Table 1.

OAR	CRANIAL	CAUDAL	LATERAL	MEDIAL	ANTERIOR	POSTERIOR
HUMERAL HEAD	Line through anatomical	Inferior edge of the head	/	/	muscles	Muscles
PROXIMAL BRONCHIAL TREE	2 cm above carena	Line through infer. pulmonary veins	aortic arch **On the left:** - left main pulmonary artery - descending aorta - lung parenchyma **On the right:** - lung parenchyma - azygos arch - SVCC	/	- aortic arch - ascending aorta - Right and left main pulmonary arteries - left atrium	Esophagus - azygos vein **On the left:** - descending aorta - pulmonary vein **On the right:** - lung parenchyma
LUNGS	Line through posterior arch of the first rib	Diaphragm	Chest wall	Large mediastinal vessels and cardiac chambers	Chest wall	Chest wall
HEART	Line through inferior edge of left main pulmonary artery	Line through superior edge of the left hepatic lobe	Mediastinal pleura and lung parenchyma	/	Adipose tissue of the anterior mediastinum	Esophagus and descending aorta
ESOPHAGUS	Line through inferior edge of the cricoid	Esophago-gastric junction	**On the left:** - left subclavian artery - aortic arch - descending aorta **On the right:** - mediastinal pleura and lung parenchyma - azygos vein - lung parenchyma	/	- trachea - carena - left main bronchus - left atrium posterior wall -thoraco-lumbar adipose tissue	- Anterior vertebral body -azygos vein
SPINAL CORD	Line through inferior edge of the cricoid	L2 Inferior edge	Vertebral canal	/	Vertebral canal	Vertebral canal
BRACHIAL PLEXUS	Neural foramina C4-C5	First half of clavicular head	- Subclavian and axillary neurovascular bundle - Clavicle	C4-T1 neural foramina C4-T1 vertebral peduncle	-jugular vein - anterior scalene muscle - pectoralis minus muscle -Neck vascular bundle (C4-C6), anterior scalenus muscle(C6-T1)	Middle Scalene muscle; First rib Subclavian vein

Materials and Methods: A dedicated thoracic radiologist, a neuro-radiologist, and three radiation oncologists were gathered to generate a three-dimensional radiologic description for the thoracic OARs on axial CT scans. Moreover, the interdisciplinary team provides anatomical boundaries detectable on planning-CT for each thoracic OAR considered.

Results: Three-dimensional descriptions of lung, proximal bronchial tree, esophagus, spinal cord, heart and brachial plexus was performed. One computed tomography atlas was developed with definition of cranial, caudal, medial, lateral, anterior and posterior limits for each OARs (Table 1).

Conclusions: The thoracic OAR contouring atlas developed in this multidisciplinary experience represents a considerable tool in our clinical practice. We believe that development of interdisciplinary atlas represents a formative tool to optimize 3D-CRT, IGRT and IMRT contouring procedures.

P049
THE COMPARISON OF TWO ATLASES TO DELINEATE OARS IN LUNG CANCER

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Introduction and Methods: Dosimetric constraints of thorax OARs have been used in institutional and multicenter trials in cooperative groups such as the RTOG, EORTC and SWOG. However the anatomic delineation of these structures has not been standardized. Aim of study is to compare Kong FM recommendations (IJROBP 2011) *vs*. our institutional recommendations ("A Guide for Delineation of Organ at Risks in Radiation Therapy" 2012) about the definition of thoracic OARs anatomo-radiological boundaries.

Results: The main differences observed were as follows: Esophagus: Both studies defined the same cranio-caudal boundaries. Antero-posterior and latero-lateral boundaries were not described in Kong study while they were delineated in our contouring tool. Brachial plexus: in the upper CT-slices the same anatomical limits were delineated in both studies. Instead, in the region of the subclavian neurovascolar bundle, a correct definition of brachial plexus anatomo-radiological boundaries was difficult and at this level different limits were found. Lungs: Kong limited lung contours to the air-inflated parenchyma without inclusion of the proximal bronchial tree, fluid and atelectasis. Our study, instead, provided cranial, caudal, medial, lateral, anterior and posterior limits. Proximal bronchial tree: Kong's study listed and described anatomical structures to contour without giving their anatomo-radiological limits, while we described them for the whole extension of the proximal bronchial tree. Moreover, in our tool, we considered heart and humeral head too, because of these OARs are often dose-limiting during thoracic RT.

Conclusions: Standardized delineations of OARs are crucial for clinical trials and daily practice. The atlases have yet to be validated by global users for its utility and reproducibility. Furthermore we are checking into clinical practice that our tool for thoracic OARs contouring is easy to use and reproducible with clearly recognizable limits. However, the Atlases should be adapted to the needs and to planning techniques employed in each single institution.

P050

PATTERN OF FAILURE AFTER ADAPTIVE RADIOCHEMOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (LA-NSCLC)

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Purpose and Objectives: Anatomic changes and tumour motion during radiotherapy are the major cause of target miss and/or over-treating normal tissue in lung cancer. There is a great deal of variation in tumour size during radiotherapy but it is still unclear if target volume reductions are warranted in the scenario of GTV shrinkage. The purpose of this trial is to analyze the pattern of failure in LA-NSCLC patients treated with concurrent chemoradiation with an adaptive approach. We report the early results of the study. Accrual is still ongoing.

Materials and Methods: From 2009, all locally advanced NSCLC patients treated at our institution undergo to weekly thorax CT. In case of tumour reduction, a CT with contrast is performed and a new simulation-based treatment planning is run up to the total prescribed dose. All patients undergo to FDG-PET before chemoradiation. At the end of treatment patients undergo to follow-up protocol with clinical examination, CT with contrast/PET with FDG and blood samples every 3 months for the first 2 years and every 6 months in the following period.

Results: Eighteen patients with tumour reduction during chemoradiation are evaluable with a minimum follow up of nine months. Median age is 66 years (range 38-79). Histology is squamous cell carcinoma in 9, adenocarcinoma in 4 and non specified in 5 patients. All patients are staged IIIA-IIIB (eight and nine, respectively). Median total dose is 60Gy with 1.8Gy/fx. Chemotherapy schedules are cisplatin-gemcitabine, gemcitabine or pemetrexed. Mean CTV at the simulation-CT (basal-CTV) and at re-planning study (new-CTV) are 186.6 and 102.9cc, respectively with a mean reduction of 47.9% (range 29.8-82.5%; 83.7cc) Mean PTV at the simulation-CT (basal-PTV) and at re-planning study (new-PTV) are 311 and 189.2cc, respectively with a mean reduction of 42% (range 21-77%; 121.7cc). Reduction in tumour size was observed at a mean dose of 36Gy. Progressive disease is distant, regional/nodal and local. Distant metastasis are reported in eleven patients. The most frequent site is brain and mean time to distant metastasis is 7.7 months. Regional/nodal relapse is reported in 3 patients. Local failure are in field in five cases; just one patients has a marginal relapse which could be related to the shrinking method. The marginal relapse in this patient occurred ten months after bone metastasis and concurrently to an infield relapse. Mean time to local relapse is 10.1 months. Actually, 10 patients are alive, four without evidence of disease. Two of these patients underwent surgical resection after chemoradiation and histological specimens did not reported neoplastic foci distant from the macroscopic disease.

Conclusions: Our experience is one of the first evaluating the clinical outcome of an adaptive strategy during concurrent chemoradiation in LA-NSCLC. Although we recognize the number of enrolled patients is limited, this approach seems feasible and the rate of marginal local recurrence (N°: 1; 5.5%) is low.

GENOMICA E PROTEOMICA IN RADIOTERAPIA: DAL LABORATORIO ALLA CLINICA

P051

HUMAN PAPILLOMAVIRUS MUTATIONAL INSERTION: SPECIFIC MARKER OF CIRCULATING TUMOR DNA IN CERVICAL CANCER PATIENTS TREATED WITH (CHEMO)RADIATION

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Aims: In most cases of cervical cancers, HPV DNA is integrated into the genome of carcinoma cells. This mutational insertion constitutes a highly specific molecular marker of tumor DNA for every patient. Circulating tumor DNA (ctDNA) is an emerging marker of tumor dynamics which detection requires specific molecular motif. To determine whether the sequence of the cell-viral junction could be used in clinical practice as a specific marker of ctDNA, we analyzed a series of serums of cervical cancer patient, primarily treated with chemoradiation.

Materials and Methods: We retrospectively analyzed serum specimens of 10 patients diagnosed with HPV16 associated cervical cancer, FIGO stages Ib to IV, for which the viral integration locus had been previously localized using the DIPS-PCR(detection of integrated papillomavirus sequences-PCR)method. Quantitative-Real-Time PCR was performed to detect ct-DNA using Sybr®Green. Sequential serum specimens, taken during the course of the disease, were also available for two of these patients, the first treated by combined chemoradiotherapy followed by utero-vaginal brachytherapy and surgery, the second treated exclusively with chemoradiotherapy.

Results: ctDNA was found in 7 out of 8 patients with tumor size greater than 15 mm at diagnosis. Analysis of sequential serum specimens showed that ctDNA concentration in patient serum was related to tumor dynamics: the ctDNA value decreased during treatment and was null by the end of therapy. Of interest, in one case, while pelvic MRI showed no significant modification, a rise of ctDNA was observed. Soon afterwards the patient presented an abdominal relapse associated with high levels of ctDNA.

Conclusions: We report that HPV mutational insertion constitutes a highly specific molecular marker of ctDNA in HPV-associated tumor patients. ctDNA was detected in most cervical cancer patients and it was found to reflect tumor burden. In addition to its potential pro-

gnostic and predictive value, HPV mutation insertion is likely to constitute a new molecular surrogate of minimal residual disease and of subclinical relapse. A prospective and pluricentric study including 200 invasive cervical carcinomas will be held, combining biological analyses of ctDNA as well as the sequencing of a representative panel of genes involved in the tumorigenesis pathway. This will be of major importance in the perspective of specific anti-HPV and targeted therapies in association with (chemo)radiation.

P052

MEK/ERK INHIBITOR U0126 INCREASES THE RADIOSENSITIVITY OF RHABDOMYOSARCOMA CELLS IN VITRO AND IN VIVO BY DOWNREGULATING GROWTH AND DNA REPAIR SIGNALS

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Aims: Multimodal treatment has improved the outcome of many solid tumors, and in some cases the use of radiosensitizers has significantly contributed to this gain. Activation of the extracellular signaling kinase pathway (MEK/ERK) generally results in stimulation of cell growth and confers a survival advantage playing the major role in human cancer. The potential involvement of this pathway in cellular radiosensitivity remains unclear. We previously reported that the disruption of c-Myc through MEK/ERK inhibition blocks the expression of the transformed phenotype; affects *in vitro* and *in vivo* growth and angiogenic signaling; and induces myogenic differentiation in the embryonal rhabdomyosarcoma (ERMS) cell lines (RD).

Methods: This study was designed to examine whether the ERK pathway affects intrinsic radiosensitivity of rhabdomyosarcoma cancer cells. Exponentially growing human ERMS, RD, xenograft-derived RD-M1, and TE671 cell lines were used.

Results: The specific MEK/ERK inhibitor, U0126, reduced the clonogenic potential of the three cell lines, and was affected by radiation. U0126 inhibited phospho-active ERK1/2 and reduced DNA protein kinase catalytic subunit (DNA-PKcs) suggesting that ERKs and DNA-PKcs cooperate in radioprotection of rhabdomyosarcoma cells. The TE671 cell line xenotransplanted in mice showed a reduction in tumor mass and increase in the time of tumor progression with U0126 treatment associated with reduced DNA-PKcs, an effect enhanced by radiotherapy.

Conclusions: Thus, our results show that MEK/ERK inhibition enhances radiosensitivity of rhabdomyosarcoma cells suggesting a rational approach in combination with radiotherapy

P053

TORC1/TORC2 INHIBITOR, PALOMID 529, MODULATES CRM1-MEDIATED SURVIVIN FUNCTION AND ENHANCES RADIATION RESPONSE IN PROSTATE CANCER MODELS

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Purpose: The phosphatidylinositol-3-kinase (PI3K)/Akt pathway is frequently deregulated in prostate cancer and associated with resistance to therapeutic intervention. In the present study, the efficacy of combined treatment with the Torc1/Torc2 inhibitor, P529, and ionizing radiation in prostate cancer cells was examined.

Methods: Six prostate cancer cell lines were exposed *in vitro* and *in vivo* to RT after pre-treatment with P529 and the clonogenic capacity as well as the *in vivo* efficacy were examined.

Results: P529 exerted anti-neoplastic and radiosensitizing effects in prostate cancer models trough different mechanisms: (i) decrease of AKT function, (ii) increase of GSK-3 activity, (iii) inhibition of CRM1-mediated nuclear export of survivin and (iv) enhance of pro-apoptotic events. The reduction of cytoplasmic levels of survivin, indeed, contributed to the induction of caspase-3 dependent apoptotic machinery determining radiosensitation with anti-proliferative/anti-survival effects. Moreover, the de-regulation of cyclin D1/survivin pathway resulted in (i) G2/M arrest, (ii) inactivation of DNA damage responses (DDR), and (iii) reduction of DNA double strand break (DSB) repair proteins such as DNA-PKcs. All these events were associated with the inhibition of DSBs rejoining, as indicated by P529 modulation of -H2AX levels after RT.

Conclusions: Here, we showed for the first time that P529 exerts its radio-sensitizing effects by modulating Akt-/GSK-3 function and disrupting the CRM1-mediated nuclear export of survivin. These processes in association with the reduction in DNA double strand break (DSB) repair mediators might be an effective therapeutic strategy to achieve synergistic anti-tumor effects in prostate cancer preclinical models.

P054

MEK/ERK INHIBITOR U0126 INCREASES THE RADIOSENSITIVITY OF GLIOBLASTOMA CELL LINES *IN VITRO* AND *IN VIVO*

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Scope: Glioblastoma multiforme (GBM) is notoriously resistant to treatment. Therefore, new treatment strategies are urgently needed. Activation of the extracellular signaling kinase pathway (MEK/ERK) generally results in stimulation of cell growth and confers a survival advantage playing the major role in human cancer. The potential involvement of this pathway in cellular radiosensitivity remains unclear. We previously reported that the disruption of c-Myc through MEK/ERK inhibition blocks the expression of the transformed phenotype of several cancer cell lines. This study was designed to examine whether the ERK pathway affects intrinsic radiosensitivity of glioblastoma cancer cells.

Methods: Exponentially growing human T98G, U87, U231, U138 glioblastoma cell lines were used. For the *in vivo* experiments the xenograft model was used.

Results: The specific MEK/ERK inhibitor, U0126, reduced the clonogenic potential of the cell lines, and was affected by radiation. U0126 inhibited phospho-active ERK1/2 and reduced c-Myc and NMyc protein accumulation suggesting that ERKs, c-Myc and NMyc cooperate in radioprotection of glioblastoma cells. The T98G and U231 cell lines xenotransplanted in mice showed a reduction in tumor mass and increase in the time of tumor progression with U0126 treatment associated with reduced c-Myc and NMYC, an effect enhanced by radiotherapy.

Conclusions: Thus, our results show that MEK/ERK inhibition enhances radiosensitivity of glioblastoma cells suggesting a rational approach in combination with radiotherapy.

P055

c-MYC TARGETING BY SHRNA OR PHARMACOLOGICAL TREATMENT REVERTS THE TRANSFORMED PHENOTYPE AND RADIOSENSITIZES THE 22RV1 PROSTATE CANCER CELL LINE *IN VITRO* AND *IN VIVO*

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Scope: c-Myc is an important regulator of many cellular processes, including proliferation, cell cycle, cell growth, metabolism, cell adhesion, motility, angiogenesis and differentiation. Further, when deregulated, c-Myc can induce immortalization, genomic instability, independence of growth factors, escape from immune surveillance and chemioresistance. Cells from benign prostate hyperplasia tissue shows c-Myc overexpression and immortalization in primary culture. Several c-Myc-based mouse models have shown the essential role of c-Myc in the earliest steps of Pca carcinogenesis. Although radiotherapy remains a very important treatment modality, Pca cells can easily become radio-resistant. The role of c-Myc in Pca radio-resistance has not been sufficiently investigated so far. We here investigated the role of c-Myc in radioresistance of human 22Rv1 in *in vitro* and *in vivo* model.

Methods: We used human 22Rv1, stably c-Myc- or scramble sh-RNA-transfected, in *in vitro* culture, clonogenic assay, and xenograft in nude mice. Radiotherapy treatment was also used both *in vitro* and *in vivo*.

Results: c-Myc silencing significantly decreased growth in culture and clonogenic potential of 22Rv1. In *in vivo* experiments tumors from c-Myc silenced 22Rv1 grew at lesser extent than tumors from un-silenced cells. Radiotherapy in combination with c-Myc silencing drastically reduced clonogenic potential and growth of tumors in 22Rv1 xenografts. The cooperation between radiotherapy and c-Myc down regulation was also observed in tumors treated with MEK/ERK inhibitor that induced drastic c-Myc down regulation.

Conclusions: The results here presented demonstrated that permanent depletion of c-Myc drastically impaired deregulated growth of human prostate cell line in vitro and in *in vivo* model suggesting that Pca may depend at significative degree on c-Myc expression.

P056

FINGOLIMOD (FTY720) SENSITIZES BREAST CANCER CELLS TO RADIATION THERAPY

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Rationale: Sphingolipids are a family of naturally occurring molecules which regulate cell differentiation, survival, motility and angiogenesis. Altered regulation of the S1P/ceramide ratio can lead to an imbalance in the 'sphingolipid rheostat' thus influencing cell fate and tissue homeostasis. Recent studies demonstrate a link between cancer cell radioresistance and activation of sphingosine kinase (SphK1), which play a key role in the balance of these important lipid signaling molecules. Preclinical evidence suggests that pharmacological inhibition of SphK1 results in sensitization of human prostate cancer cells to radiotherapy. On these bases, we sought to analyze the radiosensitization effect of the sphingosine analogue FTY720 (Fingolimod) in breast cancer (BC) cell lines.

Materials and Methods: X-Irradiation was performed using the Varian Linac 600C Linear Accelerator (6MV).A dose escalation (2,5,8 Gy) of X-irradiation was used to identify ED50.Trypan blue exclusion assay was used to investigate the antiproliferative activity of FTY720 and radiotherapy in the lapatinib resistant MDA361-LR, the human JMT-1, MDA361, and the trastuzumab-resistant KPL4 and MDA361-TR BC cell lines. FACS-analysis of Annexin V/7-AAD stained cells was used to evaluate the percentage of apoptotic cells. Western Blotting was used to evaluate apoptosis-related proteins. Morphological changes were assessed by fluorescence microscopy of DAPI-stained cells.

Results: To evaluate whether ionizing radiation and/or Fingolimod treatment could cause perturbations of cell proliferation and apoptosis, BC cells were treated with different doses of ionizing radiation and/or 5 microM Fingolimod. 8 Gy irradiation was found to reduce cell proliferation (40% of cell growth inhibition) and induce apoptosis (20% of Annexin-V positive cells). Strikingly, combination therapy with 5 microM Fingolimod strongly enhanced irradiation effects (80% of cell growth inhibition and 50% of Annexin-V positive cells). Moreover, morphological changes consistent with features of nuclear aberrations were observed in cells after treatment with 5microM Fingolimod together with 5 or 8Gy irradiation. We next evaluated whether the combination of radiotherapy and Fingolimod could affect the expression and/or the activation of intracellular proteins that are involved in antiapoptotic pathways. Combination of sublethal doses of radiotherapy (2Gy and 5Gy) and 5microM Fingolimod strongly reduced the levels of the phosphorylated, activated form of Akt, increased the levels of the tumor suppressor PTEN as well as PARP cleavage.

Conclusions: The present study highlights a role of the sphingolipid pathway in BC cells and provides scientific rationale for combination of Fingolimod with radiotherapy to overcome resistance and potentially improve outcome of BC patients.

P057

IMRT FOR LOCALLY ADVANCED OROPHARYNGEAL CARCINOMA: PRELIMINARY RESULTS FOCUSING ON THE IMPACT OF HUMAN PAPILLOMAVIRUS (HPV) STATUS AND CLINICAL RISK CATEGORIES

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Purpose: Recently, 3 groups of oropharyngeal cancer (OPC) patients (pts) with different outcomes were identified based on HPV status, smoking history and tumor stage(Ang KK 2010).This retrospective analysis aims to: i)estimate the risk group-stratified survivals in locally advanced OPC treated with IMRT or Volumetric Modulated Arc Therapy (V-MAT); ii)investigate different RT approaches in given OPC risk profiles.

Patients and Methods: Between April 2007 and November 2011, 71 stage III-IV OPC pts underwent definitive IMRT or V-MAT plus concurrent platinum based CHT (55%) with or without induction CHT with Taxotere,Cisplatin and 5-FU(45%).TNM stage was according to UICC VI ed. Pts were divided in 3 risk groups: high risk(group 1) (p16-; > 10 smoke packs/year or T4), intermediate risk-(group 2) (p16+; > 10 packs/-year if > N2b or p16- with < 10 smoke packs/year and < T4) and low risk- (group 3) (p16+; < 10 smoke packs/year; > 10 packs/year if < N2b), according to the RTOG classification. Nodal elective volume included bilateral neck except for tonsil tumor, staged cT1cN1, where only ipsilateral neck was considered. RT regimens consisted of conventional fractionation (CF) or accelerated fractionation (AF) - 66 Gy/30 frs/6 weeks or 70 Gy/33 frs/6.5 weeks.

Results: 46 of 71 pts (65%) were p16+. TNM stage was III in 3 pts and IV in 21 pts of Group 1; stage IV in 31 pts in Group 2; stage III in 2 pts and stage IV in 14 pts in Group 3. AF was used in 10 (42%), 15 (48%) and 9 (56%) pts of group 1, 2 and 3, respectively. Median follow-up was 34.4 months. Survival rates are shown in Table 1. In Group 1 AF allowed better PFS, LC and RC rates than CF, although the difference was not statistically significant. No difference was found in OS, LC and RC stratified for fraction schedules in group 2 and 3. Failures were found in 10 pts (14%) in Group 1 and 2. Local failures (LFs) occurred in 2 pts in Group 1; regional failures (RFs) occurred in 2 pts of Group 2; distant metastases occurred in 6 pts (3 in Group 1; 3 in Group 2), 2 of whom also had LRFs.

Conclusions: Low-risk pts have an excellent outcome both with CF and AF. In these pts with cN0-N2b stages, precautional nodal volume might include only ipsilateral neck nodes, due to the absence of RFs and in order to reduce toxicity. High-risk pts seem to have a better outcome with the use of AF contrary to intermediate risk pts. OPC risk group-driven treatment approaches should be further considered.

Table 1.

N 71 (%)	2-year OS	2-year PFS	2-year LC	2-year RC
Group 1 (high risk) 34%	93%	66.7%*	82.7%*	83.5%
Group 2 (intermediate risk) 44%	93%	88.8%*	100%	97.5%
Group 3 (low risk) 22%	100%	100%	100%	100%

**statistically significant; OS=overall survival; PFS=progression free survival; LC=local control rate; RC=regional control rate.*

P058

HPV-RELATED HEAD AND NECK CANCER: A MULTI-STEPS MULTIDISCIPLINARY APPROACH

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Introduction: Human Papillomavirus infection (HPV) has a causal role in several types of cancer including a subset of Head and Neck neoplasm represented by Oropharyngeal Squamous cell Carcinoma (OSCC). Multicenter studies estimated that 18% OSCC worldwide are HPV-associated. HPV-induced OSCCs display distinct clinical features: patients are often younger, have a past of smaller smoker and alcohol drinker, and have a history of virus-transmitting sex practices. This distinct subgroup of OSCC is also characterized by distinctive histopathological features, better response to chemo-radiotherapy and overall better clinical outcome. In this context, it is emergent the evaluation of advanced molecular biological methodologies which are able to prove OSCC-HPV association in clinical settings. Recently, we created a multidisciplinary team including radiotherapists, surgical pathologists and otolaryngologists. The aim of this prospective survey was to assess prevalence, cytological and histopathological features, molecular characteristics and clinical outcome of OSCC. Secondly, in view of preventing HPV-related OSCC, we administered a specific questionnaire to study population, in order to evaluate the risk assessment. The aim of this paper is to illustrate the relevant steps of this translational multidisciplinary approach, and to evaluate the diagnostic performances that molecular tests, which have been already used in the diagnosis of uterine HPV infection, would have in OSCC management.

Materials and Methods: Starting from May 2012, twice a week, all patients referring to otorhinonolaryngology outpatient department and having a suspect oropharyngeal lesion were included in the study. All participants underwent to questionnaire of 14 simple items. Oropharyngeal cytological specimens were then taken. All samples were collected into PreservCyt LBC media. For each patient, cytological Papanicolaou slide was prepared. Residual cytological specimen was then tested for the presence of HPV-DNA, by using Hybrid Capture 2 test, and for the expression of HPV E6/E7 oncoprotein, by using RT-mRNA testing in HPV-DNA positive cases. Finally, from symptomatic patients, incisional or excisional biopsies were obtained. Hystological diagnosis was regarded as gold standard.

Results: To date 5 patients were included in the study. Cytological analysis reveled atypical squamous cells in favour of malignancy. Hystological examination on biopsy specimens showed squamous cells carcinomas. Actually, all patients are candidate to receive surgery or radio-chemotherapy; treatment is still ongoing. We expect to have a proper follow-up to evaluate the preliminary results of this survey.

Conclusions: HPV-induced OSCC represents is a new disease requiring tailored treatment and prevention strategies. Although preliminary, our experience shows that a multi-steps multidisciplinary approach is feasible and desirable. The use of a specific questionnaire is essential to establish the risk assessment. In this context, follow-up studies are required to validate these preliminary data and to correlate then with clinical outcomes.

SARCOMI RETROPERITONEALI

P059

POSTOPERATIVE RADIOTHERAPY IN PRIMARY RETROPERITONEAL SARCOMAS: OUR EXPERIENCE.

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Purpose: Retroperitoneal sarcomas (RPS) are rare tumors with a generally poor prognosis. Surgical resection remains the mainstay of treatment. The purpose of the present study was to retrospectively analyze the outcomes of patients with primary retroperitoneal sarcoma treated with adjuvant external beam radiotherapy (EBRT).

Patients and Methods: Between May 2006 and April 2009, 8 patients (4 males and 4 females) with a median age of 63 years (range: 5-74) affected by RPS (histologic subtypes: 4 liposoarcomas, 2 leiomyosarcomas and 2 rabdomyosarcomas) underwent postoperative radiotherapy at the Department of Radiation Oncology, University of Rome "Sapienza". Complete surgical resection with clear margins (R0) was achieved in 3 out of 8 patients, uncertain or "close" margins in 2, while 2 patients had macroscopically (R2) and 1 microscopically (R1) positive margins. Postoperative EBRT was delivered at a mean dose of 49.8 Gy (range: 36-61.2) in 1.8-2 Gy fractions, 5 days per week. Two patients received also neoadjuvant chemotherapy.

Results: At the end of the follow-up (median 61 months), local recurrence occurred only in one patient among the R0/uncertain margins resection group (n=5), while overall survival (OS) rates were 100% in 1, 3 and 5 years. Among the R1/R2 group OS rates were 100%, 33% and 33% in 1, 3 and 5 years respectively.

Conclusions: Complete surgical resection with clear surgical margins is the standard of care of RPS, although, often this is not feasible. A combined modality therapy approach improves local control which is also translated, according to our data, in a survival benefit.

P060

RETROPERITONEAL SOFT TISSUE SARCOMA: CASE REPORT OF PRE-OPERATIVE CHEMO-RADIATION IN TWO VERY LARGE SIZE TUMORS TREATED WITHIN THE ITALIAN NETWORK ON RARE TUMORS (RTR)

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Aims: The treatment of retroperitoneal soft tissue sarcomas should be performed in referral institutions or within consolidate specific network co-operations. Here we report on the clinical history of two patients affected by very large retroperitoneal soft tissue sarcoma treated with preoperative chemoradiation within the italian RTR.

Materials and Methods: The clinical history of both patients was shared since diagnosis and through all relevant clinical steps in the web-based platform of the Italian RTR between Alessandria General Hospital and the referral institution in Milan.

Patient #1: 72-year old man, diagnosed with a 20 cm abdomino-pelvic dedifferentiaded liposarcoma. The surgeon considered the lesion resectable en-bloc but asked for a preoperative therapy to reduce tumor volume and to prevent the risk of tumor cell implantation during surgery. The patient was therefore treated with 3D Conformal Radiotherapy, dose 5040 cGy/28 fractions. Concomitant chemotherapy was not given due to the cardiac comorbidity. After 35 days from the end of radiotherapy, the patient underwent en-bloc resection of the abdomino-pelvic mass with left colon, proximal rectum and iliac left urether. The histological report indicated: "sarcoma with post therapy alterations (40% residual dedifferentiated liposarcoma and 60% post therapy alterations like sclerojalinosis and necrosis), proximal and distal colon resection margins negative".

Patient #2: 51-year old man, diagnosed with a 19 cm in diameter, left retroperitoneal spindle cell sarcoma with extensive necrosis. TC and TC/PET scans showed some adhesion of the tumor to pancreas. The surgeon suggested a preoperative therapy before the resection. The patient was treated with 3D Conformal Radiotherapy, dose 5040 cGy/28 fractions, and concomitant chemotherapy (HDC IFX, 3 courses/28 days). A wide resection of the retroperitoneal mass en-bloc with left kidney, left colonic flexure, splenectomy, pancreasectomy, partial gastrectomy, part of the left psoas muscle and part of the left diaphragm was performed. Histological examination reported: "spindle cell sarcoma with post therapy alteration in 40% of the specimen and resection margins negative".

Results: Despite large volume of CTV, the treatment planning was satisfactory for both cases, with DVH for OAR (small bowel, kidneys, liver, spinal cord)under limits set by Quantec study and tolerance was very good. Nevertheless, TC scan performed a few weeks after the end of radiotherapy treatment and before surgery did not show relevant reduction of the tumor volume. Surgery was accomplished in both cases in bloc, without microscopic positive margins. Follow-up: Patient 1 is alive at 20 months from diagnosis, but in April 2012 had a diagnosis of locoregional relapse and started chemotherapy. Patient 2 is alive and NED at 14 months from diagnosis.

Conclusions: Though only 2 cases, preoperative radiotherapy allowed accurate treatment planning, minimizing toxicity to contiguous organs, in particular to small bowel, and made it possible to deliver adequate doses to large volumes even with concomitant chemotherapy. Preoperative treatment results in high probability of complete surgery without positive margins. The treatment was delivered in two different centres (chemo-radiotherapy in Alessandria and surgery in Milan) within the RTR without any organizational issues thus confirming the efficacy of networking cooperation in rare tumours.

P061

RETROPERITONEAL SARCOMAS: MULTIMODALITY TREATMENT.

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Backgrounds: Sarcomas are a rare and diverse group of tumors that are derived from connective tissues, including bone, muscle and cartilage. Radiotherapy (RT) is an important prognostic factor in retroperitoneal sarcoma. Historically, local excision of retroperitoneal sarcomas resulted in local failure rates of 50% to 70%, even when a margin of normal tissue around the tumor was excised. As a result, the multimodality treatment became standard treatment. However, despite progress, this approach is rarely curative and the analysis of the causes of failures are helpful in treatment orientation.

Methods: From January 2000 through December 2011, 17 adults (median age, 64 years) with retroperitoneal sarcoma were treated in IRCC Candiolo by a conservative surgical excision and a postoperative radiotherapy. Liposarcoma and leiomyosarcoma represented most of the tumors and eighty percent of the tumors were of high or intermediate grade. In general, adjuvant RT is recommended for all intermediate- and high-grade sarcoma lesions. Prescription dose to the planning treatment volume (PTV) was 50-54 Gy at 1.8/2 Gy/fraction for completely resected patients and 60-66 Gy for R1 patients. Twelve patients were treated with 3DCRT and five with IMRT. Preparation for radiation therapy involves a detailed planning session to optimize and standardize patient positioning and determine the target volume, also thank to metallic clips inserted in the tumoral bed. Two patients had initial metastases. Multimodality treatment included surgery (17 patients), chemotherapy (17 patients) and radiotherapy (17 patients). Complete excision was achieved in 12 of 17 non metastatic patients. Median follow-up was 40 months.

Results: Univariate analysis were performed for local

control (LCR) and overall survival (OS). Actuarial overall 5-year survival was 70 %. The main prognostic factors for survival were initial metastases and complete resection. Adjuvant radiotherapy and complete excision was associated with reduced local recurrence. The acute side effects of radiation therapy were 2 patients with skin changes, 2 with anemia and neutropenia and 2 with diarrhea. No late toxicity was found.

Conclusions: There is good evidence that adjuvant RT improves the LCR in patients with retroperitoneal sarcoma. In our experience the compliance to the multimodality treatment explains the good results achieved.

P062

RADIOTHERAPY AND DISEASE-FREE SURVIVAL FOR PATIENTS WITH DESMOID TUMOURS: A CASE REPORT AND REVIEW OF LITERATURE

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Purpose: Extra-abdominal desmoid tumours or aggressive fibromatoses are rare, slow-growing, benign lesions derived from fibroblastic cells, with variable biological behaviour. The high recurrence rate and the tendency to invade critical structures of this type of tumours require a multidisciplinary approach. We show a case report, reviewing literature, to evidence how radiation therapy have an important role for increasing disease-free survival and to reduce local tumour recurrence.

Materials and Methods: In 2002 a 26-year-old woman was admitted complaining of a slowly-growing mass of 2 years duration, located on the upper medial surface of the shoulder. Physical examination revealed a firm, non movable and moderately painful mass attached to the scapula. The patient underwent local excision of the lesion and hystology showed features of extra-abdominal periosteal fibromatosis with low mitotic index and negative resection margins. Local lymph nodes were normal. In 2004 and 2007 the young woman had a local recurrence following surgery with complete excision of the disease. The third local recurrence occurred in May 2010. The patient received adjuvant hormone-therapy and 3D Conformational External-Beam radiation therapy (EBRT)using a 6 MV linac directed to the left chest, for a total dose of 60 Gy, with 200 cGy daily fractions (5/w), without significant side effects.

Results: Surgery represents the gold standard treatment of these tumours, even if they are characterised of a high local recurrence rate, due to their infiltrative nature. Local recurrence is a significant problem that has been reported to range from 25% to 77% at ten years. Literature shows that EBRT improves local control of desmoid tumours, in adjuvant and primary settings, mainly in adults with unresectable disease and for gross residual tumour with positive or equivocal surgical margins, also to avoid mutilating surgery. Currently the patient is in good conditions with a recurrence free survival time of 5 years.

Conclusions: Adjuvant postoperative RT improves local tumour control and could therefore reduce the recurrence rate, increasing disease-free survival period in an aggressive malignant disease, such as desmoid tumour. This study shows the impact of radiotherapy on 5 year-disease free survival. In conclusion, clinical trials can guide us choose to deliver RT immediately after surgery or wait till the relapse.

P063

IMAGE GUIDED BRACHYTHERAPY (IGBT) IN THE INTRA-OPERATIVE PLACEMENT OF TEMPORARY CATHETERS FOR PERIOPERATIVE HDR BRACHYTHERAPY IN RETROPERITONEAL SARCOMAS: A PRELIMINARY EXPERIENCE

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Backgrounds: Surgery, although still considered treatment of first choice for retroperitoneal sarcoma, does not cure the majority of patients because of poor resection outcomes and high rates of locoregional recurrences, leading frequently to death. There is plenty of evidence that adjuvant irradiation does improve local control.

Materials and Methods: In order to deliver effective doses to the tumor bed, different techniques for application of a boost dose in addition to external beam RT have been proposed. To overcome treatment facilities limitation of IORT technique and the related risk of severe late toxicities due to a single high dose fraction, we adopted an ipofractionated 192Ir HDR brachytherapy to the tumor bed, bordered by metallic clips, via intraoperatively implanted plastic tubes. In two consecutive patients, treatment was delivered with single doses of 2.5 Gy up to a total dose of 15 Gy in six fractions, twice daily with a minimum interval of 6 hours between each application. CT based image- guided brachytherapy was performed via three plastic catheters, fixed with sutures on the skin. Attention was paid to parallel positioning of the tubes in tumor bed at a approssimative distance of 10 mm one from the other, according to the Paris system. CT data set were transferred to the brachytherapy planning system (Oncentra®) and each catheter was identified individually, then an image-guided planning was performed. Target volume was identified from CT scan, surgical clip marks and intraoperatory selected regions of recurrence risk.

Results: 192Ir HDR brachytherapy to the tumor bed was easily accomplished allowing to deliver high dose boost to high risk recurrence regions. No major acute toxicity was observed. Because of a short follow up, no data about late toxicity are available yet.

Conclusions: : 192Ir HDR brachytherapy via intraoperatively implanted catheters, in order to deliver a boost dose on tumor bed for local control improving, is a feasible technique because of a good compliance profile and

neglegible rates of acute adverse effects. Longer follow up is needed to establish late toxicities incidence.

LA RADIOTERAPIA TRANSCUTANEA DEI TUMORI TIROIDEI

P064

ROLE OF EXTERNAL BEAM RADIOTHERAPY IN PATIENTS WITH THYROID CANCER: A RETROSPECTIVE ANALYSIS

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Purpose: The aim of this study was to retrospectively evaluate the locoregional control (LRC), overal survival (OS) and toxicity following External Beam Radiotherapy (EBRT) in patients (pts) with differentiated and anaplastic thyroid cance r(TC).

Materials and Methods: Between January 1997 and December 2011,79 pts with TC(46 differentiated TC: 31 papillary, 15 folliculary;14 mixed types;19 anaplastic TC)were treated with EBRT.The lesions were primarily advanced stages and included stage T2 in 11 pts(14%),T3 in 19 pts(24%),T4 in 43 pts (54%). Stage N+ disease was present in 34 pts(43%);distant metastasis before EBRT in 23 pts(29%).EBRT was administred with postoperative intent in 24 pts(30%),salvage RT after locoregional recurrence in 26 pts(33%),radical RT in 11 pts(14%) and high dose palliative RT in 18 pts(23%).Treatment tecnique was 3D CRT in 70 pts(89%),or IMRT in 9 pts(11%).The total dose was 50-55 Gy in 8 pts,55 -59,4 Gy in 17 pts and >59,4 Gy in 54 pts;the median dose to the pts treated with IMRT was 65,7 Gy.The postoperative EBRT was a dose<55 Gy in 4% of pts,55-59,4 Gy in 33% of pts,>59,4 Gy in 62% of pts; the salvage EBRT was a dose in range 55-59,4 Gy in 25% of pts and >59,4 Gy in 75% of pts;the radical EBRT was a dose <55Gy in 22% of pts,55-59,4 Gy in 22% of pts and >59,4 Gy in 55% of pts.Of the 79 pts,47 had radioactive iodine treatment and only 4had chemotherapy.

Results: Median follow up was 24 months(range 0-112 months);31 pts(39%)were alive at last follow up and 11 had no evidence of locoregional disease progression;35 pts(44%)died for TC.The LRC for all pts was 25%;20 pts had complete response after RT and only one patient with anaplastic TC was NED 19 months after radiotherapy,34 pts(43%)had persistent disease and 15(19%)developed distant metastasis after RT.Median survival(MS) for pts NED was 46 months(range 1-91 months);for pts alive with disease was 22 months and for pts who died with TC was 18.5 months. Pts with differentiated TC had a better prognosis with a MS of 36 months; anaplastic TC had poor prognosis: only three pts were alive with a MS of 27 months.Acute toxicity in this cohort included dermatitis,mucositis,laringytis and xerostomia:60 patients developed grade 1-2 toxicity and 7 pts grade 3.No significant differences in acute toxicity were identified between 3D CRT and IMRT.Late toxicity was low: one patient had a xerostomia grade 3.

Conclusions: This retrospective analysis concerns a populations with a large percentage of advanced stage of TC.The EBRT is effective for LRC in selected locally advanced or recurrent differentiated TC:in this pts the multimodality approaches using RT with high dose(>55 Gy)provide encouraging LRC and OS, with acceptable acute and late toxicity.Our results don't confirm that the use of IMRT may reduce acute and late morbidity relative to 3DCRT.Results for anaplastic TC remain insatisfactory. Additional work is necessary to define optimal role of EBRT in TC management.

P065

POST OPERATIVE NECK RADIOTHERAPY FOR DIFFERENTIATED THYROID CANCER IN ITALY: RESULTS OF A SURVEY

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Objectives: In 2012, the "Gruppo di Studio AIRO Radioterapia Metabolica" conducted a nationwide survey among Italian radiation oncology centers with the aim of evaluating the use of neck external beam radiotherapy (EBRT) after surgery in differentiated thyroid cancer (DTC).

Materials and Methods: An original survey questionnaire was emailed to all the AIRO members. A set of clinical and technical questions was developed, including the number of treatments per year, clinical indications for EBRT after surgery, EBRT timing with respect to 131-I therapy, dose prescription and technical standards.

Results: Sixty-three radiation oncologists from 35 Italian centers responded to the survey. The majority of radiation oncologists (95,2%) treated head & neck malignancies in their routine clinical practice, but only 34 (54%) delivered neck EBRT after surgery for DTC. The volume of EBRT treatments for DTC in most centers (81,8%) was less than 5 patients per year and timing with 131-I therapy was tailored to the individual patient in most cases (68,1%). Thirty-five/47 respondents (75%) considered post-operative EBRT mandatory in the presence of microscopically (R1) or macroscopically (R2) margins. In another question 35/47 respondents (75%) considered indicated EBRT also after complete resection (R0) in high-risk patients. With regard to radiation doses, R1/R0 resections were managed with doses ≤ 60 Gy by 29/45 (64,4%) of respondents and 8 (17,8%) used doses lower than 55 Gy. For R2 disease, only 4/46 radiation

oncologists (8,7%) prescribed more than 72 Gy. Intensity modulated radiotherapy (helical and/or step-and-shoot) was adopted by 37/46 (80,4%), while the remaining 9/46 used 3-D conformal radiation therapy only.

Conclusions: In Italian Radiation Therapy centers, only a small number of patients with a diagnosis of DTC were treated with EBRT. This might be due, at least in part, to a lack of consistency in this clinical setting; even experienced physicians are likely to be unsystematic and/or inconsistent in their medical decisions regarding the use of EBRT in DTC. Although the current American Thyroid Association guidelines suggest that post-operative EBRT should be considered after R0 resection in high risk patients > 45 years and with a high likelihood of microscopic residual disease, 25% of respondents did not consider EBRT indicated in this clinical situation. Concerning EBRT doses, these reports were in agreement with the current AIRO recommendations.

P066

EXTERNAL BEAM RADIOTHERAPY IN THYROID CARCINOMA

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Purpose: Surgery is the primary treatment for thyroid cancer. The role for external beam radiotherapy (EBRT) as an adjuvant to surgery for the differentiated thyroid carcinoma is controversial. Often the adjuvant EBRT is used for the anaplastic thyroid carcinoma. We evaluated the efficacy of EBRT in a small number of patients with loco-regional recurrence for differentiated thyroid carcinoma after surgery. We observed the outcome of a small group of patients with anaplastic thyroid carcinoma treated with adjuvant EBRT.

Methods: Between october 2008 And april 2012, 7 patients with recurrent differentiated thyroid carcinoma and 5 patients with anaplastic thyroid carcinoma were treated in our Institution with EBRT. In the first group (differentiated thyroid carcinoma) 5 patients (71%) received a dose of 60 Gy (fractions of 2 Gy) and 2 patients (29%) with advanced loco-regional extension of disease received a dose of 30 Gy (fractions of 3 Gy). In the second group (anaplastic thyroid carcinoma) all patients received doses of 30 Gy (fractions of 3 Gy). In the first group between diagnosis and radiotherapy all patients have undergone one or more times to surgery followed by radioiodine ablation therapy. In the second group all patients underwent surgery with macroscopic residual disease. The median age of first group was 68 years, 4 M and 3 F. The median age of second group was 69 years, 4 M and 1 F. In patients who received 60 Gy the PTV included the GTV, thyroid bed, the cervical lymphnode and the upper mediastinum. In patients who received 30 Gy the PTV included the GTV, thyroid bed and the cervical lymphnode.

Results: In the first group (differentiated thyroid carcinoma) all patients completed EBRT; 2 patients (29%) had G2 mucositis and 2 patients (29%) had G2 erithema during the treatment. After a median follw-up of 23 months (range 9-38), in the patients who received a dose of 60 Gy we observed 3 (60%) local control of disease and 2 (40%) local control with distant progression. In the patients that received 30 Gy, we observed 1 (50%) partial regression of disease and 1 (50%) partial regression of disease with distant progression. In the second group (anaplastic thyroid carcinoma) all patients completed EBRT; 1 patient (20%) had G2 mucositis and 1 patient (20%) had G2 erithema during the treatment. After a median follw-up of 2 months (range 1-4), only 1 patient (20%) is alive.

Conclusions: Curative EBRT, in patients with surgical recurrence of differentiated thyroid carcinoma, could be a viable therapeutic option for local control of disease; palliative EBRT may be considered in selected patients with advanced loco-regional recurrence of disease. In patients with anaplastic thyroid carcinoma considering the rapid evolution of the disease the role of the adjuvant EBRT is questionable; supportive care only, can be considered.

TOSSICITÀ TARDIVA IN RADIOTERAPIA: IPOFRAZIONAMENTO *VERSUS* FRAZIONAMENTO CONVENZIONALE

P067

HYPOFRACTIONATED RADIOTHERAPY IN INTERMEDIATE PROSTATE CANCER: RESULTS OF ACUTE AND LATE TOXICITY

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Purpose: To evaluate the tolerance and the clinical efficacy of hypofractionated radiotherapy in patients affected by intermediate risk prostate cancer.

Materials and Methods: Between March 2007 and November 2011, 102 patients with intermediate risk prostate cancer were treated with 3-dimension conformal hypofractionated radiotherapy. Intermediate risk was defined as clinical stage T1–T2 and pre-radiotherapy PSA between 10 and 20 ng/mL, and Gleason Score equal to <7 or clinical stage T1–T2 and pre-radiotherapy PSA between ≤20 ng/mL, and Gleason Score equal to 7. Prostate biopsy was performed to all patients to confirm the diagnosis. A total dose of 43,8 Gy was delivered to seminal vesicles and 54,75 Gy to the prostate, 3,65 Gy per fraction, three times a week for a total of 5 weeks. All patients underwent neoadjuvant, concomitant and adjuvant hormonal therapy (OT) for a total duration of 9 months. Acute and late toxicities were evaluated according to RTOG scale. The nadir PSA after radiotherapy plus 2 ng/mL was used for defining biochemical relapse (Phoenix criteria).

Results: Median follow-up was 24 months (range 3-54 months). Five patients (4.9%) developed biochemical failure: of these patients were found to have metastasis to regional lymphnode, while two patients developed bone metastasis. Six patients (5,9%) died from causes different from prostate cancer without biochemical failure, while patients died due to disease progression. Acute toxicities

(within 3 months from the end of RT) were as follow: Grade 1 Genitourinary (GU) toxicities were 43,4%, while 10% presented Grade 2 toxicities; Grade 1 Gastrointestinal (GI) toxicities were 9,8 %, Grade 2 GI toxicities were 11%. Late GU and GI toxicities Grade 2 recorded at the last follow-up were 3,5% and 4,8% respectively. No patient developed grade 4 toxicity. 2-year BFS and 4-year BFS were 94,4% and 92% respectively.

Conclusions: The hypofractionated schedule used is well tolerated with a low rate of acute and late grade ≥ 2 gastrointestinal and genitourinary toxicities. Hypofractionation is useful to obtain high rate of tumor control also if longer follow-up is needed.

P068

PROPOSAL OF A NEW METHOD TO STANDARDIZE THE CONTOURING OF THE SUPERIOR CONSTRICTOR MUSCLE FOR HEAD AND NECK CANCER PATIENTS TREATED WITH RADIOTHERAPY: PRELIMINARY RESULTS OF A COLLABORATIVE STUDY FROM THE AIRO HEAD AND NECK WORKING GROUP

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Aims: Irradiation of the constrictors muscles seems to be of crucial importance in the development of radiotherapy-related late dysphagia for patients treated in the head and neck region. Aim of this study is to standardize the contouring of the superior constrictor muscle (SCM)on the Simulation Computed Tomography (CTsim).

Materials and Methods: Three CTsim of patients treated for head and neck tumor were used. The three CTsim were selected because a corresponding Magnetic Resonance (RM), performed in the same period, was available. The SCM was contoured by an expert radiologist on each MR. MR scans were then non-rigidly registered with the corresponding CTsim. SCM contours were then propagated on the CTsim and used as a gold standard contours. To the study participants was asked to contour the SCM on the CTsim of each patient, using both a standard and a new method (higher extension on the skull base and anterior margin near a theoretical pterigo-mandibular raphe for the new method). The procedure has been repeated three times. Each operator provided 18 contours (three SCM contours for each patient using both contouring methods). The inter-observer variability, the intra-observer variability and the agreements of provided contours with the gold standard ones were evaluated using a DICE Similarity Coefficient (DSCinter), a Covariance Index (COVintra) and a DICE similarity coefficient (DSCgold) method, respectively.

Results: Twelve centers and 17 radiation oncologists took part to the study for a total of 306 SCM contours. Preliminary results showed both inter-and intra-variabilty to be statistically reduced using the new method. Moreover, the agreement between the provided contours and the gold standard ones, were higher using the new method. Results are summarized in the following Table 1.

Table 1.

	Standard method	New method	P value
Inter-observer variability (DSCinter mean+/-SD)	0.46±0.14	0.50±0.14	<0.01
Intra-observer variability (COVintra mean+/-SD)	0.45+/-0.6	0.41+/-0.6	<0.01
Agreement with gold standard (DCSgold mean+/-SD)	0.26±0.12	0.29±0.13	<0.01

Conclusions: Preliminary results showed that the new proposed method provides a higher agreement between the SCM contour drawn on the CTsim and the ones drawn on the MR scans reducing the inter- and intra-observer variability. Further analysis related to the qualitative study of critical areas and dosimetric impact of this variability are ongoing.

P069

WHAT IS THE PRICE FOR FUNCTIONAL SURGICAL ORGAN PRESERVATION IN LOCALLY ADVANCED SUPRAGLOTTIC CANCER? LONG-TERM OUTCOME FOR PARTIAL LARYNGECTOMY FOLLOWED BY RADIOTHERAPY IN 32 PATIENTS

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Aims: To evaluate patients treated with a surgical organ preservation therapy for locally advanced supraglottic tumor.

Materials and Methods: We retrospectively reviewed all

patients treated with conservative surgery and postoperative radiotherapy for locally advanced (stage III and IV) squamous cell carcinoma of the supraglottis between 2000 and 2010. Clinical outcome, late laryngeal toxicity, and the correlation with treatment-related risk factors were assessed.

Results: Thirty-two patients were analyzed (28 male, median age 61 yrs). Endoscopic surgery was used for 18 patients (13 CO2 laser and 5 robot-assisted surgery). Median postoperative radiotherapy dose to the remnant larynx was 59.4 Gy (range 39.6-66.6). Concomitant radiotherapy was administrated in 18 patients. The median follow up was 38 months (range 5-115 months). Overall survival and disease free survival at five years were 73% and 66%, respectively. Three (9%) patients experienced local recurrence (after 22, 25 and 40 months) and were treated with total laryngectomy. The larynx preservation rate was 93%. At least one severe treatment-related late laryngeal toxicity (severe chondritis, chondronecrosis, laryngeal stenosis, need of enteral nutrition) was experienced by 11 (34%) patients. Two patients developed severe chondritis and 2 patients developed chondronecrosis. Six (19%) patients suffered from clinically relevant late laryngeal stenosis (due to soft tissue fibrosis) requiring medical treatment (one patient) and/or mechanical endoscopic enlargement (5 patients). At the last follow-up 3 patients (9%) needed enteral nutrition The "functional larynx preservation rate" (absence of tracheostomy and/or enteral nutrition at last follow up) was 78.5%. The prognostic factors for severe late toxicity were found to be gender (females had a worse prognosis), the extension of the surgical procedure (supraglottic *versus* more extended surgey), the removal of the arytenoids and the association with concomitant chemotherapy. No statistically significant differences were found between patient treated with endoscopic and open surgery

Conclusions: We confirm the literature data on the feasibility and efficacy of a surgical organ preservation strategy for locally advanced supraglottic tumors. However, the high rate of severe late toxicity requires further study to improve patient selection, the surgical procedure and the radiotherapy technique.

P070
IMAGE-GUIDED ROBOTIC RADIOSURGERY TREATMENT AS SALVAGE THERAPY FOR LOCALLY RECURRENT CHORDOMAS

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Purpose: Combining maximal surgical resection with high dose proton radiation therapy is reported currently the best management of patients with chordoma, we evaluated the efficacy and safety of Cyberknife streotactic radiosurgery as primary, or salvage management for chordomas following combined therapy.

Methods: sixteen patients with recurrence chordomas, 13 males and 3 females were treated with Cybernife Stereotactic Radiosurgery at our Institution. The series included 20 lesions. Salvage Ck radiosurgery was performed after surgery for 5 lesions, surgery and radiotherapy for 7 lesions, surgery plus proton therapy and radiotherapy for 3 lesions, radiotherapy alone for 4 lesions and as monotherapy in 1 patient.The median age of the patients was 64 years (range, 35–81 years). Forty percent of the tumors were located in the mobile spine, 35% inside the cranium, and 25% in the sacral region. The mean tumor volume was 128.0 mL (range, 12.0–457.3 mL), and the median dose of 35 Gy (range, 24.0–40.0 Gy) was delivered in 4 - 5 sessions. The median follow-up period was 33 months (range, 4 –75 months).

Results: 10 patients experienced recurrence, The local control rate at 36 months was 58.5 %, with an overall survival of 61%. The most part of complications observed were decrease vision or diplopia, lower cranial nerve palsies, hypestesia, transiet pharestesias and radiculopathy. In one patients a grade 4 spinal cord neurotoxicity was registered.

Conclusions: CyberKnife-based SRT is a feasible approach for locally recurrent chordomas. Further experience and longer follow-up are needed to evaluate the role of CK in the treatment of local recurrences and to identify patients most likely to benefit from it.

P071
HYPOFRACTIONATED ADJUVANT WHOLE BREAST RADIOTHERAPY IN ELDERLY WOMEN: LATE TOXICITY

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Purpose: A variety of hypofractionated radiotherapy schedules using fraction sizes between 2 and 3 Gy has been proposed after breast conserving surgery. Minimizing toxicity and inconvenience of treatment, especially for elderly women (≥ 65years), should lead to greater use. The purpose of this study is to assess short-term late toxicity in a hypofractionated whole breast irradiation schedule for elderly women.

Materials and Methods: Between February 2008 and November 2010 we treated 20 elderly women with operable invasive early-stage breast cancer with a hypofractionated schedule of external beam radiation therapy. The median age was 75 years (range 66-85). Eighteen patients (90%) had tumours that were ≤ 2cm in diameter. The axillary lymph nodes were negative in 17 patients. Seventeen patients had invasive ductal carcinoma and 4 patients had invasive lobular carcinoma. Two patients had estrogen - receptor negative disease, 18 patients had received adjuvant aromatase inhibitors and 2 patients had received adjuvant systemic therapy. Radiation therapy was delivered using two opposed tangential fields. Most patients were treated with 6MV x-rays. Median whole-breast irradiation dose prescribed in the ICRU reference point (isocentre) was 40.05Gy (range: 40-42.5Gy) administered in 15-16 fractions of 2.5-2.67Gy, 5 fractions/week, in 3 weeks. Using the original planning computer tomography scans the entire breast was delineated. The DVHs histograms were accepted just if PTV was included in 95-

107% of isodoses curves. Boost irradiation to the tumor bed with the doses of 2 to 3 Gy/fraction was performed in 4 cases with electrons of 9 e 15 MeV.

Results: All the patients had achieved a median follow up of 18 months (range 17-48 months). Late toxicity was scored according to the Radiation Therapy Oncology Group criteria. At 12 months 45% and 5% of patients presented with clinical grade 1 and grade 2 fibrosis respectively and 5% presented grade 1 hyperpigmentation. At 24 months, with 12 patients evaluated, just 1 patient (5%) showed grade 2 late fibrosis. The remaining patients were free of side effects.

Conclusions: In our experience hypofractionated schedule offer a good feasibility in terms of short-term late toxicity. For elderly women the hypofractionated radiotherapy by shortening overall treatment time should improve the acceptance of treatment. Further investigations are necessary to better elucidate the late skin toxicity in the context of hypofractionated irradiation.

P072
COMPARISON OF LATE TOXICITY OBSERVED AFTER CONVENTIONAL OR HYPOFRACTIONATED RADIOTHERAPY FOR BREAST CANCER IN PATIENTS WITH LARGE BREAST VOLUME

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Aims: in order to evaluate late toxicity in large breast patients we report a comparison of two fractionation schedules : hypofractionated (42.4 Gy in 16 fractions with or without boost 10 Gy in 4 fractions) *vs* conventional fractionation (50 Gy in 25 fractions with or without boost 10 Gy in 4 fractions) among patients with early stage breast cancer and large breast volume treated after conserving surgery.

Materials and Methods: We evaluate retrospectively late toxicity between two groups of patients affected by breast cancer stage I-II, with large breast volume. All patients underwent CT based treatment planning and breast volume was calculated with TPS algorithm, they were classified according to breast volume and to this criteria: small breast < 400 cc , medium breast 400-800 cc , large breast >800 cc. Our evaluation include 32 large breast patients treated in our Institution with hypofractionated treatment from June 2008 to November 2011, compared with same number of large breast patients treated with conventional fractionation whit same characteristics. Patients were evaluated at the end of treatment every 6 months. The SOMA-LENT scoring system was used for assessment of late complications. Median follow-up was 38 months (range 56-6 months).

Results: After radiotherapy completion two groups were evaluated every 6 months to assess late toxicity. Conventional treatment group show : 18/32 (56.3%) no toxicity G0, 12/32 (37.5%) Hyperpigmentation and Telangiectasia G1, 2/32 (6.2%) fibrosis G2. Hypofractionated group show : 22/32 (68.7%) no toxicity G0, 11/32 (34.4%) Hyperpigmentation and Telangiectasia G1, 1/32 (3.1%) fibrosis G2. There were no significant differences in toxicity between the two groups.

Conclusions: There were no unexpected severe toxicities. Hypofractionated adjuvant radiotherapy following breast-conserving surgery for breast cancer has comparable late toxicity to a conventional radiation schedule. Hypofractionated treatment is more convenient for patients, has equivalent morbidity and should be considered in this patient group. Our results need to be evaluated for a longer time, but actually our results show that the hypofractionated radiotherapy not increase risk of late toxicity compared to standard fractionation. This fractionation seems to be effective with acceptable side effects.

P073
EXCLUSIVE ELECTRON INTRAOPERATIVE RADIOTHERAPY (IORT) IN EARLY-STAGE BREAST CANCER: A MONOINSTITUTIONAL EXPERIENCE

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Aims: IORT (Intraoperative radiotherapy) is one of the different technical procedures in partial breast irradiation; a high single fraction dose is delivered directly to the tumor bed during surgery, after the primary lesion has been removed, allowing great precision in the release of the dose and, at the same time, reducing the dose and toxicity to adjacent healthy organs.

Materials and Methods: From June 2007 to October 2011 we treated 110 patients with early-stage breast cancer submitted to quadrantectomy and intra-operative radiotherapy. The selection criteria included tumor size < 2.5 cm, age > 48 years, post-menopausa, absence of intraductal component. Total dose of 21 Gy prescribed at 90-100% isodose was delivered in all cases. IORT was delivered using a dedicated linear accelerator and different range of electron energies (6-10 MeV). Patients were evaluated 1, 3, 6 and 12 months after surgery, and thereafter every 6 months, to look for early, intermediate, late complications, and other events. The aim of the study was to evaluate the effectiveness of IORT in terms of local control, quality of life, and disease-free survival.

Results: The patients were followed with an average follow-up of 27 months, with a range between 2 and 54 months. 6 patients (5.5%) presented delay of scaring. In 10 patients (9.1%), breast ultrasound showed the presence of a fluid stratum with hotbed of liponecrosis in correspondence of the scar, however during the following visit didn't show the persistence of fluid layer. 5 patients (4.5 %) developed fibrosis in the area next to the scar. The development of fibrosis has been progressive during the first weeks after surgery, and than slowly regressed. In 9 patients (8.2%) cutaneous retraction of scar was observed, more evident at first controls, with tendency to a gradual attenuation. 3 patients (2.8%) developed local recurrence. 2 patient (1.8%) developed distant metastasis. 2 patients died, 1 of whom for progression of breast cancer and 1 for other causes. Overall survival was 91.9%.

Conclusions: IORT in initial stage breast cancer could be an appropriate therapeutic alternative in selected patients and although it remains investigational, longer follow-up to confirm results are required.

P074

PREDICTING LATE FAECAL INCONTINENCE AFTER HIGH-DOSE RADIOTHERAPY FOR PROSTATE CANCER: APPLICATION OF ARTIFICIAL NEURAL NETWORK CLASSIFICATION ON A NEW LONGITUDINAL DEFINITION

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Objectives: To study the application of artificial neural network (ANN) classification for the prediction of late faecal incontinence (linc) following high-dose prostate cancer (PCa) radiotherapy (RT).

Materials and Methods: 586 patients (pts) recruited in the AIROPROS0102 trial were analysed. A new longitudinal definition of linc expressed as the average score of incontinence in the first 36 months after RT was used. Information was recorded on co-morbidity (with particular attention to hypertension, cardiovascular history, diabetes mellitus, auto-immune diseases), previous abdominal surgery and use of drugs (anticoagulants//antiaggregants, antihypertensives, hypoglycaemic or insulin). Rectal dose-volume histograms of whole treatment were recorded for all pts and the % volume of rectum receiving more than 20—>70Gy (named V20Gy—>V70Gy) were considered. The overall population was split into a train and a test set. The train set was used to optimize the inner weights and biases of the ANN. To avoid data over fitting we limit the number of inputs and hidden neurons. The test set was used to independently verify the generalization capabilities of the model. A value of longitudinal linc equal or greater than one was arbitrarily considered as the endpoint, because this score selected those pts with persistent symptoms.

Results: 36/586 pts had a baseline incontinence score>0 and were excluded from the analysis. 22/550 pts had a positive endpoint: they were split in 366 (15 positive) and 184 (7 positive) cases for train and test set, respectively. Five variables were identified: V40Gy (continuous variable), surgery, seminal vesicles irradiation, use of anticoagulants, and presence of haemorrhoids. The resulting ANN (4 hidden neurons) was able to correctly predict linc with sensitivity and specificity values of 80% and 68%, respectively for the overall population. Area under the ROC curve (AUC) was 0.84. Adding acute incontinence information as a further ANN input variable, sensitivity and specificity increased to 80% and 95%, respectively, and AUC increased to 0.92.

Conclusions: ANN combined to the selection of significant input variables and a longitudinal definition of linc resulted to be a powerful tool to predict RT morbidity in PCa pts. This kind of model might help to predict/possibly avoid the single pt unnecessary worsening of quality of life, introducing treatment's corrections to better tailor the treatment to pt's characteristics.

P075

LATE TOXICITY IN HEAD AND NECK CANCER PATIENTES TREATED WITH CONVENTIONAL FRACTIONATION IN 3DCRT OR HYPOFRACTIONATION USING SIB-IMRT

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Purpose: The aim of this paper is to analyze late toxicity in locally advanced head and neck cancer treated with conventional fractionation in 3DCRT or hypofractionation with SIB-IMRT.

Materials and Methods: From June 2007 to May 2011, 81 consecutive patients (clinic pathological characteristics of patients are detailed in Table 1) affected by III/IV stage head and neck cancer were treated with RT± concurrent cisplatin (100mg/mq dd 1-22-43 in 22 pts; 30 mg /mq weekly in 48 pts, no CHT in 11 pts). 67 pts received also neo-adjuvant chemotherapy (TPF or TP) for 2-3 cicles before CRT. 3DCRT was delivered in 38 pts (June 2007-February 2009): dose prescription was 70/2Gy in 35 fractions to GTVs with a 1cm-margin and 50/2Gy in 25 fr to negative nodes. Hypofractionated radiotherapy (IMRT-SIB) was delivered in 43 pts (November 2008 -May 2011): dose prescription was 69.9/2.33Gy to macroscopic disease, 60/2Gy to lymph nodes at high risk of subclinical involvement and 54/1.8Gy to lymph nodes levels at low risk of subclinical involvement in 30 fz.

Results: 72 pts were valuable for toxicity (4 lost at follow-up). The mean follow-up was 33 months (range 6-60 months). Five patients died during treatment (3 during 3DCRT+CHT, 2 during IMRT-SIB) because of acute toxicity. All 72 pts complete prescribed radiochemotherapy, without any interruption due to treatment. Late toxicity was evaluated according to RTOG common toxicity criteria, relative to skin, pharynx and oral cavity. In the group of pts treated with conventional radiotherapy the most common late sites effects affected oesophagus (G2: 9pts, G3: 7 pts, G4: 2pts), salivary glands (G2: 18 pts, G3: 4 pts and G4: 3 pts), connective tissue (G2: 10 pts, G3: 3 pts and G4: 3 pts), skin (G2:10 G3:4). In the group of pts treated with IMRT-SIB the most common late sites effects affected oesophagus (G2: 1 pts), salivary glands (G2: 8 pts). No late reaction≥G3 have been reported.

Conclusions: IMRT may be useful in reduction of late dysphagia and salivary gland toxixity incidence. Producing highly conformal dose distributions around the target, IMRT may reduce the dose delivered to non-involved mucosa and to other tissues whose damage causes these sequelae. Radiochemotherapy is feasible and well tolerated in locally advanced HNSCC, even in patients pre-treated with neo-adjuvant chemotherapy.

Table 1.

		Cases
Gender	Male	**61**
	Female	**20**
Cancer site	Oral cavity	**5**
	Oropharynx	**17**
	Larynx	**25**
	Hypopharynx	**15**
	Nasopharynx	**24**
Stage	III	**20**
	IVA	**44**
	IVB	**17**
Histology	Epidermoid	**59**
	Others	**22**
RT schedule	Conventional	**38**
	Hyperfractionated	**43**
Concomitant CHT	cisplatin 100mg/mq dd 1-22-43	**22**
	cisplatin 30 mg /mq weekly	**48**

P076

USE OF INTENSITY-MODULATED RADIOTHERAPY (IMRT) RADIO-CHEMOTHERAPY IN THE EXCLUSIVE TREATMENT OF CARCINOMA OF THE ANUS: THERAPEUTIC OUTCOME AND TOXICITY

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Aims: Combined radio-chemotherapy is the reference treatment of anal cancer because it has resulted in equivalent overall survival with higher colostomy-free survival rates. This treatment has a potential toxicity that can increase the treatment breaks and the overall treatment time, with negative impact on the outcomes. Intensity-modulated radiation therapy (IMRT) has been proven to deliver a higher radiation dose to the target, reducing that to pelvic organs, resulting in a lower rate of acute and late morbidity. Aim of this work is to present a mono institutional experience of 20 patients affected by squamous cell carcinoma of the anus treated with IMRT plus concomitant chemotherapy.

Materials and Methods: From January 2008 to April 2012, 20 patients with squamous cell anal cancer were treated with IMRT and concurrent chemotherapy. All the included patients were staged with abdominal and pelvic CT, pelvic MRI, rectal endoscopic ultra sound and digital rectal examination (DRE). Radiation course consisted in delivering 45 Gy/25 fractions, 5 days a week to PTV1 defined as the primary tumor plus pelvic and inguinal nodes followed by a boost of 15 Gy/8 fractions to the primary tumor (PTV2). IMRT plans were generated using commercial inverse planning software (Pinnacle) and patients were treated with a 10-MV linear accelerator (DHX, Varian), using a dynamic multileaf collimator. Concurrent chemotherapy consisted of mitomycin C (10mg/m , day 1 and 29) and 5-FU (1,000mg/m2/day, c.i., day 1-4 and 29-32). Follow-up was performed every three months for the first two years with DRE, pelvic MRI or endoscopic ultra sound (plus biopsy twice a year) and CT or CT/PET every 6 months. Acute and late toxicities were graded by RTOG/EORTC and LENT-SOMA scales respectively.

Results: Median age of the patients was 65,9 years (range 38-84), fifteen were female and five male. Four of them presented with T2 disease, 11 with T3 and five T4. All patients but one completed the prescribed treatment in the scheduled time. Acute grade 3 gastrointestinal, genitourinary and skin toxicities were observed in 3, 2 and 5 patients respectively, with treatment break longer than 3 days. No grade 4 acute toxicity was observed. As for late toxicity, 4 patients developed transitory legs edema, with no evidence of vascular injury Fifteen patients are alive without any evidence of disease and 5 are dead for local and/or systemic progression of disease. The 3-year local relapse free survival was 75% and the 3-year colostomy-free survival rate was 70%. With a median follow-up of 27 months (range 4–40), no patients experienced any late grade ≥ 3 toxicity.

Conclusions: IMRT with concomitant chemotherapy in anal carcinoma improves, in our experience, the therapeutic outcomes, thanks to higher doses delivered to the target. Very significant results were the 3-year colostomy-free survival rate of 70% and the limited late toxicity in the medium follow-up.

P077

ADJUVANT HYPOFRACTIONED RADIOTHERAPY IN EARLY BREAST CANCER: A PRELIMINARY EXPERIENCE

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Purpose: To evaluate the acute and late reactions for breast cancer patients (pts) treated with hypofractionated radiotherapy schedule (hypoRT).

Materials and Methods: Between July 2010 and December 2011, 68 non-metastatic breast patients (pts) aged 49-83 years (mean age:66) were treated with hypoRT after conservative surgery; the prescribed dose was 42.56 Gy /16 fractions to the whole breast, given five days a week , followed by a sequential boost on the tumor bed of 10 Gy in 4-5 fractions. All the pts had the following characteristics: age>49 years old, conservative surgery for T1-T2 tumors, positive ormonal receptors

(ER, PgR), no lobular tumor and not infiltrated or close margins after surgery. No pts received adjuvant chemotherapy and all but one underwent sentinel node dissection. Time between surgery and radiotherapy was 2-13 weeks (median 7 weeks) in all but one patient (RT after 16 weeks for a post-operative complication). All pts but nine received hormonal therapy concurrent with radiotherapy: 45 pts (66,1%) had Anastrozole, while the others got Letrozole or Tamoxifene +/- LHRH-A. Pts underwent to a 0,5 cm slicing treatment planning computer tomography in supine position. Radiation therapy was delivered by three dimensional radiation therapy (3D-CRT), using generally two 6 MV tangential fields for the irradiation of whole breast while tumor bed boost was delivered using two or three 6 MV fields. Set-up was checked during the first three sessions and then weekly. The following dosimetric parameters were considered: V95% for the PTV coverage; V20 Gy, V30 Gy and mean dose for ipsilateral lung; V 25 Gy, V30 Gy, mean dose and maximum dose for the heart in left breast irradiation. Side effects were recorded according to EORTC/RTOG scales.

Results: All pts underwent weekly toxicity controls: acute skin reactions score is the worst registered, usually at the end of the treatment; after RT pts were evaluated every 4-6 months. Median follow-up was 11 months (4-20). The acute skin toxicity was G1 in about 80% (55 pts) of the cases, while 14,7% (10 pts) had G2 and 3 pts (4,4%) were classified as G0. No G3 toxicity was registered. Related to the late skin toxicity we didn't score G2, while 80,8% (55 pts) showed G0 score and 19,2% (13 pts) had G1 toxicity. All the pts got excellent or good cosmethic results. No other adverse effects were registered.

Conclusions: The hypoRT schedule chosen(the same as the "Canadian" schedule used by Whelan et al. for the whole breast RT), seems to be safe and feasible, related to the mild acute toxicity scored, the acceptable long term effects and the good cosmethic results, even if we added a dose by boosting the tumor bed. It has been proposed to a particular setting of patients with early breast cancer with pathologic and biologic favourable risk factors. In our experience there are not differences between conventional and hypofractionated radiotherapy in terms of acute and late side effects, according with literature. We have no long term follow-up to estimate the rate of relapse and local control; anyway our inclusion criteria, according with literature, seem to be safe and advised.

P078

IPOFRACTIONATED CHEMORADIATION IN LOCALLY ADVANCED HEAD & NECK CARCINOMA: LONG TERM RESULTS

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Backgrounds: The aim was to evaluate the efficacy of moderately accelerated intensity modulated radiation therapy (IMRT/VMAT) along with weekly cisplatin or erbitux following induction chemotherapy (IC), in patients with locally advanced unresectable head and neck cancer (HNC).

Patients and Methods: Patients with stage III or IV locally advanced HNC, without progressive disease after three courses of induction chemotherapy (Cisplatin plus 5-Fluoruracil in IRMA H&N 1 or Docetaxel plus Cisplatin plus 5-Fluorouracil in IRMA H&N 2), received concurrent weekly Cisplatin 30 mg/m2 or erbitux 400 mg/m2 plus simultaneous integrated boost IMRT/VMAT. 67.5 Gy/30 fractions (IRMA H&N 1, 2 and 4) or 70.5 Gy/30 fractions (IRMA H&N 3) were delivered to the primary tumour and involved nodes, 60 Gy/30 fractions to the high risk nodal areas and 55.5 Gy/30 fractions to the low risk nodal areas.

Results: 71 patients (M/F: 56/15; median age: 58 years, range 30-79) with UICC stage III (n=12) and IV (n=59) were included. 37 (52%) patients received CF (cisplatin and 5-fluorouracil) and 34 (48%) patients, DCF (docetaxel cisplatin and 5-fluorouracil). As far as acute toxicity, 17/71 (24%) patients experienced Grade III mucositis during concurrent chemoradiation, while 4/71 (6%) experienced severe (Grade III-IV) pharyngeal-oesophageal toxicity. Four-year actuarial Grade II (mostly moderate dryness of mouth or telangiectasies) and Grade III (mostly fibrosis) late toxicity free survival were 55.2% and 86.6%, respectively. Four-year local control (LC) and Overall Survival (OS) were 56.9% and 45.7%, respectively. Moreover, no differences in term of LC or OS were found according to different IC or total dose.

Conclusions: In our experience, a moderately accelerated chemo-IMRT/VMAT was feasible after IC. Intensive supportive care strategies should be defined in order to better manage radiation induced toxic effects. Considering that mostly of patients were IV stages H&N cancers results in term of LC and OS may be considered strongly encouraging.

P079

HYPOFRACTIONATED ACCELERATED CONCOMITANT BOOST IN HIGH-RISK BREAST CARCINOMA: FINAL RESULTS OF THE MARA-2 PHASE I-II TRIAL

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Aims: To evaluate the results in terms of late toxicity and local control of an intensified regimen of accelerated IMRT-based postoperative radiotherapy.

Materials and Methods: In the MARA-2 study, patients with high-risk breast carcinoma undergoing breast-conserving surgery were included. Inclusion criteria were pre-or perimenopausal patients with clear or close (< 3 mm) surgical margins, and postmenopausal patients with close surgical margins. Patients with pT4 pathologic stage, presence of metastatic axillary's nodes, prescription of nodal irradiation, were included. Exclusion criteria were positive surgical margins and presence of distant metastasis. Prescribed dose to the breast was 50 Gy (2 Gy/fraction delivered by forward-planned IMRT), while the tumour bed total dose was 60 Gy (concomitant 10 Gy boost, 2.4 Gy/fraction). Overall treatment time was 5 weeks (25 fractions).

Results: Three hundred and seventy-eight patients were included in the analysis. Median age was 50 yrs (range 25-82). Pathological stages were distributed as follows: T1: 237; T2: 131; pT3: 6; pT4: 4; pN0: 229; pN1: 90; N2: 39; N3: 20. R0: 314; margin "close": 64. Acute grade ≥ 3 skin toxicity was seen in 8/378 (2.1%) patients. At a median follow up period of 52 months (range; 7-100 months), 10 (2.6%) patients had grade ≥ 2 late skin toxicity, while 38 (10.0%) patients had late subcutaneous toxicity > G2. Six patients showed local (4 pts; 1%) or nodal (2 pts; 0.5%) relapse.

Conclusions: Accelerated hypofractionated concomitant boost in medium-high risk breast cancer was administered with acceptable toxicity, with local control and long-term toxicity similar to conventional treatment.

P080

SHORT COURSE RADIOTHERAPY OF SKIN CANCERS IN ELDERLY PATIENTS: LONG TERM RESULTS OF A PHASE I-II STUDY

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Aims: Skin cancer is the most common tumor. Particularly high incidence is recorded in elderly patients. Aim of this report was to evaluate feasibility and efficacy of short course radiotherapy for small (< 3 cm) skin cancer in elderly patients (> 70 years).

Patients and Methods: A phase I-II study was designed. Inclusion criteria were biopsy proven skin cancer (epithelial skin cancer) and lesions ≤ 3 cm without invasion of muscles and bones. A radiation dose of 30 Gy over 6 days, 5 Gy per fraction, was delivered to the tumor plus a margin of 2 cm for basal cell carcinoma and 3 cm for squamous cell carcinoma. The majority of patients were treated by electron beam (83%), while a minority (17%) by photon beam. Local control and acute and late toxicity were analyzed.

Results: 36 patients (basal cell carcinomas: 18, squamous cell carcinomas: 14, other: 4; median age 80, range 70-90) were analyzed. Median follow-up time was 15 months (range: 1-58 months). Grade 1 (53%) and grade 2 (33%) acute skin toxicities were recorded. G1 subcutaneous late toxicity has been observed in 16 patient (44%). 7 (19%) local recurrences were recorded.

Conclusions: Short course radiotherapy in patients older than 70 years is well tolerated with good local control in small skin cancers.

P081

HYPOFRACTIONATED IMAGE-GUIDED RADIOTHERAPY FOR PROSTATE CANCER: OUTCOMES OF 153 PATIENTS TREATED AT REGGIO EMILIA HOSPITAL

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Purpose: The objective of the present study is to estimate the local control and early and late toxicity of a hypofractionated IGRT for prostate cancer.

Materials and Methods: Between January 2008 and December 2011, 153 patients with prostate cancer were treated for radical intent with IGRT using hypofractionated intensity-modulated radiation therapy (IMRT) and simultaneous integrated boost with Tomotherapy. According to NCCN classification, the patients were stratified in low, intermediate and high and very high risk. Regarding radiation volumes and doses, CTV1 included the prostate, CTV2 consisted of CTV1 plus seminal vesicles, CTV3 consisted of CTV2 plus pelvic nodes. CTVs were expanded to PTV by 0.8 cm in all directions except posterior direction (0.5 cm). All patients were treated in 28 fractions. For low risk patients, PTV included PTV1 up to a total dose of 70 Gy. For intermediate risk patients, PTV included PTV1 and PTV2 up to a total dose of 70-72.8 Gy and 56-61.6 Gy, respectively. For patients at high risk or with positive pelvic lymph nodes, PTV included PTV1, PTV2 and PTV3 up to a total dose of 70-72.8 Gy, 56-61.6 Gy and 50,4 Gy, respectively, plus a nodal boost on N+ (63 Gy). The hormonal therapy was performed in intermediate and high risk patients. The worst acute rectal, intestinal and genitourinary toxicities were scored according to the Radiation Therapy Oncology Group criteria (RTOG). All patients were followed during radiation therapy and every 6 months for toxicity rating and PSA.

Results: The radiation treatment was performed and completed in all 153 patients. Median age was 68.5 years and median GS was 7. Concerning radiation treatment, 49% of patients were treated concomitantly to prostate-seminal vesicles and 6% to prostate-seminal vesicles and pelvic lymph nodes; seventy (45%) patients were treated

to prostate only. Seventy-six (49.7%) out of 153 patients were also treated previously and concomitantly with hormonal therapy; the mean duration time of HT was 25 months. Acute genitor-urinary toxicity was recorded as follows: 42% G0, 46% G1, 11.1% G2, no G3. Acute rectal toxicities were: 72.5% G0, 16.3% G1, 10% G2, no G3. Sub-acute GU toxicity, evaluated at 3 months after RT completion, was reported as follows: 79.2% G0, 15% G1, 5% G2, 0.6% G3. Sub-acute rectal toxicity was 91.7% G0, 6.7% G1 and 1.7% G2, no G3. At last follow up visit, grade >G2 late GU and GI toxicity rates were 8.5% and 0%, respectively. The rates of the worst grade >2 late GU and GI toxicity seen at any time during the follow up period were 5.8% and 1.7%, respectively. No chronic GI toxicity >3 was observed. Two patients developed G3 GU late toxicity at 24 months after RT completion. At median follow up time of 28.6 months, only three patients (2%) developed biochemical failure. At last follow up, 96.7% of patients are alive without biochemical relapse.

Conclusions: Hypofractionated radiotherapy is clinically feasible and more convenient than conventional schedules for patients with prostate cancer treated with radical intent. The preliminary results in terms of late effects are encouraging, reporting a low rate of GU and GI late toxicity. Longer follow-up is needed to determine if this low rate of toxicity will be translated in a persistent low rate of late toxicity.

P082

ACUTE AND LATE TOXICITY WITH HYPOFRACTIONATED RADIATION THERAPY FOR EARLY BREAST CANCER COMPARED TO CONVENTIONAL RT

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Purpose: The objective of the present study is to evaluate toxicity and cosmetic outcome in breast cancer survivors treated with hypofractionated adjuvant radiotherapy and to identify risk factors for toxicity, with special focus on the impact of age, comorbidities and chemotherapy. For comparison, a group of 65 patients with similar characteristics and consecutively treated with conventional fractionation was retrospectively selected.

Materials and Methods: From April 2010 and December 2011, one 174 women with early breast cancer were treated with hypo fractionated radiotherapy, after conserving surgery. The patients received 40.05 Gy in 15 fractions. The boost to the tumor bed was administered with a total dose of 9 Gy in 3 consecutive fractions in 39 women due to young age (< 50 yrs) or to positive margins. Eligibility criteria were: T<5 cm, age>18 years, no indication to lymph nodal RT (<3 positive lymph-nodes). Patients with history of contralateral breast cancer, multifocal disease, serious non-malignant disease, severe mental or physical disorders were excluded from the study. Physician-rated toxicity and cosmetic outcomes were prospectively assessed during yearly follow-up after radiotherapy.

Results: In the hypo fractionated group, the mean age was 69 years. 11% and 27% patients were affected by diabetes mellitus and hypertension, respectively. 13% had tumors that were 2 cm or larger in diameter; 9.7% had estrogen-receptor–negative disease and 24 % had high-grade disease. Pre-operative chemotherapy was administered in 9 patients; adjuvant systemic therapy and hormone therapy were given in 29 patients, while 9 and 96 patients received chemotherapy or hormone therapy alone, respectively. The mean follow-up was 12.2 months (range 4-24 months). The median time from surgery was 29 days, with overall median treatment duration of 22 days. At last follow up all patients are alive without local recurrence. By the end of RT 18% of the patients treated with hypofractionated RT developed no toxicity, while 55.7% showed grade 1 and 13.3% grade 2 acute skin toxicity. Only one patient experienced a grade 3 acute skin toxicity. In the control group, early G1 reactions were observed in 24 patients (42%); 19% of patients showed G2 acute toxicity and only one patient developed G3 acute reaction. Neither grade 4 skin ulceration nor soft tissue necrosis was observed. Late toxicity was assessed after 6 months from RT completion in 120/174 patients in the hypofractionation group and in 51/65 patients in the standard RT group. Late toxicity according to the RTOG criteria was observed in 9 patients (7.5%) in the hypofractionation group and in 4 patients (8%) in the conventional fractionated radiation group. The difference was not statistically significant. Cosmetic result was assessed and scored at the RT end and 6 months later: at last follow up, 71% of women in the control-group as compared with 68.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome.

Conclusions: Our results confirm the feasibility of the hypofractionated radiotherapy with 2,67 Gy per fraction to a total dose of 40,05 Gy in patients with breast cancer. All patients well tolerated the treatment with excellent compliance. If compared with conventional RT group, the hypofractionation not seems to increase the late toxicity. Long-term follow up is need to confirm this finding.

P083

SHORT-COURSE HYPO-FRACTIONATED PREOPERATIVE RADIOTHERAPY COMBINED WITH CHEMOTHERAPY IN RESECTABLE LOCALLY ADVANCED RECTAL CANCER COMPARED WITH LONG COURSE CHEMO-RADIATION THERAPY: LOCAL CONTROL AND TOXICITY

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Purpose: To evaluate clinical outcome after preoperative short-course radiotherapy (SC-RT) for locally-advanced resectable rectal cancer in terms of local control (LC) and toxicity. For comparison, a group of 30 patients with similar characteristics and treated with long course concomitant chemo-radiation (LCRT) therapy was retrospectively selected.

Methods: Patients with locally-advanced rectal cancer treated at our Hospital with pre-operative SCRT or LCRT were analyzed. SCRT consists of single doses of 5.0 Gy in four fractions within one week up to a total dose of 20 Gy. For LCRT, standard fractions of 1.8 Gy/d are given 5 times a week up to a total dose of 50.4 Gy. Radiotherapy-related toxicities will be assessed using the Radiation Therapy Oncology Group (RTOG) Common Toxicity Criteria. Toxicity will be evaluated weekly during the therapy and at follow-up 3 months, 6 months, 1 year, 2 years and 5 years after treatment by standard forms. Quality of life was evaluated in both groups with EORTC QoL (C-30 and C-38), Faecal Incontinence QoL, and International Index of Erectile Function questionnaires (IIEF).

Results: 67 patients treated with SCRT were analyzed and compared with 30 patients treated with pre-operative LCRT. The patients characteristics of the two groups of patients are similar, with no statistically significant difference as regard age, gender, PS score, presenting symptoms, site of tumor and tumor markers, pathological types, clinical staging and pathological staging. The median follow-up was 114 months (range 48-178) for the hypofractionated arm and 63 months (range, 36-92) for the standard arm. No statistically significant difference in terms of OS was observed between two groups. The tolerance of patients to hypo fractionated RT was not different from that for conventional radiotherapy. No treatment-related deaths were reported. In both group the toxicity observed was generally mild. The most relevant toxic reactions included rectal tenesmus, diarrhea and constipation. No patient interrupted the SC-RT or radiochemotherapy and delayed the operation because of these acute toxicities. Acute radiation toxicity occurred in 11 patients in arm 2 (LCRT), while there was no reported acute toxicity in arm 1 patients (SCRT), with a statistically significant difference. The most common one was radiation enteritis (mainly of grade II), followed by dermatitis (grade I), and lastly cystitis (grade I). Regarding chemotherapy toxicity, grades 3 and 4 haematological toxicity was not frequently encountered in our study, with the most common toxicities being grades 1 and 2 anemia (63%) and leucopenia (45%), none resulting in treatment interruption. Overall sphincter preservation rate was 75% and 87% in the Arm 1 and 2, respectively. Peri-operative mortality, within 30 days from surgery, was not observed. Early mild post-operative were observed in 16 patients (24%) in Arm 1 and in 6 (20%) in Arm 2, with no statistically significant difference. Late post-operative complications were observed in 5 patients (7%) in the SCRT group and 2 patients in the LCRT group. The quality of life analysis is in progress.

Conclusions: Preoperative SC-RT combined with chemotherapy for locally-advanced resectable rectal cancers was well tolerated. This treatment resulted in favourable LC, OS, low rates of toxicity and satisfying QoL when compared with long-course chemo-radiation therapy.

P084

LATE TOXICITY OF PREOPERATIVE RADIOTHERAPY FOR RESECTABLE RECTAL CANCER: COMPARISON OF TWO DIFFERENT FRACTIONATION SCHEDULES

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Purpose: This study aims to test the impact on late toxicity of hypofractionated neoadjuvant radiotherapy compared with conventional fractionation.

Materials and Methods: Between 2003 and 2011, 133 patients (pts)/347 rectal cancer pts referred for radiotherapy, 82 men and 51 women, median age 71 years (range 46-92), with biopsy proven stage II or III rectal adenocarcinoma, received 3D-conformal neoadjuvant radiotherapy as component of their treatment. For 102/133 pts (76.7%) treatment was chosen after discussion in Interdisciplinary Group of Care: SC-RT was indicated in node negative T3 tumours and in pts unsuitable for chemotherapy and/or for sphincter preservation. SC-RT (25 Gy in 5 fractions of 5 Gy with surgery within one week) was administered in 45 pts (33.8 %), while 88 pts (66.2%) received LC-RT (45 Gy in 25 fractions of 1.8 Gy and surgery after 6-8 weeks). Of them, 76 pts (86.4%) received concurrent chemotherapy (LC-CRT): oral capecitabine (825 mg/m2 twice daily for 7 days/week) in 4 pts (5.2%), continuous infusion of 5-fluorouracil (225 mg/m2 over 24 hours for 7 days/week) in 60 pts (79%), infused 5-fluorouracil (225 mg/m2/d) combined with oxaliplatin (60 mg/m2 weekly) in 12 pts (15.8%) included in a study protocol. All pts were staged according to national and/or international guidelines. All treatments were planned on computed tomography images. In LC-RT, clinical target volume included the pelvis with or without external iliac nodes, according to clinical stage. In SC-RT, the cranial border was at the level of S2-S3 inter-space. Abdominoperineal resection was performed in 20 pts (15%) after LC-RT and in 10 pts (7.5%) after SC-RT; 50 pts (37.6%) in LC-RT group and 25 pts (18.8%) of SC-RT group underwent anterior resection: 18 pts (13.5%) in LC-RT group and 10 pts (7.5%) in SC-RT received left hemicolectomy or abdominal transanal resection. Adjuvant chemotherapy was given 4-6 weeks after surgery, according to postoperative pathology. Pts were followed-up every 6 months for 2 years and then annually to assess postoperative complications and late toxicity (recorded according to RTOG toxicity scale).

Results: Median follow-up was 40 months (range 6-88) in LC-RT group and 30 months (range 8-60) in SC-RT group. All pts (100%) underwent surgery. Local relapse occurred in 12 pts (9%) of LC-RT and in 6 pts (4.5%) of SC-RT. Postoperative mortality occurred in 2 pts (1.5%), one for each group. One pt (0.75%) in SC-RT and 4 (3%) pts in LC-RT developed delayed wound healing.

Two pts (1.5%) in LC-CRT group had adhesive intestinal obstruction, while 6 pts (4.5%) (2 in SC-RT, 3 in LC-CRT and 1 in LC-RT) had anastomotic leakage. Late toxicity is shown in the Table 1.

Conclusions: Our results show that both SC-RT and LC-RT are well tolerated. In particular, SC-RT does not increase postoperative late complications and late toxicities. Further observation is required to better define the impact of preoperative radiotherapy schedules on survival, downstaging an local control to identify the best treatment modality.

Table 1.

	SC-RT (N=45)	LC-RT (N=88)	P (χ2)
Bladder toxicity ≥ grade 2			
≤ 12 months	1 (2.2%)	4 (4.5%)	0.25
> 12 months	1 (2.2%)	3 (3.4%)	0.25
Fecal incontinence			
≤ 12 months	0 (0%)	4 (4.5%)	0.10
> 12 months	0 (0%)	2 (2.2%)	0.25
Anastomotic stricture			
≤ 12 months	0 (0%)	1 (1.1%)	0.25
> 12 months	0 (0%)	1 (1.1%)	0.25
Bowel toxicity (grade 2)			
≤ 12 months	2 (4.4%)	4 (4.5%)	0.9
> 12 months	0 (0%)	2 (2.2%)	0.25

P085

ACUTE AND LATE TOXICITY USING TRADITIONAL IMRT VERSUS HYPOFRACTIONATED IMRT – SIB IN PROSTATE CANCER RADIOTHERAPY. A PRELIMINARY RESULTS

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Purpose: Whit IMRT is possible irradiated different targets at different dose concurrently. This treatment is simultaneous integrated boost (SIB). We used IMRT-SIB in order to give a hypofractionated dose. Hypofractionated radiotherapy (HR) deliver a larger biological-equivalent dose to the tumour than conventional treatment in 1.8–2.0 Gy fractions, whit lower incidence of late normal tissue reactions. We compare acute and late toxicity after conventional dose delivered with IMRT to the prostate *versus* IMRT-SIB delivered to the same target.

Patients and Methods: Between January 2005 and December 2011, 72 patients with localized prostate cancer were treated with IMRT at our Service; between January 2010 and December 2011, 61 patients with localized prostate cancer were treated with HR IMRT SIB. 72 patients were treated with IMRT to the prostate (80 Gy – 2 Gy fractions to prostate gland and 68 Gy – 2 Gy fractions to seminal vesicles). 61 patients were subjected to IMRT-SIB up to 70 Gy in 28 fractions (2.5 Gy/fractions – EQD2 79.9 Gy) to the prostate gland and 63 Gy in 28 fractions (2.25 Gy/fractions – EQD2 67.5 Gy) to the seminals vesicles. The dose is equivalent to 80 Gy in 40 fractions, based on the linear-quadratic model/ratio of 1.5 Gy. Acute and late gastrointestinal and genitourinary toxicity were scored using RTOG criteria. In the second group, late toxicity was analyzed only in the 12 patients treated in 2010 with HR IMRT - SIB.

Results: Acute GI toxicity ≥ grade 2 occurred in 23% of patients treated with IMRT and in 7% subjected to IMRT-SIB. Acute GU toxicity ≥ grade 2 was observed in 22% treated with IMRT and 3% IMRT/SIB. At 2 years, the incidence of late GI toxicity ≥ grade 2 was 18% for IMRT, and 12% for IMRT/SIB. We have not observed a late GU toxicity ≥ grade 2 with IMRT that with hypofractionated IMRT – SIB.

Conclusions: In conventional dose, boost adds a dose to the surroundings of the boost volume and increase the dose in the boost volume. The dose distribution from the large fields has a higher dose, which wholly or partly coincide with the target volume of the boost, whit SIB the large and the boost fields are planned simultaneously. SIB reduce the dose to rectal wall. NTCP for severe proctitis was reduced by almost a factor of 2 for all patients irradiated to 78 Gy. In our work IMRT-SIB enables dose escalation up to 79 Gy with a lower rate of acute and late gastrointestinal and genitourinary toxicity compared to IMRT.

P086

HYPOFRACTIONATED RADICAL RADIOTHERAPY IN ELDERLY PATIENTS WITH MEDICALLY INOPERABLE STAGE I–II NON-SMALL-CELL LUNG CANCER: A CORRELATIONAL ANALYSIS BETWEEN TOXICITY AND TUMOR VOLUME

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Aims: For larger or centrally located tumors as well as for subjects with lymph nodes involvement SBRT may be of limited valiance. In this population the optimal radiotherapeutic regimen has not been defined. Based on these considerations, we undertaken a study in order to measure the performance of a hypofractionated regimen of 60 Gy delivered in 20 daily fractions. The primary purpose of study was to estimate the local tumor control at 2 years as well as the modifications in the lung function parameters at 6 and 12 months.

Methods: We described the results of a hypofractionated regimen (HFRT) in a cohort of elderly patients with stage I–II non-small-cell-lung cancer (NSCLC), tumor size≥3 cm and ineligible for surgery. HFRT was delivered

in 20 daily fractions of 3Gy per fraction with a total dose of 60 Gy. The median PTV was 145 cm3. a correlational analysis between toxicity and tumor volume was performed by ROC curves and sesitivity analysis.

Results: The local tumor control was 63.9% at 2 years. The incidence of distant recurrence rate at 2 years was 50%. The overall-survival (OS), the cause-specific survival (CSS) and the disease-free-survival (DSF) at 2 years were 55.6, 57.1, and 38.9%, respectively. The median OS, CSS, and DFS was 25.4 (CI 95% 21.7–32.9), 26.7 (CI 95% 22.5–33.5) and 23.4 months (CI 95% 18.6–30.1), respectively. The two clinical parameters with a positive influence on OS were a KPS≥90 (HR 1.16; p = 0.013) and tumor size≤4 cm (HR 0.763; p = 0.011). No significant change in lung function parameters was measured at 6 and 12 months. ROC curve analysis indicated that for PTV volume greater than 260 mm3 a significant (p=0.025) correlation with grade 2 acute toxicity was documented. Differently, no critical volume was documented for late toxicity.

Conclusions: For patients with larger or centrally located tumors as well as for subjects with lymph nodes involvement SBRT may be of limited valiance. Although the performances of our regimen were lower than the ones achieved by SBRT, our therapeutic option may offer a lower incidence of complications against a satisfactory local tumor control.

P087

DOSIMETRY ASSESSMENT FOR LONG TERM COSMETIC OUTCOME AND LATE SKIN TOXICITY AFTER 3D-HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY IN EARLY BREAST CANCER: OUR EXPERIENCE

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Aims: We evaluated retrospectively the long term effects of WB-hypo on cosmetic outcomes and late skin toxicity related to some dosimetric parameters suitable from 3D planning.

Materials and Methods: We reviewed the data from 400 consecutive early breast cancer patients (mean age 75 years) after breast conservative surgery who entered in the adjuvant WB-hypo RT schedule from 2004 to 2011. Primary selection criteria were below: a) age > 60yrs; b) pT1-2 pN0 M0 breast cancer; c) breast conserving surgery. All patients (pts) received adjuvant systemic therapy according to the prognostic factors. PTVbreast (br) consisted of the residual breast parenchyma plus margins. The prescribed dose was 42.56 Gy in 16 fractions. Cosmesis was graded according EORTC cosmetic rating system while late radiation toxicity was assessed with the RTOG/EORTC late skin and subcutaneus radiation toxicity scale v.2.0. Patients whose breast separation along the central axis even exceeded 25 cm were included (25brs). All patients were evaluated at 1 month after radiotherapy, every 5 months for 5 years and anually thereafter. The two-tailed Fisher exact-test was used to compare outcomes between the study groups.

Results: During the dosimetric evaluation 187/400 pts were excluded from WB-hypo because on planning assessment hot spots over 110% of the PD to > 10% of PTVbr could be predictive of a dangerous double-trouble effect according NCTP model. These patients were treated with standard fractionation (STD-A group). The remaining 213 pts received the hypofractionation (HYP-B group). Patients with breast separation > 25 cm were 85/187 in the A group and 64/213 in the B group. Cosmetic results and late toxicity were analyzed in pts with greater than 4 years follow-up: 83/187 in the A group and 150/213 in the B group (40/83 pts in the A group and 50/150 pts in the B group had breast separation > 25 cm). Late skin and subcutaneus toxicity for the A group was recorded in 20/83 pts (24%): G2-G3 toxicity in 8 pts (9.6%) and 12 pts (14%). In the subset group A25br G3 toxicity occurred in 10 pts with mean breast volume 1800 (1500-2100). Late skin and subcutaneus toxicity for the B group was recorded in 15/150 (10%); G2-G3 toxicity in 10/15 (7%) and 3/15 (2%) pts. In the subset B25br G3 toxicity occurred in 3 pts with mean volume breast 1500 (1330-2000). Cosmetic outcome was evaluated in the A group excellent or good in 50 pts (61%), fair 20 pz (24%), poor in 13 pz (15%). In the B group it was excellent in 110 pts (73%), fair in 35 pts (23%) and poor in 5 pts (3%). The difference in worse cosmetic outcome was p< 0.05 for the A group. For worse skin toxicity a statistical significant difference (p= 0.03) was found for the A group altough the standard RT delivered. For pts with breast separation > 25 cm no significant difference was found for worse skin toxicity (p= 0.42). In the multivariate analysis the mean volume of PTV breast > 1400cc, the V110 > 10% of the PTVbr were related to G3 late skin toxicity (p= 0.02 for the A group).

Conclusions: Up to now there are no data on parameters predictive for late normal tissue toxicity and cosmetic outcome in WB-hypo radiotherapy. In our experience V110 > 10% of the PTVbr and a mean volume PTV breast > 1400cc were 3D dosimetric criteria useful for selection of pts eligible to WB-hypo RT. Better-powered studies and a longer follow-up are necessary to confirm the role of these findings.

P088

HYPOFRACTIONATED CONFORMAL RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER WITH LOW-RISK NODAL INVOLVEMENT: TOXICITY AND OUTCOME FROM A DOSE ESCALATION PHASE STUDY II

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Introduction: A consensus is emerging in the literature that the ∂/ß ratio for prostate cancer ranges from 1 to 4. These values are either equal or less than the ∂/ß ratio for the rectal mucosa where the most significant late toxicity

occurs. This lower ∂/ß ratio for prostate cancer than for the surrounding late-responding normal tissue creates the potential for therapeutic gain. Appropriately designed schedules using large fractions could result in increases in biochemical control with no increase in late sequelae.

Pourpose: Based on these hypothesis we propose a phase II protocol to assess quality of life outcomes, acute and late toxicity of hypofractionated regimens with three-dimensional conformal radiotherapy and Image-guided radiotherapy.

Materials and Methods: Between 2008 and 2011, 41 prostate cancer patients with a nodal involvement risk <20% (Roach index) have been treated to the prostate and seminal vesicles with 70 Gy (2.5 Gy/fraction five weekly) and an overall treatment time of 5.5 weeks. All subjects underwent ultrasound-guided transrectal placement of 3 gold intraprostatic fiducial markers. Daily on-line image guidance adjustments were made according to the location of the fiducial markers. All patients received neoadjuvant and concomitant androgen deprivation therapy (ADT). Acute and late genitourinary (GU) and gastrointestinal (GI) toxicities were scored according to the Radiation Therapy Oncology Group (RTOG) grading system. Median follow-up was 12 months (range, 6-30 months).

Results: Fiducial marker placement proceeded without complications. Acute genitourinary(GU) toxicity manifested in 12 patients (28%) as grade 1 or 2 uretritis. One patients developed urinary retention, requiring catheterisation; no patient had episode of gross hematuria. No cases of acute gastro intestinal (GI) toxicity grade 2 were observed. One patient present GI toxicity grado 2 according to the RTOG/EORTC score. No significant change in the International Prostate Symptom Score at 3 months in patients with available follow-up was found. The actuarial biochemical relapse-free survival was 98%.

Conclusions: In patients with localized prostate cancer, acute and late toxicity were minimal after dose-escalation administering five-weekly 2.5 Gy to a total dose of 70 Gy, with 3DCRT. Further prospective trials are warranted to further assess the best fractionation schemes for these patients.

P089
LATE TOXICITY IN LOCALIZED PROSTATE CANCER: HYPOFRACTIONATED *VERSUS* CONVENTIONAL RADIOTHERAPY

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Introduction and Aims: Although hypofractionation has been used in the past in the treatment of prostate cancer, some concern exists regarding the potential late toxicity that could be generated to the normal tissues using such hypofractionated regimens. The use of hypofractionation approach is based on the assumption that prostate cancer is highly responsive to fraction size with a low a/b ratio. Our study aims to compare late gastrointestinal (GI) and genitourinary (GU) toxicities with a randomized analysis of hypofractionated *versus* conventional radiotherapy for localized prostate carcinoma.

Patients and Methods: This analysis was designed to randomize 40 patients with localized prostate cancer treated with radical radiotherapy at the Radiotherapy Department of Foggia from September 2008 to July 2009. Patients were stratified according to stage, Gleason score and prostate-specific antigen level. Most of patients (77.5%) were classified at intermediate-risk according to Partin score while 22.5% were classified at low-risk. The intermediate-risk group received hormonal therapy started between one and three months before radiotherapy and continued during the entire radiotherapy course. Radiotherapy was delivered using four to six coplanar 10-18 MV photon beams with a dose of 72-78 Gy in 7-8 weeks at 2.0 Gy per fraction (Arm A, conventional fractionation) for the randomized 20 patients *vs*. 64.8-70.2 Gy in 5 weeks at 2.7 Gy per fraction (Arm B, hypofractionation) for the randomized 20 patients. Gastrointestinal (GI) and genitourinary (GU) toxicities were scored according to the RTOG/EORTC system. Efficacy of treatment, based on clinical, radiologic and prostate-specific antigen data, was also evaluated every 3 months for 2 years and every 6 months subsequently.

Results: Median follow-up was 37 months. All patients received the prescribed dose without interruption. No statistical differences were observed regarding GI and GU late toxicities in both groups since 35% of patients reported frequency of urination or nicturia in hypofractionation group *vs* 40% in conventional group. None of the patients experienced grade 3 or 4 toxicity. Only one patient in the hypofractionated arm presented an actinic proctitis, moreover he suffered from a pre-existing hemorrhoidal disease.

Conclusions: No statistical significant differences were observed in late toxicities between hypofractionated and conventionally fractionated radiotherapy. Our study confirms that hypofractionated radiotherapy is a promising regimen for localized prostate cancer and that linear-quadratic formula is a reliable radiobiological model. We can conclude that the hypofractionated schedule is well tolerated and the incidence of clinically significant late GI and GU toxicity after conventional and hypofractionated radiotherapy appears to be similar. Longer follow-up is necessary to better evaluate the efficacy of the two regimens.

P090
HYPOFRACTIONATED REGIMEN IN PROSTATE CANCER PATIENTS. A MULTICENTER STUDY

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Introduction: To evaluate feasibility and toxicity of hypofractionated regimen in the treatment of prostate cancer using 3D conformal technique or IMRT.

Materials and Methods: Patients with localized pro-

state cancer were treated with hypofractionated regimen of 2,7 Gray die in 24 fractions with a total dose of 64,8 Gray on the prostate. Seminal vesicles were put out of the fields when a total dose of 45,9 Gray was delivered. Dose constraints were: rectum: V50 < 33%; femoral heads: V36 < 50%; bladder V59 < 50%. In all patients toxicities were evaluated weekly during treatment.

Results: From 22.04.10 to 06.12.2011 a total of 25 patients entered on the study. Median age was 77 years old (range 61-86). All had adenocarcinoma with a median Gleason Score 6 (3+3) (range 5-9). A median value of PSA at diagnosis was 11,25 (range 4,4- 28,20). 14 patients were submitted to total androgenic block. Late genitourinary toxicity was: G0 (20 pts: 80%), G1 (5 pts: 20%). Eight patients (32%) had G1 rectal toxicity and G3 toxicity was reported in two patient (8%).

Conclusions: The hypofractionated regimen used in this study seems to be feasibile with very low toxicity profiles. Longer follow-up is necessary to evaluate long term results.

P091

PROPHILACTIC USE OF D-MANNOSE AND CRANBERRY EXTRACT IN THE PREVENTION OF RADIO-INDUCED ACUTE AND LATE CYSTITIS DURING CONVENTIONAL AND HYPOFRACTIONATED RADIOTHERAPY

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Aims: The major criticism of radiotherapy on the pelvis area is the presence of many dose-limiting organs and structures: the rectum, the urinary bladder and the small bowel. In the bladder the main side-effect is acute cystitis, that can lead to symptoms of late toxicity, with persistent hemorrhage, fibrosis and loss of contractile capacity. Natural substances from cranberry and multivitamins have demonstrated their usefulness in the prevention of radio-induced bladder toxicity. CYSTOMAN100 is a natural food vitamin from D-Mannose, a concentrated extract from cranberry and Vitamin C. In this paper we present our experience using Cystoman 100 to prevent bladder radio-induced toxicity in patients irradiated for pelvic tumours (rectal, prostate and gynaecological), with conventional or hypofractionated radiotherapy,.

Materials and Methods: From October 2009 to November 2011, Cystoman100 was administered to 46 consecutive patients treated on the pelvis: all of them were instructed to assume the drug from the very first session until 30 days after the end of radiation course, with a prophylactic intent. The patients were examined weekly during radiotherapy and then monthly for the first 6 months. Two groups of patients affected by prostate (22) and rectal tumours (19) were analyzed separately.

Resutls: All the 22 prostate cancer patients underwent hypo-fractionated regimen (3.10 Gy/fr/4 fr per week with total dose of 62 Gy). Regarding the acute toxicity, in this group 10 patients (45,4%) did not report any symptoms; for the late toxicity,12 (55,5%) were free of symptoms. In the cohort of 19 patients with rectal tumours, 17 underwent pre-operative neo-adjuvant radio or chemo-radiotherapy and 2 received post-operative adjuvant chemo-radiotherapy. Of the former, 11 patients underwent radiotherapy with conventional fractionation (50,4 Gy/28 fr), with concomitant i.v. 5-FU or oral Capecitabine. The other 5, deemed "unfit" because of general conditions, age and/ or co-morbidities, received hypofractionated radiotherapy only (25 Gy/5 fr). Of these 19 patients 8 (42,1%) did not develop any acute toxicity and none of them presented late toxicity during the follow-up. All the examined patients completed the radiotherapy cycle and no grade 4 acute or late bladder toxicity was observed.

Conclusions: The prophylactic use of Cystoman100 for the prevention of actinic cystitis in patients undergoing pelvic radiotherapy was satisfactory and recommended. The drug was highly tolerable, allowing the completion of the radio or radio-chemotherapy course within the planned time As it has been demonstrated that any interruption is related to worse results in terms of local control, there's the possibility that this continuative treatment modality strongly affects tumour control. Longer follow up times are necessary to confirm these data that need to be validated in multi-centric studies.

P092

FEASIBILITY AND EFFECTIVENESS OF HYPOFRACTIONATED RADIOTHERAPY IN VERY ELDERLY PATIENTS

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Aims: As life attendance is strongly increasing in last decades, cancer incidence in elderly is becoming a new social problem, due to the lack of evidences about the effectiveness and tolerance of cancer therapies in this population. Infact the elderly are traditionally excluded from clinical trials and often sub-treated for the supposed reduced normal tissue tolerance to cancer therapies with aging. Radiotherapy in particular is badly used in elderly patients and, in any case, with very few fractions, non-curative schemes and simple planning modality. The aim of this study is to analyze the impact of age on the compliance and the tolerance of radiotherapy in a cohort of 53 patients oldest than 85 years treated in our Institution with curative or palliative intent from January 2008 to April 2012.

Materials and Methods: Several variables were analyzed, referred both to patients (age, sex, cancer site, performance status, co-morbidities, self activity) and to treatment (aim, fractionation, total dose). Radiotherapy related toxicity and subjective response to irradiation were reported.

Results: From January 2008 to April 2012 in our Institution were treated 46 patients, with 53 treatments; 24 of them were female and 22 male. The site of treatment was: bone metastasis in 13, skin carcinoma in 5, bladder cancer in 5, ano-rectal tumours in 8, breast carcinoma in 7, lung cancer in 5, head and neck tumour in 4, brain metastasis in 2, esophageal cancer in 2 and uterus cancers in 2 patients. The median age was 86 years (range

85-102). The main co-morbidities were cardio-vascular disease in 60% of the patients, obstructive pulmonary disease in 40%, diabetes in 20%, brain disorders in 30% and other co-morbidities in 10% of them. All patients were treated with hypofractionated regimens with dose/fr from 2,20 to 8 Gy. Total doses ranged from 45 to 70 Gy in the curative setting (12 patients mainly breast and head and neck tumors) and from 20 to 30 Gy in the palliation. The radiotherapy compliance was high with 66% of treatments completed in the planned time and 76% of them executed in outpatient regimen. Toxicity was very limited (15%) for the most of patients treated with a palliative intent, while it was high in patients with head and neck tumors, submitted to curative treatment. Palliative response was evident in 34/39 courses, with decrease of analgesic drug dosages and a positive impact on quality of life.

Conclusions: Radiotherapy is an important resource in the management of very old patients affected by cancer, particularly in a palliative setting. In our experience it was particularly effective for bleeding, obstructive symptoms and bone metastasis pain control. When used with curative intent it was well tolerated in breast tumors and in early stage lung cancer who underwent to stereotactic radiotherapy. For this reason radiotherapy with curative intent should not be withheld in selected elderly patients.

P093
LATE TOXICITY OF HYPOFRACTIONATED *VERSUS* CONVENTIONAL WHOLE BREAST IRRADIATION

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Purpose: Radiation therapy after lumpectomy is an integral part of breast-conserving therapy for early stage breast cancer. Conventionally, the standard schedule used worldwide is 60 Gy in 30 fractions in a 6 weeks time, so a great variety of hypofractionated schedules has been proposed in the last years to shorten the overall treatment time. The aim of this study is to assess short-term late toxicity of hypofractionated whole breast irradiation in a mono-institutional series.

Materials and Methods: From September 2010 to April 2012 we treated 60 consecutive patients with invasive early stage breast carcinoma after conservative surgery with a hypofractionated schedule of three-dimensional conformal external beam radiotherapy. The whole breast received 42.56 Gy in 16 fractions over 22 days while the lumpectomy cavity was treated with a sequential boost of 10 Gy in 4 fractions. PTV coverage ranged between 95% and 107% of the prescription dose (cut-off for hypofractionation in our Institution). For comparison, we retrospectively selected a group of 60 patients with similar characteristics treated with conventional daily fractionation of 2 Gy to a dose of 50 Gy in 25 fractions, followed by a 10 Gy boost. Early and late skin toxicity were scored according to the RTOG/EORTC criteria in both groups of patients.

Results: At a median follow-up of 12 months (range 20-2), all patients are alive and disease-free. 15% of patients in the hypofractionated arm underwent adjuvant chemotherapy before starting radiation therapy *vs* 25% in the conventional group; systemic hormone therapy was administered in 66% and 76% respectively while adjuvant trastuzumab in 3% and 6%. At the end of treatment (no breaks due to toxicity in both two groups), in the hypofractionated group 30% of patients presented grade 1 acute dermatitis (*vs* 12% in the conventional group), 10% had grade 2 (*vs* 28.3% in the conventional fractionaction); no one showed grade 3 toxicity (*vs* 5% in the conventional arm). At 6 months we observed 1.6% of grade 2 skin toxicity (moderate edema) in both two groups. At >12 months, with 25 patients assessed, we didn't find any significant skin toxicity.

Conclusions: Our results showed a good feasibility of the accelerated hypofractionated schedule in terms of reduction of overall treatment time with similar short-term late toxicity compared to the conventional fractionation. A longer follow-up is necessary to assess long-term toxicity.

P094
ACCELERATED HYPOFRACTIONATED RADIOTHERAPY *VERSUS* CONVENTIONAL FRACTIONATION IN THE TREATMENT OF PLEURAL MESOTHELIOMA: PRELIMINARY TOXICITY DATA

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Aims: To compare the toxicity data from two different types of radiotherapy treatment for pleural mesothelioma; accelerated hypofractionated radiotherapy for patients undergoing pleurectomy/decortication (P/D) and conventional fractionation radiotherapy for those submitted to extrapleural pleuropneumonectomy (EPP).

Materials and Methods: From January 2008 to December 2011, we analyzed a population of 21 patients with pleural mesothelioma (T1/4, N0/2, M0). Nine patients underwent pleuropneumonectomy and adjuvant conventional fractionation radiotherapy while 12 were submitted to pleurectomy/decortication and adjuvant radiotherapy with accelerated hypofractionated radiotherapy. All patients were treated using helical tomotherapy. Cisplatin-Pemetrexed-containing chemotherapy (4-6 cycles) was administered in 17 cases. Respiratory functional examinations were performed before and after therapies.

Results: The dose prescription was 50/54 Gy in 25/27 daily fractions after EPP and 25 Gy in 5 daily fractions at the reference isodose (60-70%) with an increasing dose inhomogeneity up to 37.5-40 Gy inside the reference isodo-

se for those undergoing P/D. Mean follow up was 16 months (range 3-48). The dose constraint used in the opposite lung was V5/5 Gy for both treatments (Figure 1 and Figuere 2). Acute and late toxicity was recorded according to the RTOG scale (Table 1 and Table 2). No cases of grade 4/5 pneumonitis were observed. There were no toxicity-related deaths. G1/G2 dyspnea, cough and pain were recorded as acute toxicity, while G2 dyspnea and cough were registered as late toxicity in patients receiving hypofractionated radiotherapy.

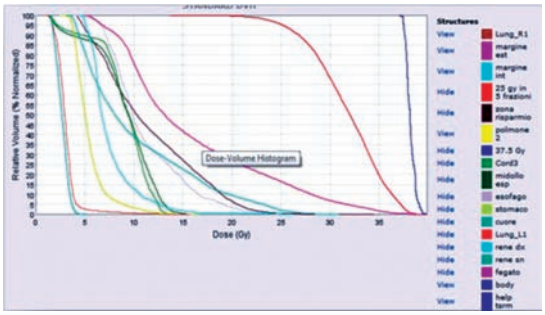

Figure 1. DVH accelerated hypofractionation.

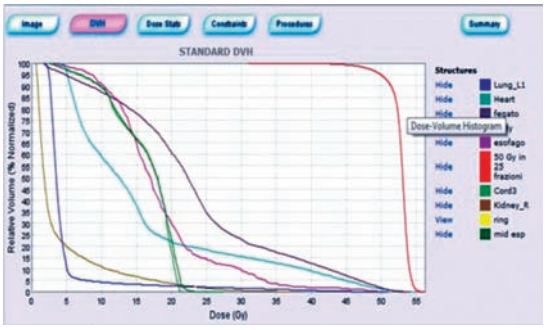

Figure 2. DVH conventional fractionation.

Table 1. Hypofractionated radiotherapy.

Toxicity (RTOG scale)	1		2		3-4	
	No.	%	No.	%	No.	%
Dyspnea	8	67	4	33	-	-
Cough	5	42	-	-	-	-
Fever	2	17	-	-	-	-
Esophagitis	2	17	-	-	-	-

Table 2. Conventional fractionation.

Toxicity (RTOG scale)	1		2		3-4	
	No.	%	No.	%	No.	%
Dyspnea	6	67	3	33	-	-
Cough	3	33	-	-	-	-
Fever	-	-	-	-	-	-
Esophagitis	2	22	-	-	-	-
Fatigue	7	78	-	-	-	-

Conclusions: Our results show that hemithorax adjuvant radiotherapy is feasible after EPP but also total pleural irradiation in lung presence using accelerated hypofractionated radiotherapy with helical tomotherapy is feasible and safe. Toxicity was acceptable for both treatment schedules. It is important to respect established dose constraints to organs at risk (1) and especially to the controlateral lung (2).

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P095

ADJUVANT HYPOFRACTIONATED RADIATION THERAPY FOR DCIS AFTER CONSERVING SURGERY: EXPERIENCE OF U.O. RADIOTERAPY OF PISTOIA

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Aims:To evaluate the incidence of locoregional recurrence (LRR) and the cosmetic results in a group of patients with breast cancer treated with a hypofractionated schedule of adjuvant radiotherapy after conservative surgery.

Materials and Methods: In total, 107 patients with pTis breast cancer underwent radiotherapy treatment after conservative surgery at the Radiotherapy of Pistoia Hospital. The dose delivered was 44 Gy (2.75 Gy daily fraction). The tumour bed boost (10-15 Gy) was given in 20,6% of patients (22/107) by electrons with a hypofractionated schedule (250 cGy daily fraction).

Results: After a median follow up of 6.6 years (29 – 176 months), 2.1% of patients (2/107) had breast relapse. No patients developed nodal recurrence (supraclavicular, axillary and internal mammary nodes). Considering the late toxicity, we found that 97 (90,7%) patients had grade 0 or grade 1 late toxicity, 8 patients (7,5%) had grade 2 late toxicity. No patients developed grade 3/4 toxicity.

Conclusions: Hypofractionated RT in DCIS patients resulted in an effective treatment in terms of local control with good cosmetic results.

P096

HDR BRACHYTHERAPY IN SKIN CANCERS: TOXICITY AND OUTCOME OF IPOFRACTIONATED *VERSUS* CONVENTIONAL SCHEDULE

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Aims and Backgrounds: Brachitherapy in skin cancers is a interesting alternative to conventional radiotherapy

because offers personalized and collimated treatment (also in multisite cancers) and due to ipofractionation used in our Center the treatment time is shorter than conventional RT. Otherwise the leterature data for these treatment are few. So we performed this rewiew to evaluate outcome and toxicity.

Methods: From August 1999 to September 2010, 118 consecutive pts. with skin cancer (20% squamous cell) (5% with cancer larger >4 cm) were enrolled in this perspective study: HDR treatment consisting of twice-daily fractionation of 350 cGy each, 6 hour apart final dose delivered 49 Gy as esclusive modality or as postoperative treatment for positive margins. To provide the maximum coverage of the tumor the implants were performed with afterloading spaced (at least 1 cm) catheters embedded in personalized surface molds or interstitial implant both planned with a semi-3-D technique aided by simulator. Radiopaque markers for target definition around the cancer were obbligatory (minimum space 5 mm maximum 10 mm). So implant dosimetry was performed as 100% of prescription at each skin marker. The follow up consisted in clinical examination of each cancer site. We studied the pts. with a minimum follow up of 5 years. For failure cases a rewiew of dosimetry was performed.

Results: The eligible pts. were 93, the median follow up 84 months (range 60-96). The cosmetics results were poor in 6% of cases; the only important toxicity was a telangectasia of the skin. The local relapse were 10% (9 cases) especially for bulky cases (6), for 3 of these cases a full-dose reirradiation was performed after the dosimetry rewiew without severe toxicity. The cases of missing target 3% (3 cases). The BED resulted in 65 Gy for final dose of 49 G.

Conclusions: This treatment schedule is effective as the conventional schedule and can be used in skin cancers with a good compliance of the treated pts. (seven days for total treatment). HDR brachytherapy is a tecnique with a good learning curve that offers personalized treatments without radiation damage to OAR (as eye) in alternative to conventional radiotherapy. Actually this schedule is the standard for skin cancer in our Center.

P097
LATE TOXICITY OF HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY AFTER CONSERVATIVE SURGERY

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Purpose: To evaluate late toxicity, in relation to dosimetric dose distribution of a hypofractionated schedule for whole breast radiotherapy (RT) with a concomitant boost to the tumour bed after conservative surgery of early breast cancer.

Materials and Methods: From Dicember 2010 and Dicember 2011, 62 breast cancer patients (4 bilaterals) pT1- pT3 pN0-N1, received hypofractionated whole breast RT after conservative surgery. Median age was 54 (range 37-76). Treatment plans with opposing tangential fields (6/15MV) were generated according to ICRU criteria on contiguous 5-mm axial CT images obtained in supine position that included the entire breast, heart and lungs. Prescribed dose to the clinical target volumes (CTV) was 45Gy in 20 daily fractions plus a concomitant electron boost delivered to the tumor bed once a week to a total dose of 5Gy in 4 fractions. Treated volume (TV), considered as the volume included in the 95% isodose, was contoured. Volume and dose volume histograms (DVH) were evaluated for CTV and TV. Late toxicity was evaluated using the SOMA-LENT scoring system and the numeric rating scale (NRS) to evaluate subjective symptoms starting 6 month after the end of RT (range 6-16 month).

Results: The rate of treated breasts presenting with any late toxicity was 59%. Fibrosis, breast oedema, teleangectasia and lymphedema were observed in 67%, 31%, 3% and 5%, respectively. No G4 and only 1 G3 lymphedema was reported. Patients were also evaluated for subjective symptoms. Breast pain, hitching and burning sensation were reported by 44%, 13% and 21% respectively.Mean CTV and mean TV were 745cc and 1207cc in patients with late toxicity and 510cc and 918cc in those without any sign or symptom. In patients with toxicity maximum dose was found more frequently in the region of the submammary fold outside the CTV (33%) while it was inside the CTV (37%) for patients without any toxicity. Morover the latter subgroup presented a lower percentage of maximum dose on the skin (15% *vs* 40%). TV mean dose was greater than CTV mean dose in 44% of patients with late toxicity *versus* 15% of the other group.

Conclusions: In our experience late toxicity of this hypofractionated schedule do not exceed data reported in literature for conventional fractionation. Our results suggest a relationship between the size of irradiated volumes, localization of maximum dose and toxicity. We also observed that a higher mean dose in the TV than in the CTV could lead to an increased occurrence of late toxicity.

P098
RECTAL TOXICITY 7 YRS AFTER HIGH-DOSE RT FOR PROSTATE CANCER: CLINICAL AND DOSIMETRIC PREDICTORS

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Purpose: To evaluate the prevalence of late rectal bleeding (lrb) and of late fecal incontinence (linc) after high-dose radiotherapy (RT) in prostate cancer patients (pts)

accrued in AIROPROS0102 trial (RT doses: 70-80Gy, 1.8-2Gy/fr, median dose 74Gy) and to model the relationship between lrb/linc and clinical/dosimetric factors.

Materials and Methods: Self-reported questionnaires of 515 pts with a minimum f-up of 6yrs (median 7yrs) were analyzed with respect to lrb and linc. The correlation between pre-treatment morbidities, hormonal therapy, drug prescription, presence of diabetes or hypertension, abdominal surgery prior to RT, presence of G2-G3 RTOG acute toxicity, presence of G2-G3 acute fecal incontinence, pelvic nodes and seminal vesicles irradiation, mean rectal dose, dose-volume histograms constraints (from V20Gy to V75Gy) and lrb/linc was investigated by uni- and multivariate (MVA) logistic analyses. 347/515 pts had at least 3 toxicity questionnaires in the first 36 mos after the end of RT. Correlation between the mean score of fecal incontinence in the first 36 mos and linc at 7 yrs was also investigated.

Results: 32 G1, 2 G2 and 3 G3 lrb were registered. 50 G1, 3 G2 and 3 G3 linc were reported. Lrb (grade≥1) was only correlated to V75Gy (continuous variable): p=0.02, OR=1.07. The prevalence of grade≥1 lrb at 6 yrs was significantly correlated with incidence of G2-G3 lrb in the first 3 yrs after RT treatment: 42.3% in pts with G2-G3 bleeding in the first 3 yrs *vs* 5.6% in G0-G1 pts (p<0.0001, chi-squared). Linc (grade≥1) was correlated to multiple variables. In MVA, V40Gy (continuous variable, p=0.09, OR=1.015), presence of abdominal surgery before RT (p=0.004, OR=4.7), presence of haemorrhoids (p=0.008, OR=2.6) and presence of G2-G3 acute incontinence (p=0.007, OR=4.4) resulted to be correlated to linc. The prevalence of linc≥1 at 7 yrs was significantly correlated with the mean incontinence scores in the first 3 yrs after RT treatment: 37.3% in pts with mean score ≥0.5 *vs* 10% in pts with mean score < 0.5 (p<0.0001, chi-squared).

Conclusions: A fraction of pts is still experiencing rectal toxicity symptoms 7 yrs after RT: 7.2% lrb and 10.9% linc. Prevalence of toxicity at 7 yrs is significantly correlated to incidence in the first 3 yrs after RT treatment, this is an indication of a chronicization of symptoms, with late fecal incontinence playing the major role.

P099

TOMOTHERAPY *VS* VMAT *VS* TANGENTIAL FIELDS TO REDUCE CARDIOVASCULAR COMPLICATIONS IN LEFT BREAST CANCER PATIENTS

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Purpose: Radiation therapy (RT) to the breast has been shown to increase cardiovascular mortality in left breast cancer patients (1-2). The present study is a critical evaluation of 3 different radiotherapy techniques. Coverage of the left breast and the dose volume histogram (DVH) of the myocardium, left anterior descending coronary artery, diagonal arteries, right breast, and left lung are considered.

Patients and Methods: A patient with left breast cancer and cardiopathy underwent conservative surgery and adjuvant chemotherapy and was then referred to our Unit for adjuvant RT. We matched the cardiac multi-slice computed tomography (CT) scan with a routine planning CT scan. The coronary arteries, myocardium, left lung, and right breast were identified as organs at risk (OAR). A total dose of 47.25 Gy in 21 daily fractions was prescribed. Three different radiotherapy techniques were trialed: (1) tangential opposed fields and the Pinnacle treatment planning system (TPS), (2) intensity modulated arc therapy (IMAT) and correlated TomoTherapy TPS, and (3) volumetric modulated arc therapy (V-MAT) and the CMS Monaco TPS.

Results: Although the target dose coverage was satisfactory for all three techniques, a greater dose uniformity was obtained using tomotherapy (mean dose 48.52 +/- 1.17) (Table 1).

Table 1.

	Tangential Opposed	IMAT	VMAT
	Mean Dose/ Maximum Dose (Gy)		
Target	48.2/53.2	48.5/52.3	47.5/52.3
Diagonal arteries	1.8/6.4	5.6/7.7	1.9/**3.8**
Left anterior descending artery	3.4/17.9	6.3/13.2	4.3/**9.0**
Myocardium	1.9/41.8	5.5/31.1	2.0/**26.7**
Right breast	0.1 /1.0	4.1/16.3	0.1/**1.3**
Left lung	3.4/50.0	5.8/48.6	3.8/**46.9**

Conclusions: Rotational techniques allowed us to reduce the irradiated heart volume because of the higher conformity to the target *vs* tangent fields. The V-MAT technique, which enabled us to select the best width for modulated arcs, would seem especially suitable for the treatment of left breast cancer.

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P100
THE EVALUATION OF THE PSYCHOLOGICAL DISTRESS IN ELDERLY BREAST CANCER PATIENTS RECEIVING ADJUVANT NORMOFRACTIONATED OR HYPOFRACTIONATED RADIOTHERAPY

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Purpose: Epidemiologic reviews have shown that elderly breast cancer patients treated are less likely to receive the standard locoregional treatment, especially radiotherapy. The aim of this study is evaluate the psychological impact in elderly breast cancer patients receiving adjuvant normofractionated or hypofractionated radiotherapy.

Materials and Methods: Between 2010 and 2011, 8 women (median age, 81 years) with non-metastatic, Stage T1 or T2 tumours, were treated with breast-conserving surgery and adjuvant RT. They underwent wide tumour excision and lymph node dissection, followed by adjuvant RT. Four patients received hypofractionated radiotherapy. They received either a HF-RT schedule, which delivered a total dose of 42.5 Gy (17 fractions) to the whole breast , with no subsequent boost. The others four patients received standard three-dimensional conformal RT (3D-CRT), 50-50.4 Gy/30-33 fractions. All the patients received a test PDI (Psychological Distress Inventory) to evaluate the psychological impact of treatment and recognise the needs. The PDI test consist in 13 item. The test was administrated twice, at the start of treatment and at the end. For a score over 35 the test was considered positive for distress.

Results: All the patients who received hypofractioned radiotherapy obtained a score under 35 and they no needed psychological support. The patients who received standard RT registered a score up 35 and underwent to psychological evaluation.

Conclusions: The hypofractionated radiotherapy might be an acceptable alternative to 3D-CRT for treating the elderly. It provided similar results in terms of relapsed free survival, in terms of toxicity compare to standard adjuvant whole breast radiotherapy and should considered also for quality of life and patient's wishes.

P101
HYPOFRACTIONATED VERSUS CONVENTIONALLY FRACTIONATED IN PROSTATE CANCER. ANALYSIS OF LATE TOXICITY IN 3DCRT

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Introduction: Because alfa/beta ratio of prostate cancer is lower in the tumor than in the surronding late responding normal tissues, the equivalent total dose delivered to the former will translate in a significant reduction of the total equivalent 2 Gy dose absorbed by the latter, with a potential decrease in the late side-effects. The aim of the study is to estimate rectal and urinary tract toxicity when prostate and seminal vesicles receive hypofractionated (310 cGy die) *versus* conventionally fractionated 3DCRT.

Materials and Methods. Seventy consecutive patients were treated with hypofractionated 3DCRT 310 cGy die 62 Gy on prostate and vesicles from 09/2009 to 12/2010. The mean age was 72 years (median 73 years, 54-81). All patients were divided according to NCCN (National Comprehensive Cancer Network) prognostic classification into favourable group 8 patients (12%), intermediate group 26 patients (38%) and unfavourable group 34 patients (50%). The mean PSA at the diagnosis was 24 ng/mL, median 11,6 ng/mL (range 1.84-465). The Gleason score was: 2-6 38%; 7 29%; 8-10 33%. Hormonotherapy (HT) was administrated in 64 patients (92%). Patients treated with total androgenic deprivation (TAD) were 61%, peripheral antagonist 31%, and LH-RH 8%. The mean treatment time was 38 days. The mean follow-up was of 15 months, median 16 months (range 6-25). All patients were clinically evaluated for urinary and rectal complications according RTOG/EORTC late toxicity scale. Accoding to American Society for Therapeutic Radiology and Oncology (ASTRO) a rise by 2 ng/mL or more above the nadir PSA was considered the standard definition for biochemical failure after RT with or without HT.

Results and Conclusions: Late genitor-urinary (GU) toxicity ≥ G2 was recorded in 3% and late gastrointestinal (GI) toxicity ≥ G2 in 10.4%. In our experience with conventional fractionation 80 Gy 3DCRT GU ≥ G2 was recorded in 9% and GI ≥ G2 in 6%. Our experience demonstrates that hypofractionated 3DCRT 310 cGy die 62 Gy on prostate and seminal vesicles is safe and effective. Rectal and urinary complication are similar to conventional fractionation treatment. Hypofractionation allows reduction of overall treatment time, without severe toxicity. Longer follow-up is necessary to support the result of the present study on late toxicity

P102
HYPOFRACTIONATION IN BREAST CANCER: ANALYSIS OF LATE TOXICITY

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Purpose: The aim of this retrospective analysis was to assess the late toxicity in women with breast cancer treated with radiotherapy at 40,05 Gy in 15 daily fractions +/- boost 10,67 Gy in 4 daily fractions.

Patients and Methods: Between October 2009 and December 2010, 56 patients referred to our centre were submitted to postoperative radiotherapy with hypofractionated schedule; 48 (85,7%) also received a boost on tumor bed. Their mean age was 59 years (median 56,5; range 35-80). 35 patients (64,2%) were at clinical stage I, 14 patients (25%) at stage II, 7 (12,5%) stage III. Of these 47 (84%) received hormonotherapy. Before radiotherapy, 21 (37,5%) underwent to chemotherapy. Patients were

treated with 6-15 MV photons. The mean treatment time (total days between the first day and the last day of treatment) was 28 days (median 32, range 19-38). The principal endpoint was late toxicity on normal tissue. The toxicity was evaluated according to the radiation morbidity scoring criteria (RTOG/EORTC). We used the Yates's chi-square test for statistical analysis.

Results: 11 patients (19,6%) showed acute skin toxicity of grade 1, 8 pts (14,3%) grade 2; no case of grade 3 toxicity. The mean follow-up was 18 months (median 23, range 1-24); 12/56 (21,4%) patients were lost to follow-up. We divided the patients into 4 groups: those who had late skin toxicity and who had not, those who had fibrosis and who had not. We divided each group in others subgroups: those who received chemo, those who had acute toxicity and those who had neither acute toxicity and chemotherapy (see Table 1). As regard late skin toxicity, we verified that the relation between chemotherapy or acute toxicity and late toxicity was not statistically significant (P>0,05); in contrast, the correlation was statistically significant with the development of fibrosis (P<0,01).

Conclusions: Our data on late effects of hypofractionation are comparable to those found in literature (START study: mild change was graded 30,8% and marked change was 3,0%). They show that hypofractionation can be a satisfactory alternative to conventional fractionation, allowing the same effectiveness in a shorter time. We observed that there is not statistically significant correlation between the development of late toxicity and chemotherapy and previous acute toxicity, except for fibrosis.

Table 1.

	Late Skin Toxicity	No Late Skin Toxicity	Fibrosis	No Fibrosis
N. of patients	13	31	11	33
Chemotherapy	6	11	2	14
Acute toxicity	6	10	4	13
No cht, no acute toxicity	1	10	5	6

P103

ACUTE AND SHORT TERM LATE TOXICITY IN ADJUVANT BREAST CANCER RADIOTHERAPY. A MONO-INSTITUTIONAL COMPARISON BETWEEN TWO REGIMENS OF HYPOFRACTIONATED WHOLE BREAST IRRADIATION (ACCELERATED AND MODERATELY) WITH WEEKLY CONCOMITANT BOOST AFTER CONSERVATIVE SURGERY

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Aims: Several randomized trials have demonstrated that hypofractionated whole breast irradiation is not inferior, for selected patients, to conventional regimen , with comparable local control and cosmetic results. Important advantages are certainly treatment time and cost reduction. The purpose of this study is to compare acute and short term late toxicity of two hypofractionated regimens applied in our Radiotherapy Department among breast cancer patients submitted to conservative surgery: accelerated hypofractionated whole breast irradiation (AHWBI) and moderately hypofractionated whole breast irradiation (MHWBI).

Table 1.

	230 x 20	300 x 13
Istologia	Duttale: 101 Lobulare: 13 Dutto-Lobul: 2 Tubulare: 3 Scars Diff: 1 Metapl: 1 Mucinoso: 2 Papillare: 2 Cribriforme: 1 Midollare: 2	Duttale: 54 Lobulare: 6 Dutto-Lobulare: 1 Tubulare: 1 Mucinoso: 1
T	IS 4 ypT0 2 1A 9 1B 28 1C 59 2 25 1 1	IS 2 1A 3 1B 13 1C 32 2 11 1 Mic 1
N	23 + 16 N + 7 N Mic	8 + 6 N + 2 N Mic
ER	Pos 108 Neg 19	Pos 51 Neg 11
PGR	Pos 94 Neg 33	Pos 51 Neg 11
Chirurgia	32 Quadr + DLA 95 Quadr + LS 1 Tumorectomia	12 Quadr + DLA 47 Quadr + LS 3 Tumorectomia
Chemio	1 CMF 28 FEC + TAX 11 FEC 1 AC 7 TC 8 Herceptin 71 IN AROM	4 FEC 4 AC 3 FEC+ TAX 35 IN AROM
OT	34 TAM 5 Non specificata	13 TAM 3 Non specificata

Table 2.

	AHWBI	MHWBI
End RT	G0 31.2% G1 62.3% G2 6.5%	G0 17.1% G1 73.5% G2 9.4%
1 Months	G0 55.9% G1 44.9% G2 0%	43.2% 53.6% 3.2%
6 Months	G0 70.6% G1 29.4% G2 0%	G0 76.7% G1 22.3% G2 1%
12 Months	G0 83.9% G1 16.1% G2 0%	G0 88.7% G1 11.3% G2 0%

Materials and Methods: At Radiotrherapy Department of Sanremo Hospital from January 2010 to December 2011 sixtyfive breast cancer patients were assigned, after conservative surgery, to receive 39 Gy (AHWBI) in 13 fraction with weekly concomitant boost of 1 Gy for 3 fractions to the tumor bed. In the same time interval 128 patients have been treated with moderately hypofractionated whole breast irradiation: they received 46 Gy (MHWBI) in 20 fraction with weekly concomitant boost of 1.2 Gy for a total of 5 fractions to the tumor bed. Early and late toxicity has been analysed according to the Radiation Therapy Oncology Group criteria.

Results: Median age of women of AHWBI group was 74 years old while median age of patients of MHWBI group was 58 years old. Patients characteristics are reported on Table 1. Overall median treatment duration was 21 days for AHWBI and 33 days for MHWBI. After a median follow up of 9 months (range 6-12 months), all patients are alive and disease free. Early and late toxicity of the two groups patients are reported on Table 2. No significant differences have been noted in both groups between patients receiving or not receiving chemotherapy. No patient discontinued radiotherapy for toxicity or developed G3 early or late toxicity.

Conclusions: These unconventional radiotherapy regimens demonstrated to be both well tolerated and comparable in acute and short term late toxicity. A satisfactory cosmesis has been ever obtained. A longer follow up is necessary to confirm these favourable results.

P104
EARLY GLOTTIS CANCER: CAN WE GAIN SOMETHING WITH A HYPOFRACTIONATED TREATMENT?

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Purpose: We compared the standard treatment to a hypofractionated one in terms of local control of disease, acute and late side effects, tolerability for the patients and quality of voice in patients with early glottis cancer.

Materials and Methods: From 1999 to 2011 we treated 52 patients (pts) with diagnosis of glottis carcinoma. They were: 4 females and 48 males, 22 current smokers, 28 ex-smokers and 2 never smoked. Six pts had verrucous carcinoma and 46 had squamous cell carcinoma G1 (12/46), G2 (22/46) and G3 (4/46). Four pts (7.69%) had *in situ* disease, 32 (61.53%) were cT1a, 8 (15.38%) were cT1b and 8 (15.38%) were staged as cT2. We submitted every pt to neck US and chest RX. Pts were divided into 2 Arms with respect to daily fraction and total dose. Arm-1: 22 pts received 66 Gy in 33 2 Gy daily fractions. Arm-2: 30 pts received 60 Gy in 25 2.4 Gy daily fractions. All pts underwent airways evaluation every 2 weeks. Quality of voice was evaluated before, at the end of RT and at every FU. Our protocol included perceptual analysis of dysphonia (GRBAS) and Voice Handicap Index.

Results: The median follow-up (FU) was 15.46 months with a 86.6% one-year DFS and 100% one-year OS. In Arm-1 median FU was 16 months with a 72.7% DFS: 6 pts had a relapse during the first year and were encouraged to undergo surgery. In Arm-2 median FU was 15.8 months with a 100% local control. Acute side effects were: Arm-1: G1 (2/22), G2 (18/22) and G3 (2/22) dysphonia; G1 (4/22), G2 (16/22), G3 (2/22) dysphagia; G1 (15/22) and G2 (7/22) vocal cord oedema; G1 (18/22) and G2 (4/22) radiodermitis. Arm-2: G1 (6/30), G2 (22/30) and G3 (2/30) dysphonia; G1 (10/30), G2 (18/30), G3 (2/30) dysphagia; G1 (8/30) and G2 (22/30) vocal cord oedema; G1 (19/30) and G2 (11/30) radiodermitis. After one year follow-up dysphagia, vocal cord oedema and radiodermitis were not reported in both groups. G1 dysphonia persisted in 18/22 patients in Arm-1 and in 16/30 in Arm-2. G2 dysphonia was reported in 1/22 in Arm-1 and in 8/30 in Arm-2. Full recovery of voice occurred in 3/22 and in 6/30 for Arm-1 and Arm-2 respectively. Forty pts completed the VHI test: no significant difference in the two arms was observed.

Conclusions: Despite the short FU, results from the 2 arms are comparable. We reached good results in terms of OS and DFS. The hypofractionated schedule was well tolerated by patients because of its shortness and mild acute side effects. Quality of voice strongly improved at one year FU.

P105
HYPOFRACTIONATED RADIOTHERAPY IN NON-MELANOMA SKIN CANCER: COMPARISON BETWEEN THREE DIFFERENT SCHEDULES

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Purpose: Evaluation of the 3 schedules in non-melanoma skin cancer in elderly patients.

Materials: From 1999 to 2011 we treated 84 patients (pts) with diagnosis of non-melanoma skin cancer. We assigned them to 3 different groups of RT according to KPS, age and easiness to get to the hospital. Briefly, pts with lower KPS or living more than 20 Km away from the hospital were included in the shorter schedule. First group: 28 pts (4 T1, 14 T2, 4 T3, 6 T4), median age 77.28 years, KPS>80, 6/28 had positive margins. These pts were treated with conventional RT: total dose 60 Gy in 30 daily fractions, 5 days/week. Second group: 28 pts (2 T1, 16 T2, 8 T3, 2 T4), median age 81 years, KPS 60-70, 10/28 had positive margins. These pts were submitted to RT using a hypofractionated RT: total dose 60 Gy in 20 fractions, 5 days/week. Third group: 28 pts (4 T1, 16 T2, 8 T3), median age 87.5 years, KPS 40-50 or living 20Km away from the hospital, 6/28 had positive margins, 22/28 received definitive RT. These pts were treated with hypofractionated RT up to a total dose of 36 Gy, 6 Gy/fraction, 2/week.

Results: Median FU in the first group was 17.57 months. We reported complete response (CR) in 16/28 pts

(57,14%), partial response (PR) in 10/28 pts (35.7%) and relapse (PD) in 1 pt at the end of the first month of FU. Pts were monthly re-evaluated and, in case of PR, we continued with an "active surveillance" approach. In case of PD, we proposed a re-treatment with hypofractionated RT. In the second group we had a median FU of 17.35 months. CR was achieved in 14/28 pts (50%), PR in 14/28 pts (50%) with persistence of disease in 6/28 pts (21.42%) and progressive remission in 8/28 cases (28.57%). In the third group the median FU was 13.35 months. We reported 16 cases (57.14%) of CR and PR in 12 pts (42.85%): in 4 cases we proposed a re-treatment, same schedule, achieving a CR at the end of further 2 month. Late reactions consisted in G2 fibrosis and skin thinning with no difference between the 3 groups. Pts undergoing eyelid RT were evaluated by an ophthalmologist before, during and every 3 month after the end of RT: no worsening of lens condition was observed.

Conclusions: The 2 hypofractionated schedules gave good results in terms of CR; acute side effects did not require treatment interruption and late toxicities were not statistically different in the 3 groups. Elderly pts undergoing the 2/week schedule well tolerated the treatment that, in other ways, they would have refused.

P106
ACUTE AND LATE TOXICITY IN RELATION TO TREATED VOLUMES IN THE MILDLY HYPOFRACTIONATED POST-OPERATIVE OR SALVAGE TREATMENT OF PROSTATE CARCINOMA WITH RAPIDARCTM (RA-IMRT)

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Scope: To assess the difference in the toxicities of a mildly hypofractionated IMRT treatment for prostate cancer patients, in postoperative or salvage setting delivered to the prostatic bed only (Group A) or, to the prostatic bed and pelvic lymph nodes (Group B), using a LINAC with RapidArcTM technology, TrilogyTM – Varian (RA-IMRT).

Materials and Methods: Between February 2010 and February 2012, 216 pts, were treated in post-operative (114 pts) or salvage setting (102 pts). 105 pts were irradiated to the prostatic bed only (Group A) and 111 pts were treated to the prostatic bed and pelvic lymph nodes (Group B). Pelvic RT was added in case of pN1, or cN0/pNx, if the estimated risk of lymph node involvement was > 30%. RA-IMRT was delivered using a mildly hypofractionated schedule. The CTV-T included the prostatic bed only; margins to PTV were 10 mm in all directions, except 5 mm posteriorly, and in the case of prostatic bed plus pelvic lymph nodes, the volumes were obtained including the delineation of the internal iliac, upper external iliac, and lower common iliac vessels on each slice up to the lower border of lumbar L5. RTOG/EORTC genitourinary (GU) and gastrointestinal (GI) acute toxicities were prospectively registered. Follow-up evaluation was performed every 6-12 months thereafter.

Results: All but one pt. completed the RA-IMRT course (median overall total treatment time was 44 days, range 32-67 days); for 1 pt in relation to the worsening of the general conditions treatment was stopped after 27/30 fractions. After a median follow-up of12 months (range 6-25) GU and GI acute and late toxicities (the last recorded for 104 pts.) for Group A and Group B were as follows (Table 1 and Table 2). The toxicity data were analyzed with Fisher test and no statistical difference were found between the toxicities grade of group A and B (p =0.67).

Conclusions: According to RTOG/EORTC scale no significant statistical differences in toxicities were observed in the two Groups (Group A prostatic bed only RT; Group B prostatic bed + pelvic RT), despite larger volumes in case of pelvic irradiation ((Group B). Based on our findings we make the hypothesis that innovative RT technologies allow for safe irradiation of larger volumes. Such hypothesis should be tested within further prospective investigation including large patient series with long follow-up data. Co-analysis of potential impact of patient-, treatment- and tumor-related variables is also warranted.

Table 1. Acute toxicity (RTOG/EORTC).

GU	Group A (105 pts)	Group B (111 pts)
0	70 (67%)	68 (61%)
1	24 (23%)	29 (26%)
2	8 (7%)	13 (12%)
3	3 (3%)	1 (1%)
GI	**Group A (105 pts)**	**Group B (111 pts)**
0	61 (58%)	52 (47%)
1	32 (30%	46 (41%)
2	12 (12%)	12 (11%)
3	0	1 (1%)

GU, Genitourinary; GI, Gastrointestinal.

Table 2. Late toxicity (RTOG/EORTC).

GU	Group A (48 pts)	Group B (56 pts)
0	29 (60%)	36 (64%)
1	14 (30%)	16 (29%)
2	2 (4%)	3 (5%)
3	3 (6%)	1(2%)
GI	**Group A (48 pts)**	**Group B (56 pts)**
0	37 (77%)	44 (79%)
1	6 (13%)	8 (13%)
2	3 (6%)	2 (4%)
3	2(4%)	1* (2%)
4	0	1** (2%)

*GU, Genitourinary; GI, Gastrointestinal; *, Rectal bleeding requiring blood transfusion; **, Proctopaty with ano-rectal ulcer-fistula.*

P107

EXTERNAL BEAM RE-IRRADIATION FOR LOCAL RECURRENCE OF PROSTATE CARCINOMA AFTER RADICAL OR POST-OPERATIVE/SALVAGE RADIOTHERAPY: EVALUATION OF TOXICITIES AND OUTCOME

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Purpose: To retrospectively evaluate external beam re-irradiation (re-EBRT), delivered to the prostate or prostatic bed for local recurrence after radical or post-operative/salvage radiotherapy.

Materials and Methods: Eight pts have been treated with re-EBRT at our Department between 2/2008 and 3/2012. Previously EBRT included radical RT (4 pts. with EBRT and 1 pt. with brachytherapy), post-operative RT (2 pts.) or salvage RT (1 pt.). All pts had local relapse in the prostate or prostatic bed with no distant metastasis: biopsy was performed in all but 1 pts, and all the pts. had total body computer tomography (CT) or 11C-choline positron emission tomography scan. One pt. was previously treated also with 3-CRT for lymph node recurrence with complete remission. The mean age, iPSA and Gleason Score (GS) at diagnosis were 61 yrs (49-67), 16 ng/ml (4.57-67) and 6 (4-9), respectively. The re-EBRT technique included 3D IGRT, stereotactic RT, CyberKnife and IMRT in 1, 4, 1 and 1 pt. The following schedules were employed: 25 Gy/5 fr (6 pts), 30 Gy/6 fr.(1 pt.), and 15 Gy/3 fr. (1 pt). Concomitant hormonal therapy (HT) was administered in 4 pts. Toxicity and tumor response were evaluated using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and Response Evaluation Criteria In Solid Tumors criteria. Biochemical and clinical response, using radiologic criteria, was also registered.

Results: The mean interval between the primary treatment and the clinical local relapse was 76 mo., and the mean follow-up after re-EBRT was 24 mo.(5-30).Two pts. died for the prostate cancer progression at distant sites: the interval between re-EBRT and the death was 30 mo. for each. The remaining 6 patients are alive: 5 with no evidence of disease and 1 pt is alive with disease in clinical control with HT. Acute toxicity included only 1 GU G1 event Late toxicities (> 6 months of f.u., data available in 5 pts): only 2 G1 events were reported (one GI and one GU).

Conclusions: In our single institution preliminary experience re-EBRT of local relapse of the prostate cancer appears feasible and well tolerated. Local control was excellent (non local recurrence was registered within mean follow-up of 2 years) and 63% of patients alive with non evidence of disease at 2 years. Longer follow-up and bigger patient series is warranted in order to confirm these promising early findings.

P108

ACUTE TOXICITY IN 498 PATIENTS TREATED WITH HYPOFRACTIONATED IMAGE GUIDED EXTERNAL BEAM RADIOTHERAPY (HYPO-IGRT) FOR ORGAN-CONFINED PROSTATE CARCINOMA: COMPARISON WITH A BENCHMARK RANDOMIZED STUDY FROM THE FOX CHASE CANCER CENTER

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Purpose: To assess acute toxicity of hypofractionated image-guided RT (hypo-IGRT) for localized prostate cancer and to compare it to that reported in the hypofractionated arm of the benchmark randomized study from the Fox Chase Cancer Center (Pollack A et al. IJROBP 2006; 64:518-26).

Materials and Methods: In 2008 hypo-IGRT (2.7Gy/frx26 fr to 70.2Gy, equivalent to 84.2Gy,/of 1.5Gy) was introduced in our Institute. This schedule was adopted from the Fox Chase study (70.2Gy/26 fr *vs*. 76Gy/38 fr) that used ultrasound-image-guided IMRT. Our study was notified to the institutional Ethical Committee. Inclusion criteria were as follows: cT1-T2N0M0 prostate cancer, no previous pelvic RT of prostate cancer surgery, non concomitant anticoagulant therapy or inflammatory bowel disease, written informed consent. Hormonal therapy was permitted. CTV to PTV margins were 7 mm in all directions, except 3 mm posteriorly (as Fox Chase study). CTV was prostate only (low-risk pts) or prostate&seminal vesicles (intermediate-,high-risk pts). Hypo-IGRT was performed using 3D-CRT or IMRT. Daily target localization was done with BATTM-NOMOS or ExacTracTM (X-Ray6D, BrainLAB, with use of intraprostatic fiducials) or Cone-Beam CT (On Board Imager CTTM - Varian Medical System, Linac2100 or Trilogy). RTOG/EORTC criteria were used for acute side effects. Acute toxicity was compared to that reported at the end of RT the hypofractionated arm of the Fox Chase study employing similar criteria.

Results: From 22/08/2008 to 31/03/2012, 498 pts (mean age 74 yrs) were treated. 186 pts (37.3 %) received hormonal treatment. 3D-CRT and IMRT was used in 401 (80.5%) and 97 pts (19.5%), respectively. BAT, ExacTrac and CBCT was employed in 279 (56%), 60 (12%) and 159 pts (32%: 12% Linac2100 and 20% Trilogy). All pts completed hypo-IGRT (mean duration 39 days, range 34-59). Acute toxicity at the end of RT is presented in Table 1. More pts in our series were free of any acute events, but we registered more G3-G4 GI events (no G3-4 GI was observed in Fox Chase pts). These differences might in part be explained by use of 3D-CRT in the majority of our pts (all Fox Chase pts were treated with IMRT).

Table 1.

Maximum acute toxicity at the end of hypo-IGRT	Pollack A. *et al.* hypofractionated arm n=100 pts	Present series n=498 pts
GU		
0	8%	26.6%
1°	44%	38%
2°	40%	30.5%
3°	8%	4.5%
4°	0	0.5%
GI		
0	42%	56.5%
1°	40%	31.5%
2°	18%	11.0%
3°	0	1% (5 events)
4°	0	0 (1 event)

Conclusions: Acute toxicity of hypo-IGRT seems similar to that reported in the benchmark Fox Chase study. Higher rate of severe GI acute injury might depend on use of 3D-CRT in the majority of our patients but this hypothesis should be further investigated through dosimetric comparison.

P109

EXTERNAL BEAM RADIOTHERAPY SHORT FRACTIONATION IN PATIENTS WITH BREAST CANCER: EXPERIENCE OF RADIOTHERAPY CENTER OF COSENZA

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Purpose: Radiation therapy has become accepted as standard treatment after breast conservig surgery for women with breast cancer. Usually a total dose of 50 Gy given to the whole breast is followed by a 10 Gy boost. Many authors have recently prospected shorter regimens, employing a higher dose fraction or even hyperfractionation. Purpose of our study was to appraise the morbidity and cosmesis of radiotherapy.

Materials and Methods: From November 2009 to January 2012 at the Radiotherapy center of Cosenza 30 women have been submitted to postoperative radiotherapy after breast conserving surgery for early right breast cancer (20 ductal and 10 lobular carcinoma). The treatment was delivered 5 days/week with 2 tangential fields, 6 Mv photons, to the whole breast with a total dose of 4160 cGy delivered in 16 fractions: fractionation of 260 cGy x 5 fractions/week. Large breast patients were excluded. We have evaluated 30 women, 75% pT1, 25% pT2.

Results: The cosmetic results and morbidity have been excellent, they have not been in relief remarkable toxicities in accord with the data presents in literature.

Conclusions: Our study, even if preliminary, suggest that the shorter course of radiotherapy may be an acceptable alternative to the conventional fractionation. Additional follow-up and increasing number of cases are necessary to determinate long-term local failure, morbidity and cosmesis.

STRATEGIE TERAPEUTICHE NELLE METASTASI LATEROCERVICALI DA FOCUS IGNOTO

P110

THE LATERO-CERVICAL LYMPH NODE METASTASES FROM UNKNOWN PRIMARY TUMOURS THERAPEUTIC OPTIONS: OUR EXPERIENCE

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Aims: The management of patients(pt)with cervical lymphnode metastases from unknown primary tumours is a major challenge in oncology. The optimal management of this tumours is still controversial because a standard therapy has not been identified yet. Various options have been proposed: neck dissection alone, neck dissection with post-operative radiotherapy, nodal excision (for a small single node) with post-operative radiotherapy or radiotherapy (followed by salvage surgery). Neck dissection followed by post-operative radiotherapy is generally accepted as a standard approach,whereas the question of the extent of radiotherapy (both sides of the neck and the pharyngeal mucosa or ipsilateral neck node areas) is still unresolved. There is no evidence supporting the use of chemotherapy for these patients.

Materials and Methods: From April 2005 to May 2012 twenty patients, 3 women and 17 men with the median age of 62 years (range 36 -83) were treated.Neck dissection was performed in 6 pt while 14 pt underwent single lymph node sampling only. Only 15 pt had a biopsies of potential sub clinical tumour sites in pharynx (nasopharynx, tonsil, base of tongue) and larynx. All patients received Chemotherapy and radiation treatment including irradiation axis and pharyngeal lymphnodes reaching a DTF of 60 Gy on N+;only 1 pt received 20 Gy for palliative treatment and 2 pt received a total dose of 51Gy and 56Gy respectively. One patient died for other causes.

Results: The our end-point was the locoregional tumour control at the primary tumour bed and neck and the toxicity. Toxicity was evaluated according to RTOG/EORTC criteria.Acute toxicity was Xerostomia for 3 pt, skin G2 6pt, G1 6pt, dysphagia G2 6 pt, G1 1 pt and G0 13 pt. Late toxicity was Skin G3 1 pt mucose G3 1 pt,Xerostomia 4 pt, dysphagia G2 1 pt. Only 2 patients had bone metastases and 1 patients presented progression disease,and one presented local release. These patients received a DTF below 60 Gy. The others (80%) are free of disease to date.

Conclusions: This study has said that patients with neck node metastases from occult head and neck cancer have clinical features and prognosis similar to other head and neck malignancies when treated at the dose greater than or equal to 60 Gy su GTV received the irradiation to both sides of the neck and the mucosa in the entire pharyngeal axis and larynx, having significantly less loco-regional failures and progression disease with a well tolerated treatment.

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RADIOCHEMOTHERAPY FOR UNKNOWN PRIMARY HEAD AND NECK CANCER: OUR EXPERIENCE

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Purpose: To review the outcome of patients with cervical lymph node metastases of squamous cell carcinoma of unknown primary site.

Materials and Methods: Patients with lymph-node metastases of squamous cell carcinoma of unknown primary site, treated between October 2006 and November 2011 with radiochemotherapy, were retrospectively analyzed. The primary end-points were overall survival and local control; the secondary endpoints were acute and late toxicity.

Results: A total of 18 patients were included. Of these patients, 14 (78%) had Stage N2 disease or greater. All patients underwent neck computed tomography, positron emission tomography-computed tomography, and examination under anesthesia with directed biopsies. Four (22%) patients performed ipsilateral radical neck dissection, five patients (28%) was undergone to escissional biopsy and 9 patients (50%) didn't receive any surgical intervention. Of 18 patients, 14 (78%) received concurrent radiochemotherapy, and four (22%) also underwent to induction chemotherapy. Median dose of Intensity-Modulated Radiotherapy was 70 Gy. With a median follow-up of 20 months (range: 6-106 months,2-years overall survival and local control rates were 65% and 88%, respectively. Acute toxicity (> Grade 3) was observed in 5 patients (28%). Xerostomia was a common late side effect (45% > grade 2).

Conclusions: Radiochemotherapy for patients with cervical lymph node metastases of squamous cell carcinoma of unknown primary site is a reliable treatment. The 2-years outcome is generally good with a toxicity profile acceptable.

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RADIATION THERAPY IN THE MANAGEMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA OF UNKNOWN PRIMARY

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Purpose: The aim of our study was to retrospectively review outcome in terms of overall survival (OS) and disease free survival (DFS) of patients referred to our institution with head and neck cancer of unknown primary (CUP), treated with radiotherapy alone or with concomitant chemotherapy.

Patients and Methods: Between September 2005 and December 2011 a total of 22 patients with CUP were treated at our institution (18 men and 4 women), with a median age of 69 years (range 35-81). All patients underwent diagnostic fiber optic endoscopy with multiple biopsies of pharyngeal mucosa and PET/CT scan, except for 1 patient who underwent only MRI. Clinical and pathological stages were N1 (1 patient), N2a (4 patients), N2b (12 patients) and N3 (1 patient). 17 patients received ipsilateral neck dissection and 5 patients underwent only local biopsy or fine needle aspiration. Radiotherapy was delivered in 6 patients using 3D conformal technique and IMRT in 16 patients. Concomitant chemoradiotherapy was delivered in 10 patients. Radiation volumes included bilateral neck nodes and pharyngeal mucosa in 20 patients, and in 2 cases only the ipsilateral neck was included. The oral cavity and larynx were included in the target if adjacent nodes were affected. The involved nodal dose was 60-70 Gy (median dose 66 Gy), and the contralateral nodal and mucosal dose was 50-60 Gy (median dose 66 Gy).

Results: With a median follow-up of 30 months (range 6 - 66), the 2-year actuarial locoregional control rate was 64% and disease specific overall survival was 72%; the 3-year actuarial locoregional control rate was 57% and overall survival was 64%. 55% of patients disease free at 2 years received chemotherapy compared to 40% of patients with a progression of disease. 90% of patients disease free had previously received neck dissection.

Conclusions: In our institution radiation therapy for CUP of head and neck district has provided good overall and disease-free survival. In a relatively older cohort of patients (compared to other reported series), better results were reached with aggressive approach with chemotherapy and, above all, surgical neck dissection.

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CERVICAL LYMPH NODE METASTASES FROM UNKNOWN PRIMARY: TARGET VOLUMES AND MANAGEMENT STRATEGIES

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Purpose: The aim of this retrospective study was to evaluate the efficacy and toxicity of radiation treatment in patients affected by cervical lymph node metastases from an unknown primary site (CUP), focusing on management strategies such as surgery, radiotherapy, chemotherapy integration and choice of target volumes (extensive irradiation including pharyngeal mucosa and bilateral neck nodes *versus* ipsilateral neck irradiation).

Materials and Methods: From May 2002 to April 2012 19 patients affected by cervical lymph node metastases from CUP underwent 3D conformational radiotherapy. At staging we found N1=5,2%, N2a=26,3%, N2b=36,8%, N2C=10,5 %, N3=21,2%. Eleven patients were treated with postoperative radiotherapy (5 of them

received concomitant chemotherapy); 8 patients underwent exclusive chemoradiotherapy. All patients underwent extensive irradiation.PTV II (bilateral cervical lymph nodes and pharyngeal mucosa) received 50-54 Gy, PTV I (boost on N+ or in surgical bed when high risk factors were present) received 60-68 Gy (2Gy/fraction).

Results: At the end of treatment 13 out of 19 patients (68,4 %) obtained complete remission of disease (RC) and 6 patients (31,6 %) had persistent nodal disease. Out of total cases we observed disease free survival (DFS): 52,8% (10 out of 13 patients with RC at the end of therapies) with medium follow up (f.u.) of 45 months, (range 6-117), nodal persistence disease:31,6%, recurrent nodal disease:5,2%, primary tumour occurrence 5,2%; one patient died in RC for idiopathic pulmonary fibrosis. Considering only patients who underwent postoperative extensive irradiation we observed a DFS rate of 72,7% (medium f.u. 49 months, range 6-117). Out of patients who underwent exclusive RT we had 2 patent in RC (f.u. 15 and 45 months). During treatment G1 and G2 mucositis, dermatitis, dysphagia, odynophagia were recorded but only five G3 events in 3 cases; all patients completed the treatment. No significant late toxicity was observed at 6 and 12 months f.u.

Conclusions: Although management of cervical lymph node metastases from CUP remains debatable, as indicated in multivariate analyses treatment including neck dissection, extensive irradiation of bilateral neck nodes and pharyngeal mucosa with concomitant chemotherapy results in favourable outcomes. Results in terms of DFS in our patients who underwent postoperative extensive radiotherapy with concomitant chemotherapy are similar to other studies reported in literature.

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THE TREATMENT OF CERVICAL LYMPH NODE METASTASES OF SQUAMOUS CELL CARCINOMA FROM AN UNKNOWN PRIMARY SITE: OUR EXPERIENCE

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Backgrounds: Cervical lymph node metastases of squamous cell carcinoma from an unknown primary site constitute about 5% of the total head and neck cancer cases. Their management is a therapeutic challenge.

Methods: We analyzed data from 14 patients who underwent RT at U.O. di Radioterapia Oncologica of Viterbo, from 1998 to date. Mean age was 63.7 , with a range 34 - 84. 1 patient was cN 1, 1 N2a, 5 N2b, 6 N3a, 1 N3b. 12 underwent CT scan, 2 TC/PET scan and 3 MRI. 5 underwent lymph node dissection prior of RT. RT was delivered to bilateral neck and pharyngeal mucosa in 11 patients. 1 patient underwent bilateral neck RT for age and 2 to ipsilateral neck for palliative intent. RT dose was 56-60 Gy after surgery and 66-70 Gy for up front treatment, 1.8-2 Gy/die. Chemotherapy was administered in 5 pts; 1 was escluded for cirrhosis, 3 for age, 2 for palliation, 3 for low KPS. All pts were followed up.

Results: 2 pts , with advanced disease didn't complete RT for worsening of clinical status. Both died in few weeks period. All the other patients completed RT. 3 achieved a partial response to treatment and underwent salvage surgery. 2 are still alive, 1 stopped FUP. 9 pts achieved a complete response: 5 after neck dissection performed before RT or RT+CHT and 4 after completion of RT or RT+CHT upfront. 2 are alive after 6 and 11 years, 2 had a lymph node relapse (after 6 and 7 months from RT) and underwent surgery. They are alive at 3 and 4 years. 2 pts had lung cancer 1 y after the end of primary treatment: 1 patient had liver metastases (from adenocarcinoma) and she died few months later. The other patient died for lung cancer with mediastinal lymph node metastases.

Conclusions: The optimal management of these pts is not well established. In our series the most frequent relapse were recourrent lymph node metastases and new lung cancer. The role of neck dissection is not well established. One of the most controversial topic in radiotherapy is the irradiated volume. The benefit from extensive radiotherapy should be weighted against its acute and late morbidity and difficulties in reirradiation in the case of subsequent primary emergence. In our study, after radiotherapy (with or without chemotherapy) no emergence of the primary tumor was observed.

P115

ORAL CAVITY ACUTE TOXICITY IN RADIOTHERAPY FOR HEAD AND NECK CANCER: OUR EXPERIENCE WITH LACTOBACILLUS BREVIS CD#2

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Objectives: To evaluate the efficacy of CD#2 therapy in patients with head&neck cancer treated with radiotherapy(RT) or radiochemotherapy(RT/CT).

Materials and Methods: We analyzed data of 42 patients(groupA) treated with radiotherapy or radiochemotherapy in our center from june2011 to may2012 compared to data of 42 patients(groupB), with similar features treated from january2009 to january2010. The groupA received CD#2 therapy, Group B received other supportive care. All pts had diagnosis of head&neck cancer. Twenty-for pts underwent to surgery before RT and 20 to concomitant chemotherapy for the groupA, while in groupB 18 pts underwent to surgery and 25 pts underwent to concomitant chemotherapy.The CD#2 was administered as follows: Thirty-seven pts started CD#2 therapy at the beginning of RT or RT/CT with recommended posology of 4-8 cp/die.Five patients started CD#2 when the RT treatment had already been started. All patients continued therapy with CD#2 for 2-3 weeks after the end of treatment. The radiotherapy was administered with 3D-Conformal therapy with conventional fractionation for a median total dose from 50Gy to 70Gy.

Results: The grade of stomatitis was as follows: GroupA gradeI 23 pts, II 16 pts, III 3 pts. GroupB gradeI 14 pts, II 35 pts, III 7 pts.In the groupA stomatitis obser-

ved during the treatment was lower compared to groupB, also the grade of stomatitis in patients CD#2 therapy was lower than the B even for the patients who started CD#2 when RT was started.At the end of RT the recovery was faster in the group A for patients who continued therapy with CD#2 for 2-3 weeks.The pts reported used dose was 3cp/die in the first two weeks of treatment, 5-6 cp/die during the last weeks.A side effect we observed in patients with xerostomia, the difficult to assume the tablets.The use of the CD#2 lasted for an average of 2-4 weeks after the end of the RT.The median follow-up was from 1 to 4 months after treatment when stomatitis completely regressed.

Conclusions: During the RT and RT/CT, treatment with CD#2 has improved the compliance of the patient undergoing treatment for Head&Neck cancer reducing the degree of toxicity observed, allowing to perform the treatment without the interruptions caused by severe grade of stomatitis and oropharingeal toxicity and, at the end of treatments, the continued use of CD#2 until resolution of the toxicity allows the resumption of food and even improves the quality of life for these patients.

P116

INTENSITY MODULATED RADIOTHERAPY (IMRT) IN THE TREATMENT OF CERVICAL LYMPHNODE METASTASES FROM AN UNKNOWN PRIMARY SITE: A RETROSPECTIVE ANALYSIS

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Introduction: Cancer of an unknown primary (CUP) metastatic to cervical lymph nodes poses a range of dilemmas relating to optimal treatment. An intensive combined treatment of neck and pharyngeal region with radiochemotherapy is an effective approach in advanced neck disease. Post-treatment neck dissection is indicated if a complete response is not recorded. We reviewed patients with CUP treated with combined treatment in our center.

Methods: A total of 4 patients with non-metastatic CUP treated between 2010 and 2012 were evaluated. Mean patients' age was 59.5 years (44-74). All patients had lymph node involvement of level I and/or II at diagnosis. All patients performed a PET-CT total body and random biopsies of pharynx as primary evaluation. Three patients underwent lymphadenectomy followed by postoperative radiochemotherapy, 1 patients underwent only lymph node biopsy. All patients had ≥ N2 disease. The histologies were: Squamous Cell Carcinoma (SCC) (2 patients), Neuroendocrine Tumor (NeT) (1) and Undifferentiated carcinoma (1). All patients were treated with IMRT (2 patients with Simultaneous Integrated Boost –SIB) and all received concomitant Chemotherapy with Cisplatin (q7 or q21). The PTV1 was the whole neck (level I-II-III-IV-V + parafaryngeal lymphnodes) + the whole pharyngeal axis and received 54 (1.8-2 Gy/fr); in one case the oral cavity and the larynx were also included in PTV1. PTV2 included the areas of initial localization of tumor completed removed by lymphadenectomy and received 60 Gy (2 Gy/fr). In the case of patient not treated with lymphadenectomy, we also delineated a PTV3, including the areas of macroscopici desease detected by PET-CT, which received 66 Gy (2.2 Gy/fr) with SIB technique. Acute toxicity was evaluated weekly according the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 scale for skin, mucous membrane, salivary glands, pharynx and blood count. Late toxicity was evaluated according to the RTOG-EORTC toxicity scale.

Results: All patients had grade ≤2 acute toxicity. All patients showed G2 dysphagia, 2 patients showed G2 mucosyte and 1 patients had G1 hematologic toxicity (leucopenia). All patients carried out the radiation treatment without interruption. One patients interrupted chemotherapy for hematologic toxicity. After a median follow-up time of 9 months (range 4-16 months), 3 patients (75%) have not evidence of disease. A patient showed omolateral lymphnode relapse and underwent salvage surgery after chemoradiotherapy. All patients are alive. Three patients show late Grade 2 Xerostomia; a patient has a too short follow-up to assess late toxicity..

Conclusions: These results suggest that chemoradiotherapy with IMRT technique allows good toxicity outcomes for patients treated for cervical node squamous cell carcinoma metastases from an unknown head-and-neck primary tumor. No severe late complications were detected. Survival and local control results are good, but a larger number of patients and a longer follow-up are needed to evaluate the long-term survival and the incidence of relapse.

P117

RADIO(CHEMO)THERAPY IN THE MANAGEMENT OF SQUAMOUS CELL CARCINOMA OF CERVICAL LYMPH NODES FROM AN UNKNOWN PRIMARY SITE (HNCUP): A SINGLE INSTITUTION EXPERIENCE WITH HELICAL TOMOTHERAPY

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Purpose: Unknown primary of head and neck squamous cell carcinoma (HNCUP) represents between 1 and 3% of new cases of HNSCC. No single standard treatment emerges from guidelines for HNCUP. Ipsilateral or bilateral neck radiotherapy with mucosal axis irradiation is widely used, with or without chemotherapy prior or after surgery. Conventional RT is associated with high doses to sensitive normal structures and adverse effects on quality of life in patients with HNCUP owing to the

volume of tissue to be irradiated; furthermore, complex PTVs and dose tolerance are limiting factors for dose prescription and potential dose-escalation. Helical Tomotherapy (HT) is a novel technique which allows the delivering of image-guided intensity modulated radiation therapy (IG-IMRT) that could result in a better dose distribution and could improve normal tissue tolerance. We report our initial experience in the treatment of HNCUP with HT using a simultaneous integrated boost (SIB).

Table 1.

Volume D1% (Gy)	Prescription Critical Dose (Gy) Structures	Mean Mean Dose Dose (Gy)	D99% Critical Structures	D95% Max Dose (Gy)	D5% (Gy)
PTV66 67.4	66 Parotid glands	65.7 30.7	62 Spinal Cord (range 12.1-63.3)	63.1 28.9	66.9
PTV60 67.2	60 Cochlea	61.2 30.9	53.6 Glottis	56.8 32.4	66.2
PTV54 62.6	54 Oral Cavity	54.5 27	48.5	47.9	60.9

Materials and Methods: Between March 2009 and December 2011 8 patients with HNCUP underwent IMRT. Of the 8 included patients, 7 were men and 1 was a woman, with a median age of 58 years. Nodal staging ranged from N1 to N3. All patients underwent neck CT or MRI, CTPET and biopsies in the suspected areas. The bilateral neck and pharyngeal mucosa were included in the target area. Radiotherapy was delivered by a SIB technique. The median involved nodal dose was 66 Gy and the minimal mucosal dose was 54 Gy. Of the 8 patients, 7 received concurrent chemotherapy, and 3 also underwent induction chemotherapy. 2 patients underwent neck dissection and 3 had undergone excisional biopsy before radio (chemo)therapy; 3 patients received definitive radiochemotherapy. Dose constraints to minimize the dose to OARs were prescribed. Megavoltage CT scans were obtained for patient alignment before each treatment. PTV doses were accorded to the following: at least 95% of the volume should be covered by the 95% of the dose; at least 99% of the volume should be covered by the 90% of the dose and at least no more than 1% should receive more than 7% of the prescription dose. Median follow-up time is 11 months (range 4-21). The most significant acute toxicities reported at treatment end were grade 2 (12%) mucositis and grade 2 (12%) neck erythema; 3 (37%) pts required short term nasogastric feeding or parenteral nutrition and 1 (12%) needed major analgesic support (tramadol, codeine or major opioids). No grade 3 and 4 late toxicities have been observed. Response rate at 6 months after treatment, evaluated with CT or MRI, were 5 CR (63%), 2 PD (local disease 1 pt and distant disease 1 pt, 25%) and 1 PR (12%), who underwent surgery. 1 pt died for progression disease. 7 pts are alive: 5 pts are disease-free, and 2 have evidence of distant disease. No occurrence of primary cancer was observed during the follow up period (Table 1).

Conclusions: HT with SIB improves homogeneity in the dose distribution and in our initial experience allows a significantly good sparing of the organ at risk with a good clinical response rate.

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CERVICAL LYMPH NODE METASTASIS OF SQUAMOUS CELL CARCINOMA WITH OCCULT PRIMARY: IS REALLY NECESSARY TO IRRADIATE ALL POSSIBLE MUCOSAL PRIMARY SITES? A RETROSPECTIVE ANALYSIS

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Introduction: Cervical lymph node of squamous cell carcinoma from an unknown primary (CUP) represents from about 1% to 5% of head and neck cancer. Neck dissection with or without postoperative radiotherapy is the standard approach for CUP, but several therapeutic options exist. Traditionally adjuvant radiotherapy is focused on bilateral neck without mucosal irradiation and chemotherapy should be reserved for patient presenting N3 patological stage and risk factors. Several trials have recently demonstrated the superiority of concurrent chemo-radiation *vs* radiation therapy alone in selected cases and other series have suggested to extend radiotherapy fields to the all possible mucosal primary sites. However these data are source of disagreement and the optimal management of CUP is still controversial. We present our five-year case study describing our model of multi-disciplinary approach and the results in terms of survival.

Materials and Methods: From 2005 to 2012 we evaluated 8 patients affected by CUP; 3 patients were female and 5 male, with a mean age of 65,6 years. Staging based on fibroscopy, CT or PET was performed in all patients. Surgery consisting in a bilateral or ipsilateral neck dissection was performed. All tumors were squamous, grading was defined as G3 in 3 patients, G2 in 2 patients and not available in the remaining. None patient presented extra capsular lymph nodal extension. About pathological stage 4 patients resulted N2; 3 patients N3 and 1 patients N1. Adjuvant radiotherapy was administered to 5 patients with a total dose of 66-70 Gy. One patients was excluded for the emergence of a serious cardiac disease. Clinical Target Volume (CTV) included lymph nodal station pathological and at risk without possible mucosal primary sites. None patient received chemotherapy.

Results: 4 patients were eligible for the evaluations, presenting a minimum follow-up of 12 months and having completed radiotherapy. We observed a median overall survival (OS) of 33,5 months (range 13-36); mean OS was 36,25 months with SD of 24,25 months. One patient died for metastasis. None recurrence was observed. Even on only four patients, a linear regression model was applied to evaluate the existing correlation between survival and age or grading. Any statically significance was found between survival and age while correlation was proved significant when overall survival was combined with tumor grade.

Conclusions: It is difficult to draw conclusive results

on a small case series, but several observations could be advanced. RT alone after radical surgery of the neck seems to be adequate to disease local control, but risk factors could influence the systemic evolution. Then chemotherapy should be administered in association to radiotherapy to improve prognosis; risk factors should be take in account when we plan to administer chemotherapy, but is necessary a better and specific definition of risk factors for CUP. In our experience we have not irradiate mucosal sites and this seems to have not influenced the local control. Nevertheless benefit of mucosal sites irradiation should be prospectively demonstrate.

CONTROVERSIE NEL CARCINOMA PROSTATICO A BASSO RISCHIO

P119

IS HIGH DOSE LINAC BASED SBRT A NEW FEASIBLE TREATMENT OPTION FOR LOW – INTERMEDIATE RISK PROSTATE CANCER? PRELIMINARY REPORT OF A PHASE I-II STUDY WITH FLATTENING FILTER FREE DELIVERY

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Objectives: To evaluate the early side effects of a short course hypofractionated accelerated high dose linac based SBRT approach delivered with Flattened Filter Free (FFF) beams in selected low-intermediate risk prostate cancer patients.

Materials and Methods: This is a prospective phase-I-II pilot feasibility study, started on February 2012. Inclusion criteria were: age ≤ 80 years, WHO performance status ≤ 2, PSA ≤ 20 ng/ml, histologically proven prostate adenocarcinoma (risk of microscopic nodal involvement ≤ 15%), T1-T2 stage, no distant metastases, no previous prostate surgery other than TURP, no malignant tumours in the previous 5 years, IPSS 0-7. The schedule was 5 x 7 Gy = 35 Gy, delivered in 5 alternative days, corresponding to an NTD2 between 70 and 85 Gy for an/estimate between 3 and 1.5 Gy, respectively. SBRT was administered using the volumetric modulated arc technique (VMAT) by RapidArc(on TrueBeam), with photon beam energy of 10 MV FFF (Filter Flattening Free) and maximum dose rate of 2400 MU/min. PTV was generated from CTV with a 5 mm of margin excluding posterior when the margin is 3 mm. Physical examinations and toxicity assessments were performed during and after SBRT according to CTCAE v3.0 and/or EORTC/RTOG Toxicity scale. Any increase in grade from base-line was considered treatment-related toxicity. Tumour response was evaluated on "ASTRO definition of PSA relapse" (+2 from Nadir of PSA). Neo-adjuvant/concomitant hormonal therapy was prescribed based on the risk according to NCCN classification (no more than 6 months). The choice of the type of hormonal therapy was tailored to the patient. To enlarge the distance between anterior rectal wall and posterior part of the prostate, in critical cases, the protocol allows the optional use of a self-absorbable hydrogel(SPACEOAR) injected by trans-perineal ultrasound guided approach.

Results: Establishing a minimum cut-off of 90 days after SBRT, 15 of the 21 enrolled patients in the protocol were evaluable for the current analysis. According to NCCN criteria, 11 out of 15 patients were low-risk patients. Median Age was 70 (range:63-75), median initial PSA was 5,8 (range:4-8,5). Median PSA was 6 (range: 6-7). Median treatment duration was 10 days (range:8-13). Five patients were submitted to hyodrogel injection(SPACEOAR) to enlage protate/rectum distance and improve plan optimization. All 15 patients analysed completed the treatment as programmed. Acute Toxicities were recorded as follow: Rectum G0 in 8/15, G1 in 7/15; Genito-urinary G0 in 7/15, G1 in 2/15, G2 in 6/15. No acute toxicity greater than G2 was found. Median treatment time using FFF beams for delivery was 126 seconds (range: 120-136)

Conclusions: Our findings suggest that linac based SBRT FFF treatment for prostate cancer in 5 fractions is feasible and well tolerated in acute setting of the first 15 patients recruited. Longer follow-up is needed for definitive assessment of late toxicity and clinical outcome.

P120

IG-IMRT *VS* HDR-BRT IN LOW RISK PROSTATE CANCER: COMPARISON OF TECHNIQUES. THE SANT'ORSOLA-MALPIGHI'S HOSPITAL EXPERIENCE

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Purpose: The objective of this study was to evaluate acute toxicity and effectiveness of two radiotherapy methods - image-guided intensity-modulated external beam radiation therapy (IG-IMRT) and interstitial high dose rate brachytherapy (HDR-BRT) - in the radical treatment of patients with low risk prostate cancer.

Materials and Methods: From February 2011 to January 2012, 22 patients with low risk prostate cancer underwent radiotherapy with radical intent at the Radiotherapy Department of S. Orsola-Malpighi Hospital, Bologna. Of these, 11 were treated with IG-IMRT, while 11 were treated with HDR-BRT. IGRT was performed by using implanted fiducial markers and daily acquisition of orthogonal portal images with EPID and subsequent position correction. The standard prescription dose was 6210 cGy in 23 fractions. HDR-BRT was performed in two fractions, 3 weeks apart; prescription dose was 1400 cGy/fraction. The median follow-up of the entire group was 5.2 months (range 2 - 10).

Results: No Grade 3 or 4 toxicity was recorded during the follow-up period in both groups. 4 patients in the IG-IMRT and 6 patients in the HDR-BRT group, showed no clinically relevant problems during the entire observation

period of three months after treatment. The average IPSS score, defined 3 months after treatment, was of 8.3 (range 2-16)in the IG-IMRT group and 7 (range 1-18) in the HDR-BRT group. Average QOL index was 1.36 and 1.18 respectively.

Conclusions: Our results showed a very encouraging acute toxicity profile in the group of patients treated with HDR-BRT, in comparison with those treated with IG-IMRT, even if higher equivalent doses were delivered with the aim of improving biochemical disease control. HDR-BRT could be a good choice for dose-escalation due to the radiobiological advantages of dose optimization that this method allows. Longer follow-up is necessary to evaluate late toxicity and biochemical control.

P121
LOW RISK PROSTATE CANCER: WHY NOT TO TREAT?

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Backgrounds and Purpose: As a result of widespread PSA testing most patients are now diagnosed with asymptomatic, impalpable and low Gleason Score prostate cancer. Tough is not yet a consensus about "gold standard" treatment for these patients that, although untreated, have a limited risk in terms of symptoms and cancer death. Therefore Active Surveillance (AS) has become an option for these patients. However an ideal regimen for AS has not been defined and currently there is not a clear evidence for the superiority of any one treatment option. We report our experience in the treatment of low risk patients with 3DCRT.

Materials and Methods: We have conducted a retrospective analysis of all patients treated in our Institute from 1/1/2005 to 1/1/2012 with a confirmed diagnosis of prostate cancer. All patients were assigned to the risk group stratification according NCCN guidelines. In the observed period we received 720 pts, 646 of whom were candidates to radiotherapy: (20%)129 pts.(Low Risk), (26%)168 pts.(Intermediate Risk), (54%)349 pts.(High Risk). In the Low Risk subgroup all patients underwent 3DCRT with 4-6 wedged fields and maximum dose prescribed was 77.4 Gy (range 70.4-77.4) to the prostate and 55.8 Gy to seminal vesicle.

Results: All the patients in the low risk group have been informed about the therapeutic option of AS but most of them refused it. In our experience the problem that most worries the patients is the anxiety for both "no treatment" and "PSA value fever". Anyhow we observed very low grade toxicity with 3DCRT and acute urinary symptoms typically resolved within 45 days of treatment completion. No patients had grade 3-4 rectal late toxicity. Only few patients experienced urethral stenosis.

Conclusions: In our experience 3DCRT is safe and well tolerated and the first choice of our low risk patients. Probably selected patients with low risk tumours could be candidates for AS as their primary management, therefore this option has some critical points yet unresolved: non uniform patient's selection, screening procedures and thresholds to activate definitive treatment are established. Again, is well documented that up to 30% of patients with Gleason score 6 at biopsy present Gleason score 8-9 at the pathological specimen. Regard toxicity some authors report high incidence of sexual dysfunction in patients that underwent prostatectomy after re-biopsy during AS.

P122
HIPOFRACTIONATED RADIOTHERAPY WITH IGRT IN LOW-RISK PROSTATE CANCER: RESULTS OF ACUTE TOXICITY

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Purpose: Hypofractionation presents crescent interest on the treatment of prostate cancer. We have evaluated the acute toxicity in patients with low-risk prostate cancer treated with hypofractioneted IGRT treated in our institution.

Materials and Methods: Between March 2007 and April 2012 we have treated 42 patients with low- risk prostate cancer (T1-T2 and Gleason score ≤6 and PSA ≤ 10 ng/ml)). The median age was 71 (range 58–82). All patients underwent prostate biopsy. Stage was cT1c in 17/42 patients (40.5%); cT2a in 13/42 patients (31%) ; cT2b in 9/42 patients (21.4%) ; cT2c in 3/42 patients (7.1%). Gleason score was 6(3+3) in all patients. All patients performed a simulation CT scan with 2,5 mm slice thickness to execute 3D conformal planning. They were immobilized in supine position with a footlocker. 28 patients (66.7%) were treated with a total dose of 45Gy on on the first 1.5 cm of seminal vescicles and 60 Gy on prostate; 3 Gy for fraction 5 times a week and a total time of 4 weeks. 14 patients (33.3 %) were treated with a total dose of 46.5 Gy on on the first 1.5 cm of seminal vescicles and 62 Gy on prostate; 3.1 Gy for fraction 5 times a week and a total time of 4 weeks. Margin from CTV to PTV was 5 mm in all directions. The external beam radiation therapy was performed with image guided technique (IGRT), with daily cone-beam TC. Follow-up evaluations were performed at 3, 6, 9 and 12 months after treatment, and every 6 months thereafter. Acute side effects were evaluated according to the RTOG/EORTC late morbidity Scoring Scale.

Results: Median follow-up was 19 months (range 2-61 months). The acute toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity in 6 patients (14.3%), grade 1-2 genitourinary (GU) toxicity in 18 patients (42.8%)%; grade 3 GU toxicity in 1 patient (2.3%). The toxicities 3 month after the end of the treatment were grade 1-2 GI in 3 patients (7.1%), grade 1-2 GU in 11 patients (26.2%). The toxicities 6 months after the end of the treatment were grade 1-2 GI in 1 patient (2.4%), grade 1-2 GU in 5 patients (11.9%). The median PSA before the start of radiotherapy was 5 (range 1.74-8.43) and at the last follow-up was 0.81 ng/ml (range 0-5.05 ng/ml).

Conclusions: This study showed that the hypofractionated radiation therapy was well tolerated with a low grade

of toxicity, but it need longer follow-up to determine possible late toxicity and local control.

P123
IMRT IN LOCALIZED PROSTATE CANCER

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Purpose: To evaluate acute and late toxicity in patients affected by low risk localized prostate cancer treated with IMRT.

Materials and Methods: From July 2008 to November 2010, 14 patients with low risk localized prostate cancer, underwent radiation therapy (IMRT) at the Radiotherapy department of "Vito Fazzi" Hospital in Lecce. Mean age was 72.5 months (range 65-80 months). The clinical stage was cT1/T2a, Gleason score <6 and PSA<10 ng/ml. This patients were treated with 78.5/2.24 Gy in 35 fractions to prostate and basis of seminal vescicles using a rotational dynamic IMRT (Serial Tomotherapy or VMAT®). The critical structures were rectum, bladder, femoral heads and penile bulb.

Results: The follow up was mean of 33 moths (range 19 to 48 months). High dose IMRT was well tolerated. Acute toxicity, measured with RTOG scale, was represented by urinary toxicity (grade 0= 10 pts, grade 1= 3 pts, grade 2= 1pts) and rectal toxicity (grade0= 8 pts, grade 1= 4 pts, grade 2= 2 pts). Three pts developed grade 1 late rectal toxicity and 2 pts grade 1 late urinary symptoms.

Conclusions: IMRT is the approach of choice for high-dose radiotherapy delivery. In our series, this treatment was well tolerated, since no patients had severe toxicity (grade 3). The 2 year biochemical control was 100%. However, additional follow up is necessary to fully define the long-term toxicity, the disease-free-survival and the overall survival. IMRT approach has been demonstrated to be useful in improving tumor coverage and sparing critical structures.

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AN INNOVATIVE METHOD TO PREDICT NODAL (N) STATUS USING AN ARTIFICIAL INTELLIGENCE APPROACH IN LOW RISK PROSTATE CANCER PATIENTS (PTS): BEYOND THE ROACH FORMULA?

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Aims: To present an innovative approach based on the methods of Artificial Intelligence to better predict N status in low risk prostate cancer pts, integrating some important clinical and therapeutic parameters (Gleason Score/sum, age, initial PSA, neoadjuvant or neoadjuvant/concomitant hormonal therapy *vs* no hormonal therapy), known before radiotherapy (RT).

Table 1.

Roach formula cut-off	False+ (FP)	False- (FN)	True- (TP)	True- (TN)	Specificity TP/ (TP+FN)	Sensibility TN/ (FP+TN)
>15%	18	12	0	634	0%	97%
>10%	136	9	3	528	25%	79%
>5%	238	7	5	426	42%	64%
Artificial Intelligence (total number of patients)*						
J48 U (24)	0	5	7	12	58%	100%
J48 O (1130)	28	0	480	622	100%	96%
J48 O/U (121)	8	0	60	53	100%	87%
Random Tree U (24)	5	6	6	7	50%	58%
Random Tree O (1130)	17	0	480	633	100%	97%
Random Tree U/O (121)	3	0	60	58	100%	95%
Random Forest U (24)	6	6	6	6	50%	50%
Random Forest O (1130)	13	0	480	637	100%	98%
Random Forest O/U (121)	6	0	60	55	100%	90%

**The number of patients seems to be different only because of the used methods. The real population accounted always for 664 pts and 12 N+ pts; O, Oversampling; U, Undersampling; O/U, Oversampling/Undesampling.*

Materials and Methods: We selected 664 "low risk" pts (D'Amico criteria) with a known N status at diagnosis from a database of the AIRO "Patterns of practice II" Study. N+ pts were defined as those with a positive contrast enhanced pelvic MRI and/or CT scan; those showing a nodal only relapse after RT were also classified as N+. 12/664 such "N+" pts (1.8%) were found. Using the Roach formula (2/3*PSA + ([Gleason-6] x 10) with a cut-off of >15%, >10% and >5% the individual risk of nodal involvement was calculated. Finally, 3 Artificial Intelligence methods (the J48 method, the Forrest Tree method and the Random Tree method) combined with 3 techniques of manipulation of the sample (oversampling, undersampling and combined under/oversampling) were used to predict the N status. The accuracy of the Roach formula was calculated.

Results: Table 1 resumes the performances of the Roach formula and of the 3 proposed methods. All the proposed Artificial Intelligence methods taking in account more clinical and therapeutic features perform better than the Roach formula. The classic approach showed a sensibility ranging, depending on the cut-off, between 0% and 42% and a specificity ranging between

97% and 64%. The 3 Artificial Intelligence methods showed showed a Specificity and a Sensibility of 100% (except for the Undersampling methods, 50-58%) and > 90% (except for the Undersampling in the context of the Random Tree method,58%, and the Random Forest method, 50%), respectively. The Random Forest method, combined to the Oversampling technique is the best method, with 98.7% of the instances correctly classified.

Conclusions: Roach formula's is suboptimal in predicting the nodal status of low risk prostate cancer patients. Non-linear relationships with more than two variables probably exist. New approaches taking into account more variables could possibly better predict the nodal status of the patients.

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CONFORMAL RADIOTHERAPY (3DCRT) IN THE MANAGEMENT OF LOCALIZED PROSTATE CANCER: OUTCOME AND ANALYSIS OF ACUTE AND LATE TOXICITY

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Introduction: At the Radiotherapy Department of "S.M. Goretti" Hospital in Latina we have been using the risk grouping system adopted by the National Comprehensive Cancer Network (NCCN) v.1.2008, to retrospectively review the records of the patients. We report our results.

Materials and Methods: From January 2002 to June 2008, 267 patients diagnosed with localized prostate cancer referred to our Department. The treatment consisted of a course of 3DCRT to the prostate (low risk) or prostate and seminal vesicles (intermediate and high risk). A total dose of 76 Gy in 38 daily fractions was delivered. High risk patients received concomitant and adjuvant hormone therapy, lasting two years as median time (range 2-76 months). From January 2002 to November 2005, a 5-fields 3DCRT technique was employed for the first one hundred patients (group 1). From December 2005 on, a 7-fields 3DCRT technique took place (group 2). We report acute and late rectal and urinary toxicity and correlation with dose-volume parameters. To state rectal toxicity, we record the dose to a volume of rectal wall (V40, V50, V60, V70, V72) for each patient.

Results: All patients received the prescribed dose. No G3 acute rectal and urinary toxicity was observed. We report G3 late rectal toxicity rates: 19% in the group 1 (5-field 3DCRT) and 4% in group 2 (7-field 3DCRT), p 0.001. No correlation was found between dose-volume parameters (V40, V50, V60, V70, V72) for rectal wall volume and the onset of late rectal toxicity. No G3 acute urinary toxicity rates was observed. Mild to moderate incontinence was reported in 2.5% of cases for each group, and uretral stenosis in 1.5% of the all series. After a median follow-up of 86.5 months (range 25-142) we report cancer specific survival (5y CSS: 99%; 10y CSS: 92%). Overal (5y OS 94.1%, 10y OS 67%), metastasis free survival (5y 93.8%, 10y 80%) and biochemical relapse free survival (b-NED 5y 87%, 10y 77%).

Conclusions: 3DCRT technique can be considered a safe and effective treatment for patients affected by localized prostate cancer. 7-field technique has a significantly better late ractal toxicity than 5-field 3DCRT. Althought no correlation was found between dose volume parameters and G3 late rectal toxicity, we suggest that a low dose of radiation therapy, given to an extended rectal wall volume causes a perfusion damage and represents the basis for mucosal ulcer event and severe rectal bleeding.

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RADIOTHERAPY OF PROSTATE CANCER IN PIEMONTE-VALLE D'AOSTA: RESULTS OF A RETROSPECTIVE MULTICENTRE SURVEY

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Aims: To investigate the standard of quality of radiation oncology in prostate cancer treatment in Piemonte-Valle d'Aosta.

Materials and Methods: The man questions were: number of patients treated with radiotherapy with exclusive or postoperatory intent, class of risk, modality of counseling, role of hormonotherapy in association to radiotherapy, treatments volumes, doses, fractionation, modality of contouring, treatment planning, organ motion control.

Results: All 13 Centres answered about years 2009-2010, whereas data about years 2004-2005 are lacking in several structures. Therefore, we now present only results about years 2009-2010. The number of patients affected by prostate cancer treated in 2009 and 2010 was 2392, equivalent to 11.5% of all patients treated with radiotherapy in this period (20.884). 1466 patients were treated with exclusive intent: 27% were classified as low risk, 35% as intermediate risk and 38% as high risk. 658 patients were treated with immediate postoperative radiotherapy and 268 with salvage radiotherapy (ratio 2.4:1). Counseling before therapy definition was carried out only in 6 Centres for the totality of

cases and in 1 Centre for 50% of cases. 64,6% of patients were submitted to neoadjuvant and/or concomitant and/or adjuvant hormonotherapy. Volumes of radiotherapy included nodal areas in 8% of patients treated with exclusive intent; this practice is reported in only 9 Centres. Pelvic nodes were included in 7% of patients irradiated in postoperative setting in 8 Centres. Main decisional criterium to irradiate the pelvis for exclusive radiotherapy was risk of N+ > 15% by nomograms. For postoperative radiotherapy, the majority of Centres includes pelvic nodes in treatment planning when histological report showed p N+.Some Centres don't use pelvic radiotherapy at all,regardless of some selection criteria,outside clinical trials.94% of patients irradiated by exclusive intent received a dose of radiotherapy >74 Gy and 60% of patients submitted to postoperative radiotherapy received a dose of at least 70 Gy. Hypofractionation was employed in 11.5% of patients in 5 Centres. Radiotherapy treatment was planned using magnetic resonance imaging (MRI) in 4 Centres, in 10.7% of patients. Radiotherapy with intensity modulation (IMRT) was used in 11% of patients treated with exclusive Radiotherapy, in 7 Centres, and in 5% of operated patients, in 6 Centres. IMRT was selected on the basis of unfavorable DVH, pelvic irradiation, hip prosthesis, age, stage. In years 2009-2010 image guided radiotherapy (IGRT) was available in 3 Centres and was employed in 10.7% of patients treated with exclusive radiotherapy and in 5.5% of patients irradiated postoperatively. A protocol to obtain empty rectum before each fraction of radiotherapy was regularly adopted in all Centres. Different protocols for bladder filling were used from different departments, as well as different treatmnet position (supine *vs* prone).

Conclusions: This survey shows that therapeutic choices in all Centres closely matches national and international guidelines on prostate cancer.A more homogeneous diffusion of new technologies (IGRT and IMRT)should further improve standard of quality. The number of patients treated with radiotherapy for prostate cancer in Piemonte-Valle d'Aosta each year is higly relevant and sharing data may help to promote important clinical studies.

P127

COST-ANALYSIS OF STAGING METHODS IN PATIENTS WITH PROSTATE CANCER AT LOW-RISK FOR RECURRENCE: THE VALUE OF BIOPTIC PARAMETERS *VERSUS* MRI BASED STRATEGIES

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Aims: Practice patterns in terms of clinical staging vary in subjects suffering from prostate cancer with low risk for tumor recurrence. The aim of this study was to perform a cost-analysis of three staging strategies in patients with prostate cancer at low risk for recurrence.

Methods: Three different strategy were planned: firstly, a strategy including PSA, DRE and TRUS without endorectal MRI and biopsy information (P1). The second strategy involves biopsy information with PSA, DRE and TRUS (P2). The third strategy consists of tumor staging with endorectal MRI strategy with PSA, DRE and TRUS (P3). These models represented the staging strategies for patients with prostate cancer and low risk for recurrence, comparing the costs of the three strategies. A decision analysis model with probabilistic sensitivity analysis was designed to evaluate the cost-effectiveness of the 3 staging protocols. Cost analysis was done from the health care perspective and as measure of impact on health, the so called outcome, in the cost effective analysis the overall survival at 10 years adjusted for general mortality was chosen. As indicators of staging efficacy the AUC value was chosen. The Incremental cost-effectiveness ratios (ICERs) was determined as follows: ICER= (differences in costs between P1 and P2 programs)/(differences in effects measured on health between P1 and P2 programs).

Results: The most cost-effective (dominant) strategies were determined for each staging strategy. The AUC values were 0.685, 0.840 and 0.890 for P1, P2 and P3 respectively. The model indicated that the expected costs for the P1 and P2 strategies were 811 euro. The expected costs for the strategy using endorectal MRI was 1091 euro. These results show that potential savings performing MRL instead of CT were 1,310 euro and 1,467 euro for PLNDP2 and P3 strongly dominated standard staging (P1) with the incremental costs (Delta C) for P2 equal to 0 € and 280 € for P3 respect to P1. For P2 and P3 the incremental outcome (Delta O) were 9.5 and 15.5 with the ICER of 0 and 18.6 respectively. These results were stable over a wide range of estimates for costs and utilities.

Conclusions: Our study found that biopsy based staging is more cost-effective than standard and MRI based strategies, for men with prostate cancer at low risk of recurrence supporting the hypothesis that MRI can be not recommended for the staging of PCA.

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ACUTE TOXICITY IN PROSTATE CANCER PATIENTS TREATED WITH VOLUMETRIC MODULATED ARC THERAPY: A SINGLE CENTRE EXPERIENCE

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Backgrounds: VMAT is an improved system of IMRT which can achieve high conformal dose distribution with improved target volume coverage and sparing of normal tissue. The aim is to report the clinical outcome in terms of acute toxicity of a radiation treatment for prostate cancer with RapidArc (RA).

Methods: 45 patients with prostate cancer (median age 73 years, range 58-83, T1: 8 patients T2: 37 patients, N0 Nx, M0 Mx, median PSA 9,47, range 3,4-26,7) were treated in an esclusive setting from April 2010 to April 2012. Mean dose prescription to the PTV ranged from 70 to 80 Gy. The PTV was the CTV with a margin of 0,9 cm in all directions except posteriorly where the margin was reduced to 0,6 cm. Daily check of patient positioning was performed for all patients by means of kV-cone beam CT (CBCT) system integrated in the machine (IGRT – image guidated radiation therapy). Genito-urinary and lower gastrointestinal acute toxicity was assessed weekly during radiation therapy and after 2 and 12 weeks from the end of it, according to RTOG Criteria.

Results: No severe G3 acute rectal toxicity was observed and only 2 patients experienced G3 urinary toxicity for gross hematuria; wherease G2 rectal and urinary toxicity was found in 3 (7%) and 8 (18%) patients, respectively. No difference in severe toxicity (G2/G3) was observed in the group of patients who received a prescription dose >74 Gy (23/45, 51%) compared with patients who received a dose <74 Gy (22/45, 49%). All treatments were completed without interruptions related to patients. Actually all patients achieved a biochemical response with decrease in the PSA index (Table 1).

Conclusions: On the base of these clinical results, more aggressive fractionation schemes (hypo-fractionation and simultaneous integrated boost (SIB) modalities to discriminate between prostate, seminal vesicles and pelvic nodes) have been introduced in our Centre, since January 2012.

Table 1.

N° patients		45	
Age (years)	Median and range	73 (58-83)	
Stage	T1	8 (18%)	
	T2	37 (82%)	
Gleason score	4	1	
	5	0	
	6	27 (60%)	
	7	13 (29%)	
	8	1	
	9	2	
	10	1	
PSA at staging (ng/ml)	Median and range	9,47 (26,7-3,4)	
	PSA <10 ng/ml	30 (67%)	
	PSA 10-20 ng/ml	13 (29%)	
	PSA >20 ng/ml	2 (4%)	
Hormonotherapy	Yes	20 (44%)	
	No	25 (56%)	
Dose prescription	Range	70-80	
	≤74 gy	22 (49%)	
	>74 gy	23 (51%)	
Rectal acute toxicity	G0	32 (71%)	
	G1	10 (22%)	
	G2	3 (7%)	
	G3	0 (0%)	
Urinary acute toxicity	G0	11 (24%)	
	G1	24 (53%)	
	G2	8 (18%)	
	G3	2 (5%)	
Rectal acute toxicity		**Dose ≤74 gy**	**Dose >74 gy**
	G0	17 (77%)	15 (65%)
	G1	3 (14%)	7 (31%)
	G2	2 (9%)	1 (4%)
	G3	0 (0%)	0 (0%)
Urinary acute toxicity		**Dose ≤74 gy**	**Dose >74 gy**
In patients with dose prescription	G0	3 (14%)	8 (35%)
	G1	14 (64%)	10 (43%)
	G2	4 (18%)	4 (17%)
	G3	1 (5%)	1 (4%)
PSA post RT (3 months after RT)	Median and range	1,64 (0,01-12,2)	34/45 patients (76%)
PSA post RT (6 months after RT)	Median and range	0,77 (0,01-6,6)	24/45 patients (53%)

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ADJUVANT AND SALVAGE RADIATION TREATMENT AFTER PROSTATECTOMY: WHERE DO RADIATION ONCOLOGISTS STAND?

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Backgrounds and Purpose: Current evidence from three prospective, randomized phase III trials support adjuvant radiation therapy (RT) after radical prostatectomy for patients with adverse pathologic features (APF) as it improves biochemical recurrence-free survival and overall survival. Despite this, many clinicians advocate for close observation of the patient after prostatectomy followed by salvage RT for recurrent disease. We conducted a Web-based survey to evaluate attitudes and practices of radiation oncologists (RO) regarding RT after prostatectomy.

Materials and Methods: A 34-item questionnaire was designed to capture attitudes and clinical approach of RO regarding postoperative use of RT, as well as its perceived benefits and potential side effects. The questionnaire was mounted in a Web-survey portal (surveymonkey.com) for administration. Survey invitations were emailed to all 716 RO practicing in the 147 radiation oncology centers that are listed in the AIRO roster. To increase survey participation, the survey link was also posted on the AIRO website. Descriptive statistics were generated for all variables of interest. Results. Analyzable questionnaires were completed by 154 RO (overall response rate, 21.5%). Adjuvant RT was recommended based on APF alone, or based on APF in addition to other factors (Gleason score or PSA), by 69% and 29% of respondents, respectively. The majority of respondents (78%) would recommend adjuvant RT within 3-6 months after surgery to allow time for postoperative urinary recovery. Regarding radiation planning technique preferences, three-dimensional conformal RT-more than 4 fields was indicated by 57% of respondents, followed by intensity-modulated RT (46%) and three-dimensional conformal RT-less than 4 fields (33%). Adjuvant RT doses were 64 to 66.6 Gy for 38% and 70 to 70.2 Gy for 36% of respondents. Sixty-two percent of respondents believed that adjuvant RT provides a long-term biochemical control but not overall survival benefit, and only 35% of RO agreed that adjuvant RT improves survival. Reported PSA thresholds for salvage RT were 0.2-0.3 ng/mL and 0.4-0.5 ng/mL for 43% and 23% of respondents, respectively. At adjuvant RT initiation, 9% of RO always advise patients to start hormone therapy and 77% only in patients with APF, while 11% never recommend hormone therapy. If hormone therapy is given, the majority of respondents (70%) suggest their patients take it for 2 years. Most respondents mentioned lack of recovery of urinary incontinence and of erectile dysfunction as major problem after adjuvant RT.

Conclusions: This is the first national survey regarding the attitudes and practices of RO about adjuvant RT in prostate cancer. Estimating between 1 and 2 RO per radiation oncology center dealing with RT in prostate cancer patients, we believe that a substantial proportion of RO with experience in the matter participated in the survey and therefore the survey results reflect the true, current RO beliefs toward RT. RO strongly support adjuvant RT after radical prostatectomy even though many RO do not believe that adjuvant RT increases survival despite the current evidence. Reported PSA thresholds for salvage RT show significant variability among RO. Additional research is needed to better define lower-risk subgroups of patients for whom adjuvant RT may be omitted and higher-risk patients for whom adjuvant RT should be administered.

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HORMONAL THERAPY IN LOW-RISK PROSTATE CANCER TREATED WITH RADICAL RADIOTHERAPY: IS IT CONSIDERED REALLY UNNECESSARY?

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Introduction and Aims: Management of low-risk prostate cancer remains a challenge for both urologists and radiation oncologists. Radical prostatectomy and radiotherapy are both radical treatments for localized prostate cancer, as opposite the role of hormonal therapy (HT) remains unclear. Although the majority of guidelines and published studies do not suggest the use of HT in low-risk patients, several studies have shown better outcome following combined radiotherapy and hormonal therapy in patients with low and intermediate risk. Therefore there are still doubts about the use of HT in the daily clinical practice. This analysis evaluates our experience in the clinical use of HT combined with radiotherapy (RT) in low-risk prostate cancer.

Patients and Methods: We retrospectively analyzed 87 patients with low-risk prostate cancer (cT1-T2a, PSA <10 ng/ml and Gleason score ≤6) treated with radical radiotherapy with or without hormonal therapy at the Radiotherapy Department of Foggia from January 2006 to June 2011. Median age was 74 years (range: 54-83). All patients underwent biopsy with histologically proven prostate cancer and they all were treated with radical three-dimensional conformal radiotherapy with a median dose of 76 Gy (2 Gy/die). The use, the type and the duration of HT were evaluated.

Results: Median follow-up was 42 months. Median pretreatment PSA was 6.7 ng/mL (range: 4.2-10) and median Gleason score was 6 (range: 3-6). HT was prescribed for 64.4% of patients of whom 28 patients (50%) received total androgen deprivation, 20 patients (35.7%) received bicalutamide alone (150 mg/die) and 8 patients (14.3%) received leuprorelin or triptorelin alone. Neoadjuvant HT was administered to 92.8% of patients. HT started between one and three months before radiotherapy, continued during the entire radiotherapy course and it was interrupted between three and eighteen months after the end of radiotherapy.

Conclusions: Although guidelines and most of previously published studies do not suggest the use of HT in low-risk prostate cancer patients, there are still many inconsistencies in the daily clinical practice regarding the use, the type and the duration of HT in this subgroup of patients. Our analysis suggests that most of the patients with low-risk prostate cancer still received HT in daily practice, at least in our experience. Moreover, in agreement with previously published results, our analysis seems to confirm the inconsistencies regarding the type and the duration of HT. It seems therefore necessary to better understand the role of combined radiotherapy and HT for this subgroup of patients in order to standardise the daily management of these cancer patients.

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CLINICAL PREDICTORS OF LATE RECTAL TOXICITY IN ELDERLY PATIENTS WITH LOW AND INTERMEDIATE RISK PROSTATE CANCER

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Aims: According to international guidelines, active surveillance is an alternative option to radiotherapy for patients with low and intermediate risk prostate cancer, particularly if the life expectancy is less than 10 years. Clinical predictors of an increased risk of toxicity might help to guide the choice. Objective of this study was to assess the impact of clinical factors, particularly co-morbidities, on late radiation induced rectal toxicity in elderly patients with prostate cancer.

Materials and Methods: Patients aged 70 years or older with low and intermediate risk prostate adenocarcinoma treated with either three-dimensional conformal radiotherapy (3DCRT), or intensity modulated radiotherapy (IMRT) and a minimum of six months follow up, were selected. The correlation between late grade ≥ 2 RTOG rectal toxicity and a number of factors was investigated by uni- and multivariate analysis. Standard time-to-event (survival analysis) methodology was used to assess the first reported incidence of toxicity. Events were timed from the end of radiotherapy, and the differences between the treatments groups were first tested using the log-rank test. After that a multivariate analysis was performed including all covariates that appeared to be associated with the endpoint in the first analysis (covariates with p-value ≤ 0.25). Relative risks of late grade ≥ 2 RTOG rectal toxicity according to treatment are summarized using hazard ratios (HR) with 95% confidence intervals (CI) from Cox regression models.

Results: Sixty-six patients who underwent to radiotherapy at our Institution between December 2002 and November 2011 were selected for this analysis. Median age was 74 (range 70-82) years. Sixteen patients (24.2%) had low- and 50 patients (75.8%) had intermediate-risk prostate cancer. Cumulative incidence of late RTOG grade ≥ 2 rectal toxicity at 3 years was 15.9%. At univariate analysis only age ≥75 years, EQD2 ≥ 75 Gy, and hypofractionation among other factors (previous abdominal surgery, IMRT use, pelvic irradiation, hormonal therapy, smoking and alcohol consumption, co-morbidities such as arterial hypertension, diabetes, heart disease, obesity, and Charlson Comorbidity Index) were found to be possibly associated with a higher incidence of late grade ≥ 2 rectal toxicity (p ≤ 0.25) and were retained for multivariate analysis. At multivariate analysis (see Table 1 for details) statistical significance (p-value ≤ 0.05) was reached by none of these variables, although a trend was found for age ≥75 years (p-value = 0.06).

Table 1. Multivariate analysis of potential predictors for late RTOG grade ≥2 rectal toxicity in elderly patients with low and intermediate risk prostate cancer.

Variables	Hazard ratio	95% C.I.	P value
Age ≥75 years	4.917	0.9172-26.3603	0.063
EQD2 ≥75 Gy	3.1454	0.6684-14.8023	0.147
Hypofractionation	4.2453	0.6676-26.994	0.1255

Conclusions: Ageing of population is a well known phenomenon in Western countries, so prostate cancer incidence is expected to further increase in the next years. Together with the availability of limited resources for health care expenditure, demographic change means that it has never been more important to find evidence-based treatment strategies for elderly patients. Radiotherapy for elderly patients with low- and intermediate risk prostate cancer could be not only useless but even more toxic, especially in the very elderly (age ≥ 75 years). Dose intensification strategies, such as hypo-fractionation and dose escalation, should be cautiously attempted in this patient population.

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CORRELATION BETWEEN PSA NADIR AND METABOLIC ATROPHY ON [1H]-MSRI IN LOW RISK PROSTATE CANCER PATIENTS TREATED WITH EXTERNAL BEAM RADIOTHERAPY

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Purpose: To evaluate the efficacy of magnetic resonance spectroscopy for early detection of the metabolic nadir in irradiated low-risk prostatic patients.

Patients and Methods: From November 2009 to November 2011, 22 patients with low risk prostate cancer treated with external beam radiotherapy (EBRT), underwent Magnetic Resonance Spectroscopy Imaging ([1H]-MRSI) before (T0) and after 3, 6, 12 and 18-24

months the end of radiotherapy. Our imaging protocol consisted of morphological T2-weighted high-resolution sequences, diffusion weighted sequences (DWI),[H1]-MRSI and perfusional GRE T1-weighted sequences with the utilization of a combined surface and endorectal coil. All patients underwent serum PSA determination during the follow-up.

Results: Data were processed on a dedicated software calculating both (Choline+Creatine/Citrate) and (Choline/Citrate) ratios; a prostatic metabolic atrophy (ratio=0) was demonstrated in 18 out of 24 patients at 6 months while, from a serologic point of view, only 6 out of 24 patients had a low PSA level. On the contrary, both PSA levels and imaging, suggested a prostatic atrophy in 22 out of 24 patients (accuracy 91.6%, $p<0.05$) 18 months later.

Conclusions: [1H]-MRSI permits an earlier detection of prostatic atrophy achieving in a shorter time the metabolic nadir compared to PSA only with higher accuracy rates.

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UPDATE OF MULTIDISCIPLINARY EXPERIENCE OF BRACHYTHERAPY WITH IODINE-125 IN LOW-RISK PROSTATE CANCER AT GALLIERA HOSPITALS IN GENOA

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Purpose: To show the current practice of permanent implant brachitherapy with iodine 125 at Galliera Hospital in the low-risk prostate cancer and the analysis of biochemical control of prostate cancer.

Materials and Methods: From January 2003 until now 89 pts have been implanted for low-risk prostate cancer according to the selection criteria estabilished by involved multidisciplnary team. Patients characteristics are the followings: Mean age 69.8 years, Mean PSA value 7.26 ng/mL, Mean Prostatic volume 30.3 cc, Mean IPSS 7.5, neoadjuvant H.T. in 39 pts, post BT H.T. in 16. Prescription Dose (PD)145 Gy. Dosimetric parameters of intraoperative planning are the following: prostate D90% > 145 Gy, V100 must be at least 95%; rectal D(1.3 cc) Gy < reference PD of 145 Gy; prostatic urethra D10 <150% of PD, D30 < 130% of PD.

Results: Mean PSA value at 18 months follow-up is 0.93 ng/mL; Mean PSA value at 24 months follow-up is 1 ng/mL. We observed 3 deaths for other causes and no cancer related. Most of pts worsened urinary function after BT but only twelve had acute postimplantation disuria and nine had PMR > 50 mL at 24 months. Two cases of G2 rectal toxicity were registered. Until now we have observed 3 biochemical relapses (at 36,48,60 months),treated with hormone therapy.

Conclusions: The brachytherapy treatment has confirmed to be safe, effective and well tolerated in our experience. LDR BT continues to be a valuable treatment option in comparison to External Beam Radiotherapy or Radical Prostatectomy in well selected Low Risk prostate cancer patients.

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LOW RISK PROSTATE CANCER: ACTIVE SURVEILLANCE PROGRAM IN A RADIATION ONCOLOGY CENTER

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Backgrounds and Aims: According to NCCN and NICE guidelines, Active Surveillance (AS) is an appropriate treatment option for patients (pts) with Low Risk Prostate Cancer (LRPC) when life expectancy <10y or VeryLRPC when life expectancy <20y.(1,2) We analyze the database of our AS Program to validate AS and prevent overtreatment. Secondary endpoints are clinical, biochemical or pathological progression (C, B, PP) the number of men changing therapy and the prostate cancer mortality.

Methods: In Udine, we introduced an algorithm for eligibility criteria (EC), follow up schedule (FUS) and appropriate triggers for intervention (TFI). In a prospective observational way, previous carefully information, EC were: PSAng/mL<10; Gleason<7; T1a-T2a; depending on age and comorbidity: <3 cores involved, <50% of any 1 core. FUS was: PSA, DRE every 3 months for 2 ys, then every 6 months; assuming PSA is stable recorebiopsy at 12 to 18 months and then every 3 to 5 ys until age 80; TRUS was optionally considered. TFI were: clinical progression, biochemical progression for PSA>10 (3 consecutive values) or PSA doubling time <3 years (based on at least 6 determinations) or PSA velocity >2 ng/mL/y, calculated by MSKCC software, and pathological progression for upgrading to Gleason >6 (4+3) or upsizing to >2 cores involved.

Results: Since 2000, we enrolled 42 pts with mean age of 71 (range 54-80); according to T classification, four were T1a, 1 was T1b, 27 were T1c, 9 were T2a and one was T1b; mean PSA was 5.34 (0,45-14,82); on 37 cases mean Gleason was 4.97; 23 pts undergone to recorebiopsy, 6 had another recorebiopsy and 5 pts refused. Seven pts resulted pathological free. TFI were on 13 (30.95%) pts: 2 for upgrading, 1 for upgrading+PSAV, 1 for upgrading+PSADT; 3 for upsizing, 2 for upsizing+PSADT and 1 for upsizing+PSADT&V; 3 for PSADT&V.(see Table 1) Two pts refused treatment; 7 pts went to RT; 4 pts went to Hormonal Therapy (HT); one went to surgery and one to Wait & See for concomitant worse Performance Status. Two pts changed therapy for psychological reason (one pt asked RT and one HT). At a medium follow up of 52 months (range 14-132), forty pts are alive without prostate cancer progression. One pt died at 21 months for cardiac failure and 1 pt died at 22 months for lung cancer. Then we prevent overtreatment in 29/42 (69.04%) pts according to preliminary data from PRIAS ITA Study.(3)

Table 1.

Triggers for intervention (TFI)	PTS	%
Upgrading	2	4.76
Upgrading + PSAV	1	2.38
Upgrading + PSADT&V	1	2.38
Upsizing	3	7.14
Upsizing + PSADT	2	4.76
Upsizing + PSADT&V	1	2.38
PSADT&V	3	7.14
	13	30.95

Conclusions: Biochemical and/or pathological progression were noted on 13 pts and we had no prostate cancer associated deaths. Our AS Program is feasible and is validate to prevent overtreatment for 29/42 (69.04%) pts enrolled. According to the literature, anxiety for cancer progression and fear for treatment side effects were important issues to choice or to refuse therapy.(4)

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BRACHYTHERAPY WITH I-125 SEED PERMANENT IMPLANT AND INTRAOPERATIVE PLANNING IN LOW RISK PROSTATE CANCER: OUR RESULTS AT 5-YEAR FOLLOW-UP

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Aims: To evaluate retrospectively the impact on five years Biochemical Relapse Free Survival (BRFS) and acute and late toxicity of real time intraoperative I-125 seed permanent implant brachytherapy (PB) in patients with low-risk prostate cancer.

Materials and Methods: From 2006-2012 we performed 24 LDR-brachytherapy I-125 seed implants with NUCLETRON SPOT-FIRST® intraoperative planning system. Patients were selected according to ESTRO/EAU/EORTC guidelines accounting stage T1-2 N0 M0; GS ≤ 6, iPSA ≤ 10 mg/ml, IPSS score = 10, Qmax urinary flow > 10 ml/min. Mean age was 68 years (62-77). One patient had TURP in 2003 showing a gland loss < 20%. Hormonal therapy as LH-RH analogue or bicalutamide was delivered by the urologist to achieve gland downsizing or to prevent acute urinary discomfort in 15/24 patients since the time of diagnosis and discontinued 3 months after the implant (8 months mean time). Prescription dose for all patients was: 145 Gy to the prostate gland, D90 ≥ 145 Gy, V100 ≥ 95%. For rectum D1cc was < 160 Gy and D1% for urethra was < 220 Gy. Post implant dosimetry was assessed 30 days after brachytherapy implant by the same experienced radiation oncologist on computed tomography 2.5 mm sections contouring the prostate gland only. Patients were followed-up every 3 months during the first 2 years with clinical evaluation, prostate-specific antigen (PSA) determination, uroflussometry and IPSS score and each six months later. Urinary and rectal morbidity were recorded according CTCAE v.3 criteria. Biochemical recurrence and time to recurrence were defined according to Phoenix definition.

Results: mean intraoperative planning D90 and V100 were 174 Gy (173-192Gy) and 98% (97-99.7) respectively. Mean assessed post dosimetry D90 was 115 Gy (80-183 Gy),V100 was 93% (58-97%). Only in 6 patients post implant D90 was ≥ 140 Gy and only in 3 patients V100 was ≥ 93%. Mean D90 and mean V100 were 107 Gy and 80% respectively for biochemically relapsed patients. Mean follow-up was 45 months (range 5-84): 1 patient died 24 months after PB due to severe lung comorbidity; Grade 1-2 urinary morbidity occurred in almost all patients (dysuria, urgency, hesitancy) for several weeks after PB. Acute urinary retention occurred in 3 pts and was related to pre-implant mean IPSS = 14 and urethra D1% mean dose 197 Gy (190-204 Gy); 2/3 patients had TURP. Severe urinary incontinence was recorded in 1 patient implanted two years after TURP. Only one patient developed late G2 rectal morbidity (self-limiting rectal bleeding). Three out of 24 patients relapsed (12.5%) with mean time of 22 months (12-31) to biochemical failure (BF). The relative risk (RR) to develop BF was 2.4 when post planning D90 was ≤ 115 Gy *vs*. D90 >115. The actuarial BRFS at five years was 86% for the all serie, but 100% *vs*. 79% for D90 ≥ 130 Gy.

Conclusions: I-125 brachytherapy is a good option in low risk prostate cancer and no severe morbidity was recorded in well selected patients. An optimal implant confirms a good predictive factor for BRFS. Correct post-implant evaluation is influenced by radiation oncologist experience. TC/RMN image fusion could ameliorate post implant contouring reducing uncertainties.

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BIOCHEMICAL OUTCOME AFTER EBRT OR LDR-BCT FOR PATIENTS WITH LOW-RISK PROSTATE CANCER: TEN YEARS EXPERIENCE

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Aims: the primary endpoint of this retrospective study is to compare Biochemical Relapse Free Survival (BRFS) according to Phoenix consensus definition in the low-risk prostate cancer patients who received external beam radiotherapy (EBRT) or brachytherapy (BCT).

Materials and Methods: between January 2002 and December 2011 we evaluated in our center 61 patients with clinically low-risk prostate cancer who were eligible to radiotherapy as first treatment option. Inclusion criteria were local clinical stage T1-T2a N0 M0 prostate cancer, biopsy Gleason score ≤ 6, serum prostate-specific antigen (PSA) level ≤ 10ng/mL; for patients treated with BCT IPSS mean score ≤ 10 and Qmax urinary flow > 10 ml/min were requested according ESTRO/EAU/EORTC guidelines. The clinical parameters used for analysis included pretreatment PSA determination, radiation dose, PSA bounce, androgen deprivation and acute and late toxicity. Time to PSA failure was defined as the time of

the registration of PSA value > nadir + 2ng/mL according to Phoenix consensus definition (2006).

Results: thirty-six patients received 3D conformal EBRT. The median EBRT dose was 73.1 Gy (range: 55–86 Gy) delivered in 200 cGy daily fractions, 5fr/wk. Twenty-five patients received neoadjuvant and/or adjuvant LH-RH analogue with a median duration of 5.3 months according to urologist prescription. The mean age of the patients was 70.5 years (range: 57-81) and the mean follow-up time was 45 months (range: 6-96. Twenty-five patients were treated with I-125 seed BCT with intraoperative planning system NUCLETRON SPOT-FIRST® and received 145 Gy or 120 Gy + EBRT (1 pnt). Fifteen of the second group of patients received LH-RH analogue according to urologist prescription to achieve gland downsizing or prevent acute urinary discomfort since the time of diagnosis (8 months mean time); they discontinued LH-RH analogue 3 months after the implant. The mean age of the patients was 68 years (range: 62-77); the mean follow-up was 45 months (range: 5-84). According to Phoenix definition 2/36 patients (5,55%) treated with EBRT and 3/25 (12%) who received BCT or BCT+EBRT had a biochemical relapse. Mean time to biochemical failure detection was 42 months for EBRT and 22 months for BCT. Relative risk (RR) of biochemical relapse for BCT treated patient *vs*. EBRT patients was 2.14, but when we consider the relapsed patients in best implanted group (1/13 for post-implant D90 > 115 Gy) RR reduces to 1,37. Actuarial BRFS at 5 years for the group of patients treated with EBRT was 96% *vs*. 86% for those treated with BCT (p=0.35, ns). BCT best results were obtained for D90 ≥ 130 Gy (5-years BRFS 100% *vs*. 79%, p= 0.2). The maximal GU toxicity observed for EBRT group was grade 3 in one patient. No grade 4 GU toxicity occurred. The maximal GI toxicity was grade 2 in 19%. In the BCT group G1-2 GU toxicity occurred in almost all patients (dysuria, urgency, hesitancy) for several weeks after PB. Acute urine retention occurred in 3 patients and was related to pre-implant mean IPSS = 14 and urethra D1% mean dose 197 Gy (190-204 Gy); 2 patients had TURP while 1 patient developed urinary incontinence due to a previous TURP two years before the implant. One patient developed G2 GI toxicity (self-limiting rectal bleeding).

Conclusions: in this study cohort about clinically low-risk prostate cancer patients BFRS and toxicity for best implanted well selected BCT patients are similar to those treated with EBRT.

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LOW-RISK PROSTATE CANCER: HIGH DOSE RADIATION THERAPY (HD-RT)

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Purpose: International guidelines recommend in low-risk prostate cancer a radiation dose >74 Gy. Recent studies have shown that increasing the dose improve bPFS in all risk classes. We have evaluated feasibility of High Dose Radiation Therapy (HD-RT) in patients with low-risk prostate cancer.

Materials and Methods: From January 2008 through December 2011, 54 patients with low-risk prostate adenocarcinoma, according to National Comprehensive Cancer Network definition, were treated with radiotherapy. All patients underwent to MRI in order to confirm organ-confined PCa. HD-RT was delivered by means of IMRT, with standard daily fractionation (200 cGy) up to total dose of 80 Gy to the prostate gland; seminal vesicles have been treated up to 56 Gy; no patient received elective pelvic lymph node irradiation. All patients underwent each other week to physical examination, blood count; toxicity was recorded according to CTC vers. 3.0 scale. Patients were routinely checked after therapy to evaluate side effects and relapse.

Results: Median age was 76 years (range 60-84). The median follow-up for patients was 24 months (range, 3-50 months). The median PSA declined from 6.12 ng/mL at diagnosis to 0.33 ng/mL at last follow-up. Treatment was generally well tolerated with 28 patients (51.9%) without any Gastro-Intestinal (GI) and Genito-Urinary (GU) event. Acute toxicity was as follows: 16 patients (29.6%) developed grade 1 GU and 3 patients (5.6%) grade 2; grade 1 GI toxicity was observed in 12 patients (22.2%). No grade 3 or more acute toxicity was recorded. Fifty patients (92.6%) are evaluable for late toxicity. Three events (6%) of grade 1 GI toxicity and only 2 (4 %) grade 2 GI toxicity have been recorded after treatment completion. Three patients (6%) had a grade 1 GU late toxicity.

Conclusions: HD-RT delivered with IMRT technique up to 80 Gy, deserves very low toxicity both acute and late.

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PERMANENT BRACHYTHERAPY AS SALVAGE THERAPY FOR LOCALLY RECURRENT PROSTATE CANCER AFTER EXTERNAL BEAM IRRADIATION

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Purpose: To estimate the incidence of acute and late toxicity and to evaluate the biochemical outcome after transperineal ultrasound-guided permanent prostate brachytherapy (PPB) for local failure after initial external beam radiotherapy for prostate cancer.

Materials and Methods: Between 08/2000 and 04/2011 21 patients underwent salvage PPB using 125I for intraprostatic recurrence after external beam radiotherapy. The median patient age was 70 years (range, 52-81). According to NCCN 2012, the risk group distribution at initial diagnosis was as follows: low risk 3 patients (14.3%), intermediate risk 6 patients (28.6%) and high risk 12 patients (57.1%). The median time from first treat-

ment until salvage brachytherapy was 46 months (range, 24-111 months). The median PSA-doubling time was 8.6 months. All patients were treated using a perioperative treatment planning with dedicated hardware and software. Total re-irradiation dose was 145 Gy. Prior to PPB 13 patients were treated with androgen-deprivation therapy. Urinary symptoms (International Prostatic Symptom Score, IPSS) and uroflowmetry were evaluated before treatment: the median IPSS was 4 and the median maximum flow rate was 14 ml/sec. Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria and Houston-Phoenix definition were used for toxicity and biochemical failure evaluation, respectively.

Results: The median follow-up was 32 months (range, 8.3-88.7). Three patients developed acute urinary retention. Five patients developed mild urinary urge incontinence and 16 patients developed G2 urinary toxicity. Only 2 patients developed G2 rectal toxicity. At last follow-up 9 patients (42.8%) are alive with biochemical failure, 2 of whom with metastatic disease, and 3 patients (14.3%) died with metastatic disease. Six patients (28.6%) are alive without biochemical failure and 3 patients (14.3%) died for other causes without evidence of disease. The biochemical control rate using risk category at first diagnosis was 33%, 50%, and 41.6% in patients with low, intermediate and high risk prostate cancer, respectively.

Conclusions: Salvage PPB after irradiation is feasible with relatively low urinary and rectal morbidity. No patient had a clear evidence of intraprostatic recurrence. These early results are comparable with literature. Further experience and longer follow-up are needed to evaluate the role of PPB in the treatment of local recurrences.

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PROSTATE POSITIONING USING CONE BEAM COMPUTER TOMOGRAPHY (CBCT): INTER-OBSERVER AGREEMENT AMONG RADIATION ONCOLOGISTS AND THERAPISTS (RTTS)

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Purpose: to analyze the inter-observer agreement among radiation oncologists and technologists (RT therapists, RTTs) in interpreting cone beam CT (CBCT) images for patient set-up verification in prostate radiotherapy.

Materials and Methods: Prospective analysis of inter-observer agreement in the CBCT-based IGRT for prostate cancer was undertaken. The study was notified to the institutional Ethical Committee. Patient inclusion criteria were: cT1-2N0M0 prostate cancer, candidates for radical external beam intensity modulated volumetric arc radiotherapy (RA-IMRT) with daily CBCT-based prostate localization performed between February 2011 and March 2011; treatment volume including prostate only or prostate and seminal vesicles; no hip prosthesis, no previous radiotherapy or surgery for prostate cancer; written informed consent for the treatment. Patients treated with pelvic irradiation were not eligible. The manual CBCT-simCT registration for target alignment refinement performed immediately before treatment (on-line) by a radiation oncologist was used as reference data for evaluating the quality of RTTs corresponding assessment. All pre-treatment CBCT images were reviewed off-line independently by 4 blinded observers (one radiation oncologist, one junior and 2 senior RTT). All observers underwent a short training on CBCT images interpretation and matching procedures. CBCT images were first matched automatically and then manually refined by the observer.

Results: One-hundred fifty two cone-beam computer-tomography (CBCT) prostate positioning procedures were performed off-line by 4 observers (one radiation oncologist, 3 therapists) and benchmarked with on-line CBCT-positioning performed by radiation oncologist. Altogether, 608 CBCT-simCT comparisons were performed ending up with 2432 parameters (3 translations and one rotation). Satisfactory inter-observer agreement was found, being substantial (weighted Kappa > 0.6) in 10 out of 16 comparisons and moderate (0.41 - 0.60) in the remaining 6 comparisons.

Conclusions: Our results show good agreement between radiation oncologists and RTTs in CBCT-based prostate position verification. RTTs' CBCT interpretation seems comparable to that of radiation oncologists. These findings might be useful for department workload optimization and might allow the wider adoption of complex and evolving radiotherapy technologies.

RADIOTERAPIA E TRATTAMENTI SISTEMICI NEL CARCINOMA DEL PANCREAS: UPDATE

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INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED PANCREATIC CANCER

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Aims: Prognosis of pancreatic adenocarcinoma remains poor. Surgical resection is currently the only curative option, but the majority of patients (Pts) present with locally advanced pancreatic cancer (LAPC) or metastatic disease. Therapeutic options include systemic therapy alone, concurrent chemoradiation (CT-RT), or induction

chemotherapy (CT) followed by CT-RT. The aim of this study was to investigate the feasibility and efficacy of induction CT with gemcitabine followed by CT-RT for LAPC.

Patients and Methods: A retrospective analysis was conduced on 19 consecutive Pts with unresectable LAPC treated with 3 cycles of induction CT (gemcitabine 1000 mg/m2 days 1-8 over 21day). Those without disease progression received CT-RT. Radiotherapy (RT) was delivered to a dose of 45Gy (1.8Gy/fractions-5days/week) to the gross tumor volume and regional lymph nodes by using three-dimensional treatment planning. Continuous infusion 5-FU was given with RT.

Results: A total of 19Pts (13males and 6females, median age 69.5years) with histologically proven LAPC were treated. Eleven (58%) had tumors in the head of the pancreas and 8 (42%) had biliary stents placed prior to CT. Three cycles of induction CT were completed in 17Pts and 15Pts received CT-RT, which was completed without delay in all. Median follow-up time was 11.2months (range 6-15months). After the completion of CT-RT, 3Pts (15.8%) achieved complete resolution and 16Pts (84.2%) a partial response. Distant metastasis occurred in 6Pts (31.6%); local recurrence was only in 2 of 19Pts (10.5%). Median overall survival was 10.9months, with 1year survival rate of 44.2% Median time to progression was 9.2months. Grade 1-2 toxicities associated with induction CT were neutropenia (48%); anemia (19%); thrombocytopenia (10%); nausea (25%); anorexia (47%); vomiting and fatigue (29%). Grade 1-2 toxicities among those receiving CT were neutropenia (13%) anorexia (33%) and nausea (45%).

Conclusions: CT-RT was generally well tolerated, with the most common dose-related grade 1-2 adverse events being anemia, nausea, vomiting, anorexia and abdominal pain. In the present study the use of induction CT gemcitabine-based and followed by CT-RT improved median survival and locoregional tumor control in LAPC. 5-FU can safely be combined with external beam RT. Further consideration of radiation schedule and duration of induction CT is required to enhance the efficacy of this strategy.

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RADIOTHERAPY (IG-IMRT) USING TOMOTHERAPY AS THE FUNDAMENTAL ELEMENT OF A MULTIMODALITY TREATMENT OF PATIENT WITH UNRESECTABLE/LOCALLY ADVANCED PANCREATIC CARCINOMA: EXPERIENCE OF A SINGLE INSTITUTION

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Aims: Evaluation of overall survival(OS),metastasis-free survival (MFS), disease-free survival(DFS) and time to progression(TTP) in patients (pts) with locally advanced pancreatic carcinoma (U-LAPC) treated with radiotherapy (RT) +/- neoadjuvant (NAD) and concomitant chemotherapy (CHT).

Patients and Methods: A retrospective analysis of 19pts treated by RT+/-CHT for LAPC between 2008 and 2011. Median age was 65 years. Clinical stages at diagnosis were: IB in 1(5%)pt,IIA in 3(16%),IIB in 2(11%) and III in 13(68%)pts using AJCC TNM. For 13(68%)pts,2 treatment volumes were defined: PTV2 (gross tumor and loco-regional nodes related to subsite of origin), PTV1 (gross tumor volume and involved nodes).Median RT dose were 50.4Gy to PTV2 and 55Gy (range 50.4-66) to PTV1. 18pts 94.7%) received NAD CHT and 15 of them (78.9%) underwent concomitant CHT. 3pts(15.7%) were treated only with RT(25Gy in 5fractions) to gross tumor volume due to comorbidities.

Results: Median follow-up was 8.8 months. No patient developed G3-G4 toxicities. Other toxicities were: cutaneous (G1 in 1pt), nausea/vomiting (G1:8pts and G2:2pts),diarrhea(G1:2pts,nobody G2),asthenia (G1:4pts, G2:2pts),weight loss (G1:5pts,G2:1patient). Median overall treatment time was 39 days while hypofractionated treatments were delivered within 1week. 2pts (10.5%) underwent surgery after combined treatment (1pt achieved complete pathological response,in one other a downstaging was obtained).Median OS was 13.2months, 1- and 2-year OS were 54%±12%ES and 25%±13%ES respectively.Median MFS was 13.8 months,1- and 2-year MFS were 52%±13% and 14%±12%ES respectively. Median DFS was 8.3 months, 1- and 2-year DFS were 40%±12% and 9%±8% respectively. Median TTP was 8.3 months,1- and 2-year TTP were 39%±12%ES and 10%±9% respectively. Better outcomes were achieved in patients who underwent surgery after NAD treatment:these 2pts are still alive nowadays.

Conclusions: Treatment of LAPC is still a challenge. Multimodality approach seems to offer better results in terms of clinical outcomes especially when it gains a downstage of the tumor making surgery feasible. Even referred to a small number of pts our results are comparable to literature. IG-IMRT can offer a better toxicity profile and it should be use when an hypofractionated treatment is the best choice for the patient.

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RETROSPECTIVE ANALYSIS IN THE TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER BY EBRT + CHEMOTHERAPY: OUR EXPERIENCE

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Backgrounds and Aims: Chemoradiotherapy (CT-RT) represents the standard for borderline/locally advanced pancreatic cancer (BLA-PC), with the neo-adjuvant (borderline patients in order to obtain resectability) or radical intent (unresectable forms) with or without induction chemotherapy. The aim of this paper is to show our experience in patients with BLA-PC treated by CT-RT.

Methods: Between 2001 and 2011, 66 patients (pts) were treated at IRCC (Candiolo) and Mauriziano

Hospital (Turin). 8 patients were excluded from analysis (3 due to no follow up, 5 to treatment break). 48 pts were evaluable (28 female, 30 male): 26 with radical and 32 with preoperative intent. Mean age: 63.39 years (range 43–77). Histology: adenocarcinoma in 56 pts; 2 pts radiological diagnosis. Stage: T4 in 47 pts, T3 in 10, T2 in 1; 28 pts had nodal involvement, 2 metastatic disease. 48 pts received induction CT before concurrent CT-RT, 1 received RT alone after induction CT, 4 straightly concurrent CT-RT, 4 received RT alone. 55 pts were treated with 3D-CRT and 3 with IMRT.

Results: Average dose was 49.33 Gy (range 41.4 - 61.2 Gy) with conventional fractionation. The mean follow up was 12 months (range 1-64). 12 patients (20%) received radical surgery after combined approach: 9 out these started with preoperative intent (28%), 3 with radical intent (11%). 24 pts (14 %) underwent palliative surgery. 5 pts (8%) died during follow up, 6 (10%) had a stable disease, 1 (2%) a partial response, 46 (80%) a progression disease (PD). Local control was achieved in 20 pts (34,4%), 7 (12%) were lost to follow up; 43 (74%) cases had systemic PD, of these, 23 (39%) associated with local PD. The average relapse free survival (RFS) was 9 months (range 1-48), average local progression free survival (PFS) was 8,17 months (range 1-27). Pts undergoing radical surgery had a statistically significant (p value 0.035, HR 0,4) PFS longer than those non-operated (47 months *vs*. 20 months).

Conclusions: Our results about pts with borderline/advanced disease (>75% T4 and/or N+) are in agreement with the literature data regarding RFS and regarding pts receiving surgery after concurrent CT-RT (20%). Moreover our results show that 28% of pts enrolled in a preoperative setting completed treatment and 11% of those planned for radical treatment had a unexpected good tumor regression and then received radical surgery. This is a relatively good result considering the poor prognosis of these tumors.

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INDUCTION CHEMOTHERAPY WITH GEMCITABINE FOLLOWED BY TWICE WEEKLY ADMINISTRATION OF LOW DOSES OF GEMCITABINE CONCURRENT WITH RADIOTHERAPY IN LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA

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Aims: To retrospectively evaluate the feasibility and toxicity of chemotherapy with gemcitabine, followed by radiotherapy combined with weekly administration of low doses of gemcitabine in patients with non metastatic, locally advanced pancreatic adenocarcinoma.

Materials and Methods: From November 2002 to July 2011 20 patients were treated in our institution (8 females and 12 males). Mean age was 61.6 years (range 42-79). Exclusion criteria was extraregional retroperitoneal lymph nodes positivity. At the time of diagnosis, prevailing stages were IIb and III respectively with 7 and 5 patients, followed by stage IV (4 patients), IIa (3 patients) and stage Ia with only one patient. Tumour location: head of pancreas in 12 patients, body in 3 patients, head and body in 2 and body and tail in 3 patients. Histologic diagnosis was ductal adenocarcinoma in 19 patients, acinar cell carcinoma in one patient. All patients initially underwent two cycles of chemotherapy with gemcitabine at a dose of 1000 mg/m i.v. Patients were then reassessed. If a partial response or stable disease were documented, patients continued with radiotherapy on the pancreatic loggia with a total dose of 45 Gy (1.8 Gy/day for 5 days/week) with concomitant weekly administration of gemcitabine at a dose of 40 mg/m i.v. At the end of the concomitant treatment a new reassessment was performed. All patients with documented progression of disease continued chemotherapy with gemcitabine at a dose of 1000 mg/sqm, with biochemical and instrumental reassessment every two cycles of treatment and until progression of disease.

Results: Mean follow-up was 10 months (range 1-27). After the completion of concurrent chemoradiotherapy 4 patients (20%) achieved a stable local disease, 7 patients (35%) experienced a local progression, and in 9 patients (45%) appeared distant metastases in lungs, liver, brain and chest wall. The highest reported disease-free interval was 17 months. Prevailing side effects were nausea (40%) and anorexia (20%), while vomiting, diarrhea, asthenia, dyspepsia, abdominal pain and constipation were reported less frequently, 25% of patients did not complain of any side effect. To date 3 patients are alive, while 13 died, 4 patients were lost at follow-up.

Conclusions: In our experience, induction chemotherapy with gemcitabine followed by twice weekly administration of low doses of gemcitabine concurrent with radiation therapy seems to be feasible and generally well tolerated.

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ROLE OF INTRALUMINAL BRACHYTHERAPY IN EXTRAHEPATIC BILE DUCT AND PANCREATIC CANCERS. OUTCOMES AND TOXICITY OF TWO RADIATION SCHEDULES

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Purpose: To evaluate intraluminal brachytherapy (ILBT) in patients (pts) with malignant biliary obstruction and jaundice for extrahepatic bile duct or pancrea-

tic cancers.

Materials and Methods: We performed a retrospective analysis of 9 pts (aged 57-78 years) with unresectable extrahepatic bile duct (n = 4) or pancreatic cancer (n = 5). The pts received ILBT exclusively or as part of a definitive treatment regimen from January 2009 to august 2012. ILBT was performed with transhepatic percutaneous technique in 2 pts and with endoscopic retrograde cholangiopancreatography in 7 pts. The location and length of bile duct structure was identified with cholangiography. HDR brachytherapy was used for all patients. Six pts received 15 Gy in 3 fractions prescribed at 1 cm from the centre of the catheter twice daily with a minimum of 6 hours between treatments. Three pts received 9 Gy in one-fraction. Treatment planning was based on CT-scan with the applicator in place.

Results: The median survival was 10 and 22 months for 7 and 2 patients respectively. At this moment 2 patients are alive one of them with an hepatic transplantation. Total obstruction was resolved in 33% of patients. Pain relief was achieved in all patients in a short period of time. One patient presented biliar tract infection.

Conclusions: ILBT had a moderate local tumor effect and showed some clinical benefit in 33% of the pts in this study. Combination of this form of treatment with external radiation and/or chemotherapy should be tested in future trials. The two radiation schedules have shown the same type of acute and late toxicity. The fractionation was more comfortable only in pts with a short life expectancy. Antibiotic prophylaxis should therefore be given before, during and after the procedure. No pts presented any late toxicity.

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ADJUVANT THERAPY OF PANCREATIC CARCINOMA: IS POLICLINICO UMBERTO I, UNIVERSITÀ "SAPIENZA" ROMA AN AMERICAN HOSPITAL?!

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Purpose: Pancreatic cancer represents a difficult and unsolved oncological problem: only 10-20% of patients have resectable disease at diagnosis. Surgical resection remains the only potentially curative treatment. The addition of non-surgical treatment as adjuvant therapy has been employed to realized at least a modest improvement in survival and the management of resected pancreatic cancer remains to be clarified because there is not a global consensus about adjuvant treatment between Europe and United States. This paper describes the adjuvant treatment approach in our Department and the results of the subsequent multidisciplinary care of resected pancreatic cancer patients.

Materials and Methods: A total of 17 patients with histologically confirmed resectable adenocarcinoma of the pancreas, treated between January 2007 and May 2012 are included in this study. All patients underwent concomitant radiochemotherapy. Radiation therapy was delivered with a 3D-conformational multiple field technique at a dose of 45 Gy (in 25 daily fractions of 1,8 Gy given in 5 weeks) to the tumor bed and regional nodes, plus a 5,4 - 9 Gy (in 3-5 daily fractions of 1,8 Gy) to the field boost, with 6 - 15 MV energy photons. Chemotherapy treatment was left to the oncologist's discretion and it consisted of Gemcitabine (200 mg/m2/week) or 5-FU (200 mg/m2/die).

Results: 16 patients completed programmed treatment; one patient suspended definitively planned adjuvant concomitant treatment because of haematological toxicity G3. He was the only case of toxicity G3. At a median follow-up of 17.7 months (range 1-56), 9 patients are still disease-free survivors; 5 patients developed distant metastases and 3 patients local progression. The 2-year survival was 30%.

Conclusions: Pancreatic cancer is still one of the most aggressive cancer. Our experience in resected pancreatic cancer patients, treated with radiochemotherapy regimen, highlight that concomitant treatment is associated with survival and toxicity profile benefits.

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CLINICAL RESULTS OF NEOADJUVANT RADIO-CHEMOTHERAPY AND TARGET THERAPY IN PANCREATIC CANCER

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Purpose: The EGFR is a molecular target of considerable interest and investigation. It plays an important role in the development of pancreatic cancer. The purpose of this study is to evaluate the feasibility and efficacy of neoadjuvant radiochemotherapy (in combination with EGFR targeting therapy) for patients with borderline resectable and locally advanced pancreatic cancer.

Materials and Methods: Between January 2009 and December 2011, 25 patients (14 women and 11 men) with histologically proven pancreatic adenocarcinoma were treated with preoperative chemoradiation and target therapy. All patients had appropriated laboratory and radiographic studies conducted prior to study enrolment to meet eligibility criteria. Preoperative imaging included multidetector computed tomography (CT), endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), PET-CT and laparoscopy. External beam radiation was delivered with a total dose of 50.4 Gy with fractionation of 1.8 Gy daily for 5 days a week. Patients were treated using 3D-conformal radiotherapy, and the CTV was the primary tumour and involved lymph nodes. Gemcitabine 300 mg/mq was given weekly during radiation therapy. Cetuximab was given as loading dose 400 mg/mq on day 1, and sequential Cetuximab 250 mg/mq simultaneously with radiation. Patients were evaluated using a directed history and physical examination weekly during treatment. The occurrence and nature of any adverse events were recorded according to the National Cancer Institute Common Toxicity Criteria (version 3.0) scale. Approximately 3-4 weeks after the completion of radio-chemotherapy, an evaluation was performed regarding tumour response and resectability

with clinical examination, laboratory test, tumor markers, CT and MRI scan, PET-TC and laparoscopy. Pancreaticoduodenectomy was performed for operable patients with surgical reconstruction.

Results: The median age was 67 years (range 43-80 years). All patients had a good performance status (ECOG Score 0). None had undergone previous chemotherapy or radiotherapy. Stage disease was IIA in 10 patients, IIB in 8 patients and III in 7 patients. All patients completed concurrent radiochemotherapy. Acute toxicity from radio-chemotherapy with EGFR-inhibitors were acceptable during treatment. G3 trombocytopenia and leucopenia occurred in 4% and 35% of patients respectively. Non-hematological toxicity was: 20% G1 dermatitis/rash and 16% G2 nausea. 8 patients (32%) underwent radical surgery. 6 patients (24%) underwent palliative surgery. 11 patients didn't undergo surgery (7 showed distant progression of disease, 2 had poor performance status and 2 patients showed persistent vascular infiltration). Median survival was 11.83 months and local control at 2 years was 35%.

Conclusios: In these patients preoperative radio-chemotherapy in combination with EGFR targeting therapy was well tolerated. However the addition of target therapy hasn't showed advantages in terms of local control and survival.

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ADJUVANT RADIOCHEMOTHERAPY IN LOCALLY ADVANCED CANCER OF PANCREAS

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Purpose: We analyzed outcome of adjuvant radio-chemotherapy in the treatment of patients affected by pancreatic cancer.

Materials and Methods: Between 03/2007 and 01/2012 we treated 53 patients with postoperative radiochemotherapy affected by pancreatic cancer. The mean age was 66 years, 42 patients were with completely resected pancreatic cancer and 11 patients with microscopic residual disease (R1). 70% of patients were classified as Stage II disease and 30 % with pathologic stage III disease. All patients underwent duodenocefalopancreasectomy or distal pancreasectomy with splenectomy and locoregional lymphadenectomy. All patients received adjuvant radiotherapy (50,4 Gy – 28 fractions of 1,8Gy/die) delivered on tumor bed and locoregional lymph nodes. The concomitant chemotherapy treatment consisted of 5-FU in continuous infusion (225 mg/sm) and, starting from 2011, of oral capecitabine (825 mg x2/die).

Results: The median follow-up was 11 months. Treatment tolerance was good in 52% of patients,fairy good in 42% of patients and poor in 6% of patients. We observed RTOG G1 acute pancreatic toxicity,and typically nausea and/or vomiting,in 8 patients,and nausea and/or vomiting RTOG G2 in 10 patients,.No patient showed RTOG G3 acute pancreatic toxicity but only 1 patient showed G3 hematologic toxicity manifested with leucopoenia in which chemotherapy was definitively interrupted but radiotherapy was regulary performed in order to reach total prescribed dose. In 3 patients we observed diarrhoea RTOG G1 and in 4 patients diarrhoea RTOG G2.No definitive suspension of radiotherapy was observed in our analysis and all patients successfully finished radiation treatment.In 9 patients the chemotherapy treatment was definitively interrupted for:RTOG G2 pancytopoenia in 2 patients; RTOG G2 biliar vomiting combined with G2 epigastralgy, weight loss and G3 leucopoenia in 1 patient; pemphigus foliaceus with RTOG G2 weight loss and weakness in 1 patient; RTOG G2 dehydration combined with G1 pancytopoenia in 1 patient; RTOG G2 leucopoenia in 3 patients; and for association of RTOG G2 nausea, vomiting, diarrhoea, weight loss and epigastralgy with G1 pancytopoenia in 1 patient. No patient was hospitalized. The patients with pancreatic cancer have a poor nutrition and in our study 26 patients showed weight loss: 17 with RTOG G1 and 9 patients (17%) with RTOG G2. No G3 malnutrition was observed. We didn't observe any late radiation injury. 20% of patients relapsed at the level of loco-regional lymph nodes: 7 of them at the level of porta hepatis lymph nodes, and 4 in superior mesenteric artery lymph nodes; 4 of these 11 patients developed distant disease too in the lung and liver. 42 % of patients developed distant disease with hepatic and lung localizations, or extra-regional lymph nodes.

Conclusions: Adjuvant chemotherapy is a feasible and well-tolerated treatment for patients affected by pancreatic adenocarcinoma. Acute Toxicity is well controlled with specific therapy. For these reasons adjuvant radiochemotherapy represents the gold-standard for locally advanced pancreatic cancer.

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PHASE I STUDIES ON CONCURRENT CHEMORADIATION IN PANCREATIC CANCER: A SYSTEMATIC REVIEW

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Aims: Some phase I trials defined the maximum tolerated dose (MTD) of concomitant radiotherapy (RT) and chemotherapy in combined modality treatment of pancreatic cancer. The purpose of this analysis was to evaluate the impact of different treatment modalities (fractionation, elective nodal irradiation: ENI) on clinical outcomes in terms of MTD.

Materials and Methods: A search on PUBMED was performed, limited to English-language articles on humans, using the terms (MeSH): ("chemoradiation" OR "radiochemotherapy") AND "pancr*". The search was

limited to the last ten years. In case of multiple publications from the same institution only the most recent analysis has been used. Reviews, editorials, case reports, conference abstracts, letters and retrospective studies were excluded.

Results: The literature search identified a total of 875 publications. Twenty-one studies were selected using the described inclusion criteria. Most studies included patients with locally advanced cancer. Two studies reported on accelerated hypofractionated treatment (doses per fraction of 2.8-3 Gy). Both studies defined 36 Gy as the MTD. Hyperfractionated-accelerated treatment was tested in a study employing a fractionation of 1.5 Gy for 2 times a day; MTD was 45 Gy. Hyperfractionated treatment was tested in another study in which 2 daily fractions of 1.2 Gy were administered. MTD was not reached until the dose of 64.8 Gy. Finally, two trials used a standard fractionation of 1.8 - 2 Gy per fraction. Both studies led to similar conclusions: in one MTD was < 60 Gy and in the other MTD was 55 Gy. It should be noted that only in the first study ENI was performed. Four studies used conventional doses and fractionation of RT in combination with ENI and concurrent gemcitabine. In all these studies the MTD of concurrent gemcitabine was between 250 and 300 mg per m2. On the contrary, in a study without ENI a weekly dose of gemcitabine of 1000 mg per m2 was used, with a MTD of RT reached at 36 Gy.

Conclusions: The treatment techniques used in RT of pancreatic carcinoma have a significant impact on clinical outcomes. The use of hyperfractionated regimen allows an escalation of the total dose. On the contrary, the use of accelerated and/or hypofractionated regimens reduces the MTD that can be administered. Furthermore, ENI does not appear to limit the maximum RT dose but limits the ability to deliver a standard dose of gemcitabine.

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DEFINITION OF FIELDS MARGINS FOR TWO-DIMENSIONAL PALLIATIVE RADIOTHERAPY OF PANCREATIC CARCINOMA

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Aims: Aim of this study was to provide practical guidelines for palliative treatment of advanced pancreatic cancer (CAP) with two-dimensional radiotherapy (2D-RT).

Materials and Methods: Fifteen patients with locally advanced carcinoma of CAP consecutively treated with radiotherapy in our center underwent computed tomography (CT) simulation in the supine position. The Clinical Target Volume (CTV) included the gross tumor volume and the pancreas (both the head and the body) and the retropancreatic space. The Planning Target Volume (PTV) was defined by adding a margin of 14 mm to the CTV in the cranio-caudal direction and of 11 mm in radial direction. For each patient, 3 treatment plans were calculated using: a cobalt source, 6 MV photons and 15 MV photons (box technique). Beams were drawn using the primary collimators (without using multileaf collimators) and progressively optimized in order to respect the minimum dose (Dmin > 90%) constraint. Once the final plan was achieved, distances of the fields edges from a set of reference points (bony or duodenal landmarks) were measured. In this way, 15 AP-PA beams and 15 pairs of LL beams were defined for the different patients. Finally, the single minimal AP-PA and LL beams able to include the 15 sets of AP-PA and LL beams were defined.

Results: The results of this analysis are reported in tabular form. Guidelines are provided for treatment based on cobalt unit or Linear accelerator (both 6 MV and 15 MV photons) (Table 1).

Conclusions: This study provides information about field size and position for palliative 2D-RT of locally advanced CAP. A dosimetric study has been planned in order to identify the dose to be administered with this technique taking into account current dose-volume constraints.

Table 1. Fields definition. Reported measures represent minimal individual field margins needed to respect the PTV constraint D_{min} > 90%. Measures are expressed in millimetres.

fields	margin	
Co	6	15
60	MV	MV
anterior-posterior	cranial	from the middle of T11 vertebra: caudally 10	0	5
	caudal	from the bottom of the duodenal wall: caudally 5	15	10
	right	from the most external point of the duodenum: laterally 8	8	10
	left	from the left margin of L1 vertebra: laterally 13	15	13
lateral	cranial	same as anterior-posterior 0	5	10
	caudal	same as anterior-posterior 15	10	5
	anterior	from the anterior surface of L1 vertebra: anteriorly 93	95	93
	posterior	from the anterior surface of L1 vertebra: posteriorly 18	18	20

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NOMOGRAMS FOR THE PREDICTION OF SURVIVAL FOR RESECTED PANCREAS CANCER PATIENTS

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Aims: The purpose of this study was to assess the impact of adjuvant radiotherapy and to develop a nomogram predicting 5-year OS in pancreatic cancer patients undergoing curative surgery +/- adjuvant therapy.

Materials and Methods: Clinical data (N=955) from 9 different institutes (Baltimore, Rochester, Montpellier, Madrid, Salzburg, Verona, Campobasso, Milano, and Roma) were pooled for this analysis. Patients with different combinations of adjuvant treatments (postoperative radiotherapy, concomitant radiochemotherapy, adjuvant chemotherapy) were retrospectively included. The clinically relevant variables were: age, gender, tumor location, surgical procedure, tumor grade, microscopic residual disease, lymphadenectomy, pilorus preserving technique, tumor diameter, pathological tumor stage and pathological nodal stage.

Results: This analysis confirm that pathologic staging is essential for accurate prediction of outcome after curative surgery. In fact, at multivariate analysis T-stage, pN-stage, tumor diameter and residual disease resulted as independent prognostic factors for OS. Although retrospective, this study has collected the largest series of resected pancreatic tumors ever published in the literature. The nomogram show the significant impact of radiochemotherapy on OS above all in patients with intermediate-high risk of death within 5 years. Centers treating more than 10 patients/year achieved better outcomes. This evidence highlights the need to organize multidisciplinary pancreatic units to optimize the treatments.

Conclusions: The provided models are internally validated and able to accurately predict long-term outcome for pancreatic cancer patients with various clinical characteristics and given treatments. This multivariate approach may allow decision support in daily clinical practice, *i.e.* selection of patients who may benefit most from specific treatment options. The nomograms may be used as a tool to tailor chemoradiation based on clinical predicting factors and on risk of death, allowing an estimate of the potential benefit in the individual patient.

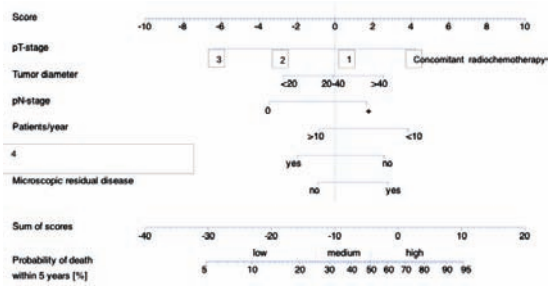

Figure 1. Nomogram for overall survival for pancreatic cancer patients predicting the probability of death within 5 years of follow-up.

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PREOPERATIVE CHEMORADIATION IN PANCREATIC CANCER: A SYSTEMATIC REVIEW

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Aims: Preoperative concurrent chemoradiation (PORT-CH) has several theoretical advantages compared to postoperative treatment: greater tumor oxygenation, higher compliance, reduced toxicity and selection of patients for exclusion from surgery with rapid metastatic spread. PORTCH is now considered a treatment option in potentially operable tumors of the exocrine pancreas (NCCN 2011.2).

Materials and Methods: A search using PUBMED was performed selecting only articles in English language. The following terms (MeSH) were used: "chemoradiation" OR "radiochemotherapy" AND "pancr*". Papers published during the last ten years were selected. Multiple publications, reviews, editorials, case reports, conference abstracts, letters, and studies with less than 25 patients were excluded.

Results: The search identified a total of 875 papers.

Of these, only 17 were selected for systematic review using the inclusion criteria. Five papers focused on patients with operable disease at diagnosis. In these studies the following results were reported: clinical response: 9-57%; resection rate: 50-74%; rate of R0 resections: 68-100%; pathologic CR rate: 0-17%. In resected patients were recorded: local recurrence rate: 0-25% (median: 11%), median survival: 19-38 months (median: 31), 5-year survival: 18-41% (median: 36%). Twelve papers, included patients with locally advanced disease. In these studies the following results were recorded: clinical responses: 2-68%; resections: 14-81% (median: 33%); R0 resections: 52-100%; pN+: 11-61% (median: 23%); pathological CR: 0-18%. In resected patients were recorded: local recurrence: 0-18%; 5-year survival: 11-53% (median: 40%).

Conclusions: Despite the inhomogeneity in terms of patient selection, evaluation criteria and treatment modalities, the results of PORTCH are promising especially in terms of median and 5-years survival. These results justify further prospective studies to optimize timing of radiotherapy and chemotherapy,treatment techniques and evaluation of dose escalation.

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2D-CONFORMAL RADIOTHERAPY: THE CASE OF PANCREATIC CARCINOMA

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Aims: The purpose of this analysis was to propose an optimized two-dimensional (2D) technique for radiotherapy (RT) of pancreatic cancer (CAP). This technique is based on a double simulation procedure that allows to solve the problem of radiographic images distortion.

Materials and Methods: We identified 5 patients with locally advanced pancreatic cancer. Treatment planning was simulated in 3 different ways: standard 2D, optimized 2D and 3D-conformal techniques. Standard 2D technique was planned with fields definition based on anatomical landmarks (bone and duodenum). 3D-conformal RT was planned with standard virtual simulation technique, three-dimensional dose evaluation and optimization. 2D optimized technique was based on manual information transfer from a diagnostic CT-scan to the simulation radiogram. In order to solve the problems of X-ray images distortion a double simulation was employed and the profile of the GTV was drawn on a radiogram produced by placing the simulator isocenter into the target center.

Results: Concerning the target irradiation, using a LINAC (10 MV), the PTV constraints (ICRU 62) were met in all patients (Dmin> 95%, Dmax <107%) with all used techniques (standard 2D, 3D-conformal, optimized 2D). Using a cobalt unit, the PTV V95% was > 95% and Dmax was < 107% in all patients. About OAR irradiation, using the LINAC (10 MV), similar results were recorded with the three techniques in terms of Dmax to both duodenum and spinal cord. Dmean of liver and kidneys was gradually improved from standard 2D to optimized 2D and finally to conformal-3D. In particular, the optimized 2D technique, compared with the standard 2D technique, allows to halve the average dose to the liver and to reduce to approximately 1/3 the average dose to the kidneys. Even with the cobalt unit a marked reduction in Dmean to the kidneys (median from 30.7% to 16.9%) and liver (median from 33.4% to 22.3%) was observed comparing the standard 2D technique with the optimized 2D technique.

Conclusions: This analysis showed that an optimized 2D technique is able to improve the dosimetric results as compared with a standard 2D technique using "standard" doses (50 Gy) of RT.

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A PRELIMINARY EXPERIENCE OF 3D CONFORMAL RADIOTHERAPY (3D-CRT) AND CONCOMITANT CHEMOTHERAPY IN PATIENTS AFFECTED BY PANCREATIC CANCER: ANALYSIS OF TREATMENT TOXICITY

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Purpose: We analyzed the acute and late toxicity of radiation therapy and concomitant chemotherapy in the treatment of patient affect by locally advanced pancreatic cancer.

Methods: From November 2009 to November 2011 in our Institution were treated 4 patients (2 patients were men, 2 were women) affected by pancreatic cancer. Two patients underwent complete resection (duodenocefalopancreasectomy or distal pancreasectomy and locoregional lymphadenectomy) and two patients were not treated surgically. Median age was 67.5 years (range 62-73). Three patients had adenocarcinoma of the head of pancreas, a patients adenocarcinoma of the body. Three patients received also Chemotherapy before RT treatment. All patients received 3D conformational radiotherapy with LINAC (6-15 Mv). The prescribed dose was 45 Gy (1.8Gy/fr) to pancreas and to drainage lymphnodes

(suprapancreatic, celiac axis, pancreaticoduodenal and those of porta hepatis) and a boost of 5.4 Gy (1.8Gy/fr) to tumor or tumor bed. Each patient required personalized irradiation fields depending on site of tumor, surgical resection, lymphnodal volumes according with preoperative and postoperative CT imaging. Three patients received weekly concomitant chemotherapy with Gemcitabine, 1 patient received CDDP. Acute toxicity was evaluated weekly according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0) scale for gastrointestinal and hematologic disorders.

Results: All patients showed treatment-related nausea: 1 patient G1 nausea; 2 patients G2; 1 patient G3 (who requested tube feeding). Two patients had hematological toxicity (1 G2 platelet decrease, 1 G2 leucopenia). Half of patients had G2 abdominal pain, 1 patient showed G2 diarrhea. At a median follow-up of 4 months (range 2-15), 2 patients died from pancreatic disease progression and another patient developed liver metastases. No patients had severe gastrointestinal late toxicity. Only a patient showed late abdominal pain.

Conclusions: Despite the small number of patients and the short follow-up, our retrospective review suggested that 3D-CRT with concomitant chemotherapy is a feasible treatment for patients with locally advanced pancreatic cancer. In spite of moderate-high acute toxicity recorded, all patients completed the planned treatment thanks to specific support therapies and multidisciplinary evaluation with Oncologist and Nutritionist. However the prognosis is poor in this setting of patients.

P154

INCREASED ORGAN SPARING USING VMAT FOR INTENSITY MODULATED RADIATION THERAPY OF PANCREATIC ADENOCARCINOMA

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Purpose: To assess the feasibility of Intensity Modulated RadioTherapy (IMRT) treatment plan, with simultaneus integrated boost (SIB) for pancreatic adenocarcinoma. In the Department of Radiation Oncology at V. Fazzi Hospital, we use VMAT® (Volumetric Modulated Arc Therapy), a novel rotational IMRT technique. This technique allows delivery of both a standard radiation dose to areas at risk for subclinical disease as well as a higher radiation dose to the tumor sub-volume at the same time (simultaneous integrated boost, SIB).

Methods: Between December 2010 and March 2012, 8 patients with primary pancreatic adenocarcinoma, who were not candidates for chirurgical treatment were treated with radiation therapy, concomitant to 5-FU continous infusion or capecitabine. The mean age was 62 years. Tumors were stage III in 5 patients and stage IV in 3 patients. All patients had been previously treated with chemotherapy. The Gross Tumor Volume (GTV) should include the bulky tumor and the clinical involved lymph nodes. Lymph nodal clinical target volume (CTV/N) should include, in addition to GTV, the superior, inferior, anterior and posterior pancreatic-duodenal, celiac, hepatic hilum and proximal mesenteric nodes in head pancreatic tumors. In the case of a carcinoma of the body and tail of the pancreas, superior, inferior, posterior pancreatic-duodenal, celiac, hepatic hilum, proximal mesenteric and spelic nodes are to be included. The final PTV was then created by adding a further margin of 1-2 mm to the CTV.

Results: Treatment was well tolerated. Grade 1/2 nausea/vomiting developed in 2 patients and Grade 1/2 hematologic toxicity developed in 5 patients. Only 1 patient had Grade 3 toxicity, a gastric ulceration that responded to medical management. Five patients had weight loss (median, 7 kg; range, 3-12 kg). No acute complications requiring treatment interruptions. The median follow-up time is 8.5 months (13.1 months in patients who are alive). Two patients converted to resectability, 4 patients have persistent locoregional disease after chemoradiotherapy, and 2 patients are locally controlled without surgery.

Conclusions: The VMAT could decrease the dose to the OARs and an increase the treatment efficiency and this regimen of IMRT with tumor-selective radiosensitization is well tolerated. The low toxicity profile compares favorably with that of protocols based on continuous-infusion 5-fluorouracil or capecitabine , and the preliminary indications of efficacy are encouraging.

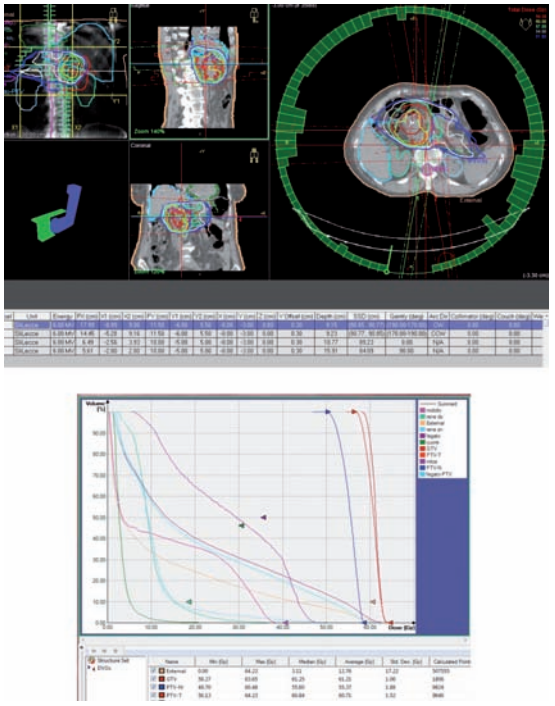

Figure 1.

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PALLIATIVE 2D RADIOTHERAPY OF PANCREATIC CARCINOMA: A FEASIBILITY STUDY

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Aims: To identify the dose to be administered with two-dimensional (2D) involved-field palliative radiotherapy in advanced pancreatic carcinoma, taking into account current dose-volume constraints (QUANTEC).

Materials and Methods: The following standard regimens were evaluated: 30 Gy with 3 Gy fractions (regimen A), 36 Gy with 2.4 Gy fractions (regimen B), 45 Gy with 1.8 Gy fractions (scheme C) and 50 Gy with 2 Gy fractions (regimen D). The following constraints were considered: spinal cord Dmax < 50 Gy, duodenum Dmax < 55 Gy, liver Dmean < 30 Gy, kidneys Dmean < 15 Gy. In case of dose/fraction different by 1.8-2 Gy, the correction of constraints using a value of alpha/beta = 3 for the late effects was carried out. The calculation of dose/volume constraints was repeated for 3 different radiation beams: cobalt unit, 6 MV photons and 15 MV photons. Standard field sizes were used and adapted according to the different types of beam, following the indications of our previous study. For each type of beam, and for each type of treatment (dose and fractionation) the percentage of patients for whom all the dose-volume constraints were respected was assessed. Treatments were considered acceptable in case of: 1) respect of the constraints for spinal cord and duodenum in all patients; 2) respect in > 10/15 patients of constraints for kidneys and liver. Therefore minor violations (< 10%) of the constraints for these two organs were accepted (in less than 5/15 patients), in consideration of the palliative aim of treatment.

Results: In regimen A (30 Gy, 3 Gy/fraction), all evaluated constraints were respected in all patients, regardless of the type of beam. In regimen B (36 Gy, 2.4 Gy/fraction), constraints were met in all patients undergoing irradiation with 6 and 15 MV photons. However, using the cobalt unit, kidneys constraint was respected only in 5 out of 15 patients. In regimes C and D (45 Gy, 1.8 Gy/fraction and 50 Gy, 2 Gy/fraction, respectively) the constraint for the kidney was respected only in 2-5 patients, depending on the energy used. Furthermore, using 50 Gy, the spinal cord constraint was not respected in 2-3 patients, depending on the used beam. Therefore only the following treatments were considered acceptable: 1) 30 Gy, 3 Gy/fraction, regardless of the used energy; 2) 36 Gy, 2.4 Gy/fraction, only for treatments performed with linear accelerator (6-15 MV).

Conclusions: Benefits of RT in pancreatic tumors should not be withheld in patients treated in centers with 2D technology only. Prospective trials, particularly in developing countries, would be useful to evaluate the efficacy in this setting of involved-fields 2D treatments using dose and fractionation defined in this analysis.

P156

LOCALLY ADVANCED/UNRESECTABLE PANCREATIC CANCER: A SYSTEMATIC REVIEW ON CONCURRENT CHEMORADIATION

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Aims: Concurrent chemoradiation is a standard option in the treatment of locally advanced tumors of the pancreas. The purpose of this analysis was to evaluate recent scientific literature to assess the impact of different treatment modalities (elective nodal irradiation: ENI, total dose) on clinical outcomes.

Materials and Methods: A search on PUBMED was performed limited to English-language articles on humans, using the terms (MeSH): ("chemoradiation" OR "radiochemotherapy") AND "pancr*". The search was limited to the last ten years. In case of multiple publications from the same institution only the most recent analysis was used. Reviews, editorials, case reports, conference abstracts, letters, retrospective and prospective studies with less than 25 patients were excluded.

Results: Our literature search identified a total of 875 publications. Overall, using the selection criteria described above, 23 studies were identified. In all studies 3D-conformal technique was used. In studies employing ENI(elective nodal irradiation) the percentage of acute gastrointestinal toxicity of grade > 3 ranged between 12% and 76% (median 30.8%). In studies without ENI the same percentage varied between 3.4% and 35.4% (median 12.6%). Median survival in patients undergoing ENI ranged between 7.3 and 15.5 months (median 10.9 months). In series in which ENI was not used, median survival varied between 7.1 and 16.8 months (median 11.8 months). In addition, studies were divided between those with higher than standard dose (> 50.4 Gy) and those with conventional or lower dose (≤ 50.4 Gy). Gastrointestinal toxicity was, in patients receiving lower dose, 3.4% -76.0% (median 23.1%). In studies with higher dose it was 12.2% -71.0% (median 25.3%). Median survival was 8.6-15 months (median 12.2 months) in patients who received a

dose > 50.4Gy and, in patients receiving a dose ≤ 50.4 Gy, it was 7.3-16.8 months (median 9.7 months).

Conclusions: ENI worsens acute gastrointestinal toxicity without improvement of survival. On the contrary, use of higher than standard doses (50 Gy) does not produce a worsening of the gastrointestinal toxicity although it is associated with an improvement in median survival. Future studies in this field should employ high-dose treatments directed solely to "visible" clinical disease.

P157

GEMOX AND HYPOFRACTIONATED RADIATION THERAPY FOR LOCALLY ADVANCED INOPERABLE PANCREATIC CANCER

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Purpose: We report preliminary clinical results on patients with locally advanced, inoperable, pancreatic cancer treated in our Unit with hypofractionated radiation therapy "sandwiched" between chemotherapy cycles.

Patients and Methods: Ten patients were treated between November 2009 and November 2011. All patients underwent a planning CT with and without contrast medium. Three different target volumes were identified: gross tumor volume (GTV), clinical target volume (CTV) 1 (including all visible adenopathies) and CTV 2 (including regional lymph nodes at risk of microscopic disease diffusion). The identified organs at risk (OAR) were the liver, kidneys, spinal cord, small intestine and duodenum and, in particular, the stomach. Patients received a gemcitabine (GEM) and oxaliplatin (OX) regimen every two weeks for 3-4 cycles, followed (15 days after completion of chemotherapy) by radiotherapy at the dose of 25 Gy (with inhomogeneity inside the target volume up to 30% of the prescription dose) in 5 fractions to the GTV and 20/25Gy to the CTV on the basis of nodal status. Treatment was delivered by Helical Tomotherapy. Patients then received a further 3-4 cycles of GEMOX, underwent restaging and received additional radiotherapy (15 Gy in 3 daily fractions prescribed again at 60-70% isodose) to the residual GTV.

Results: Documented toxicity to GEMOX was similar to that reported elsewhere. Radiotherapy was well tolerated, the most frequently encountered adverse events were mild to moderate nausea and vomiting, abdominal pain and fatigue. Almost all of the adverse effects disappeared within 2-3 weeks of radiotherapy completion.

Conclusions: Our results show the feasibility of accelerated hypofractionated radiotherapy plus GEMOX regimen in unresectable locally advanced pancreatic cancer. On the basis of such promising findings, we have designed a new phase I/II trial with the same GEMOX regimen in combination with continuous hypofractionated radiotherapy with neoadjuvant intent.

P158

POST-OPERATIVE RADIOTHERAPY AND CHEMIOTHERAPY IN PATIENTS WITH PANCREATIC CANCER: OUR EXPERIENCE

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Aims: Survival for pancreatic adenocarcinoma is low and surgery (S) remains the primary therapy for the minority of patients (pts) candidates for resection whose median survival is 18.8 months. The role of adjuvant radiotherapy (RT) is still controversial, given the results of past clinical trials. We retrospectively analyzed the impact of adjuvant chemo-RT on local control (LC) and on overall survival (OS) for pts referred to our institution undergoing to post-operative RT.

Materials and Methods: From 2003 to 2011, 18 pts, 9 females and 9 males, with histological invasive pancreatic adenocarcinoma underwent post-operative RT in our Institution. All pts had a pancreatic head cancer except one with body-tail tumor; mean age was 59 years (range 40-76), PSK ≥ 70%. The pathological staging was: pT2 pN0 in 3 cases, pT2 pN1 in 1, pT3 pN0 in 3, pT3 pN1/2 in 10 and pT4 pN0 in 1 case; WHO Grade (G) 1 occurred in 2 cases, G2 in 10 cases, G3/4 in 6 cases. Negative resection margins (R0) were confirmed in 6 pts only, microscopically (R1) and macroscopically (R2) positive surgical margins were confirmed in 8 and 4 pts respectively; the mean positive regional nodal number was 3 (range 1-12). After S, 14 pts received chemotherapy (CT) with Gemcitabine (GEM) for 2 cycles or with GEM plus Oxaliplatin (GEMOX) for 2-6 cycles followed by RT concomitant to CT in 16 cases. Two pts underwent RT alone for previously treatment with GEMOX for 6 cycles and 1 pt for hematologic toxicity to induction CT. Patients typically received 3D RT with a three/four field approach to 45 Gy in 1.8 Gy daily fractions with a sequential boost to the surgical bed of 5.4-9 Gy in 8 cases. CTV (Clinical Target Volume) consisted in tumor bed and node groups at risk. Treatment planning constraints included limiting the spinal cord to ≤ 45 Gy, both Kidneys V18 ≤ 33% if possible, liver V30 ≤ 50% and small bowel dose ≤ 52 Gy. Concurrent CT consisted in GEM 300 mg/m2/week, 4 hours before RT.

Results: The median follow-up from S was 18 months (range 7-116): 7 pts (39%) are alive with complete remission (RC) of disease, 1 patient (5.5%) died for other cause without relapse after 65 months, 1 pt (5.5%) with distant relapse lost to follow-up after 12 months, 7 pts died for disease (39%), 1 pt (5.5%) is alive with local and hepatic relapse and 1 patient (5.5%) is alive with suspect hepatic relapse. Local relapse alone (22%) occurred in 1 case after 16 months, and was associated with hepatic metastases in 3 cases. In our experience, the complete remission of disease is occurred respectively in the 75%, 62.5% and 0% of pts with R0, R1 and R2 resection. No significant differences are

found between pts with complete remission and those with relapse relative to stage, grading, age, positive node number, radiation dose and schedule induction CT. Median survival was 40 months, OS at 5 years was 51 %, calculated with Kaplan-Meier methods (Figure 1 and Figure 2). The toxicity, based on RTOG criteria, was valuated in 17 pts: nausea, fatigue, abdominal pain that required supportive therapy e.v in 2 cases (12%) and treatment interruption for 10 days in one case (6%). Hematological toxicity occurred in 4 cases (23%): Grade ≥ 3 only in one (6%).

Conclusions: The results of our analysis show a benefit with the use of adjuvant chemo-RT in the pancreatic cancer treatment, especially in R1 patients. Furthermore, the treatment is associated to a low risk of toxicity.

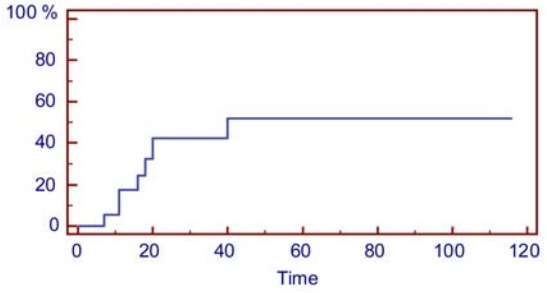

Figure 1. Probability of overall survival.

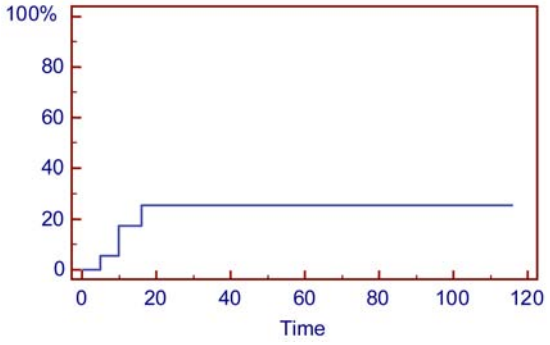

Figure 2. Probability of local recurrence.

LA RADIOTERAPIA NELLE FORME AVANZATE E/O RECIDIVATE DEL CARCINOMA DELLA MAMMELLA: QUANDO E COME

P159

VMAT REIRRADIATION IN RECURRENT INTERNAL MAMMARY NODES AFTER BREAST RADIOTHERAPY

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Aims: Volumetric modulated arc therapy (VMAT) is a novel extension of conventional intensity-modulated radiotherapy (c-IMRT) in which an optimized three-dimensional dose distribution may be delivered in a single gantry rotation. We used this technique to reirradiate a patient with recurrent internal mammary nodes after lumpectomy and breast radiotherapy. MATERIALS AND Methods: A patient 47 years-old was operated in october 2009 for ductal invasive carcinoma of the left breast, stage pT2 pN0 (sentinel node). After surgery she was submitted to chemotherapy (IV cycles of EC, Epirubicine and Cyclophosphamide, and IV cycles of Docetaxel). Between april and may 2010 she underwent radiotherapy to a dose of 50 Gy to the whole breast with a boost of 10 Gy in the superior quadrants. In Jun 2011 a breast RM documented a recurrent left internal mammary nodes and the patient started chemotherapy with Carboplatin and Gemcitabine for 8 cycles. At the restaging a partial reduction of the disease was observed. The patient referred chest pain.

Results: It was decided to irradiate just the lesion detected in the PET and RM imaging. A CT scan was performed in our Center to reconstruct the previous treatment and to calculate the new plan. The volume of CTV was 18.4 cm3, and it was expanded of 1 cm in any direction to create the PTV. The volume of left breast was 619.2 cm3. The dose prescribed to the PTV was 60 Gy in 30 fractions. For the VMAT treatment two arcs of 120° were used with a total number of 435 monitor units.

Conclusions: The treatment was completed in april 2012 and was well tolereted. We do not record any acute toxicity, except erythema G1 in the irradiated area. Performing cone-beam CT we noted a tumour reduction, but an RM performed in May 2012 documented an increased enhancement in the area of the recurrent disease. A TC and a PET are planned in July 2012 to define the disease response. At two months after the treatment conclusion the patient presented an initial fibrosis of the superior quadrants without any alteration of the skin (erythema or necrosis) and a pain resolution.

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BREAST CANCER RECURRENCE TREATED WITH RADIOTHERAPY (RT) AND HYPERTHERMIA (HT)

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Purpose: In this paper we show our experience in the use of HT to improve local sensibility to RT giving good response in term of local control (LC) e distant diffusion.

Materials and Methods: From May 2011 to March 2012 twelve patients affected by superficial recurrent breast cancer were treated at Ospedale San Camillo-Forlanini in Rome. Mean age at re-treatment was 63 years (range 47-80). We enrolled one man and eleven women who underwent total mastectomy. Histologically were invasive ductal carcinoma in 10 cases and 2 case of invasive lobular carcinoma. All patients had been previously treated with a full postoperative RT (50 - 60 Gy) and the recurrence happened at an average time of 9 years later

(range from 4 to 14). Total prescribed retreatment doses ranged from 50 Gy using photons (6 MV) to 40 Gy using electrons (6 - 9 MeV), choice based on the previous RT treatment in terms of dose, field and time from first course of RT. 2 Gy per fraction was daily delivered whereas the PTV encompassed 2 cm beyond the GTV. Twice a week the patients were treated with superficial microwave hyperthermia system that operates at 434 Mhz/max 200 W. An average temperature of 43°C was delivered to the tumor site for 60 minutes as soon as possible after irradiation. Temperature was measured through 4 thermometry probes thermocouples type T located on skin surface.

Results: The sessions were well tolerated. Only in one case the patient stopped twice HT earlier due to heat sensation, with no skin erythema. RT sessions were not interrupted. As to thermal injures, none of our patients experienced severe, acute reactions. According to EORTC/RTOG scale we had 76 % G0, 16 % G1, 8 % G2. We noted higher toxicity (G2) in fair complexion subjects. After a median follow up of 10 months (range 3 -12) the LC of the disease was complete (100%) without new local recurrence. As to population survival we did not observe significant relation between response and overall survival. During the follow up, two patient experienced bone metastases and none died because of their disease.

Conclusions: This work shows that RT and HT treatment is a good option in the management of superficial breast recurrences. Although the limited number of patients we can affirm that this technique is safe and useful, in fact we did not have any G3 toxicity and we experienced total LC. We think that RT and HT combined treatment should be the first choice in the treatment of such superficial lesions.

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PARTIAL BREAST IRRADIATION (PBI) FOR LOCAL IPSILATERAL BREAST TUMOR RECURRENCE (IBRT) IN PATIENTS WITH A HISTORY OF BREAST CONSERVING SURGERY AND ADJUVANT RADIOTHERAPY, USING INTENSITY MODULATED RADIATION THERAPY (IMRT): A PRELIMINARY EXPERIENCE AT EUROPEAN INSTITUTE OF ONCOLOGY (EIO)

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Purpose: To investigate the technical feasibility and the dosimetry of helical tomotherapy (HT) in the delivery of partial breast irradiation (PBI) for local ipsilateral breast tumor recurrence (IBRT) within a second breast conserving treatment

Patients and Methods: From January to May 2012, 6 patients, with histologically confirmated IBRT, were reirradiated using HT, after a second breast conserving surgery. All patients had already received, at first diagnosis, whole breast radiotherapy for a total dose of 60 Gy in 6 weeks delivered with two tangential photon beams and an electron boost to the tumour bed. Mean age at second diagnosis was 63 years, mean follow-up at IBRT was 116 months after the first treatment. Pathological stage was: 5 patients had a pT1 and one pT3. All IBRT where located within the previous irradiated area, 5 were in the former tumour bed and 1 outside of it. At second breast conserving therapy, axilla revition was performed in 1 patient and sentinel node biopsy in 1 patient; both of them resulted a pN0. All patients started hormonal therapy treatment at the same time of the second course of radiotherapy. Two patients received 45 Gy in 25 fractions(1.8Gy/fraction), four patients received 37,05 Gy in 13 fractions (2,85 Gy/fraction). A treatment planning CT scan was performed for each patient. A radiation oncologist identified the CTV, represented by architectural tissue distortion and ,when present, by surgical clips. The PTV was expanded by an addictional 5 mm. The organs at risk (OARs) were contoured, including the skin, ipsilateral and controlateral breast, heart,stomach, liver, aesophagus and both lungs.

Results: PTV ranged from 100 cc to 238 cc, with a mean of 119cc and median of 115cc. Coverage was adequate in all patients: volume receiving more than 107% of the prescribed dose was 5% HT provided significant decreases in mean ipsilateral lung dose, V20Gy and V5Gy, ranging from 0% and 6,5% (mean 1,85%) from 11,4% and 36,5%(mean 31,2%) respectively. Treatment delivered very low doses to the heart (only one patients received a mean dose of 0,6 Gy) in patients with a left breast tumour, as well as controlateral lung and breast dose.

Conclusions: PBI for IBRT with HT results , in our preliminary experience, technically feasible and safe. Our patients, moreover, had very acceptable acute toxicity during treatment and short follow-up.

P162

LONG TERM ANALYSIS OF COSMETIC OUTCOME AND TOXICITY IN PATIENTS TREATED WITH ELIOT BOOST AND ACCELERATED WHOLE BREAST IRRADIATION

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Purpose: to evaluate cosmetic outcome and toxicities at 14, 64 and 78 months in patients who received hypofractionated whole breast radiotherapy plus intraoperative radiotherapy as part of their breast conserving surgery

Materials and Methods: From June 2004 to

December 2006, a total of 182 patients with early breast cancer were treated with adjuvant hypofractionated radiotherapy to the whole breast after quadrantectomy and electron intraoperative boost of 12 Gy to the tumor bed. The hypofractionated schedule consists of 13 daily fractions of 2.85 Gy to a total dose of 37.05 Gy. Median age was 41 years (28-48). Of all patients, 84 were stage I, 65 were stage IIA, 17 were stage IIB, 11 were stage IIIA and 3 were stage IIIC. External whole breast radiotherapy commenced after a median of 22 days from surgery + ELIOT boost (range 16-36 days) Systemic chemotherapy was administered to 85 patients (43.7%), while endocrine therapy alone was given to the remaining cases. The timing of initiation of systemic therapy was set after the completion of radiotherapy. Late toxicity was evaluated by using LENT/SOMA criteria.

Results: At 14 months (range 10-18 months) after treatment 2 patients out of the 90 evaluated (2.2%) complained of pain, persistent (Grade 3) but subjectively light, while 5 patients (5.5%) reported occasional, intermittent pain (Grade 2). Fifteen patients (16%) suffered from a grade 2 fibrosis. At a follow up of 64 months (range 60-64 month) we evaluated 49 patients. The number of patients suffering from pain decreased (2 patients suffered a grade 2, none a grade 3); as well as the fibrosis (3 patients suffered from Grade 1 fibrosis). At 78 months (range 69 -87.4 months) Grade 2 pain was suffered from 3 patients and only 2 patients had a grade 2 fibrosis. Other side effects, such as breast pain, edema, hyperpigmentation all diminished in frequency over time.

Conclusions: Delivery of intraoperative radiotherapy boost followed by hypofractionated RT resulted in acceptable long-term toxicity and in great convenience for patients. The side effects decrease over time and they all appear as acceptable to the patients.

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PARTIAL BREAST REIRRADIATION USING ELIOT FOR IN- BREAST TUMOR RECURRENCE AFTER PREVIOUS QUADRANTECTOMY AND WHOLE BREAST IRRADIATION

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Purpose: To determine the outcome after salvage breast-conserving surgery (BCS) and partial breast reirradiation by using intraoperative radiotherapy (ELIOT) for women with local in-breast tumor recurrence (IBTR).

Materials and Methods: From 2000 to 2012 , 81 patients who had small recurrent breast carcinomas at a median of 10 years after initial BCS plus whole breast radiotherapy (WBRT) underwent a further quadrantectomy and followed by partial breast irradiation using ELIOT. In 31 of patients the local recurrence occurred in the same site of the breast as the primary tumor, while in 48 cases relapse involved different quadrants. The margins of resection were free of tumor in 77 patients, whereas microscopically involvement was seen in the remaining cases. ELIOT single dose ranged from 18 Gy to 21 Gy, depending on site of relapse (same quadrant as the primary tumor) and on timing between WBRT for primary and ELIOT for recurrence. The median applicator diameter used was 4, and the median electron energy was 7.

Results: At a median follow-up time of 40 months (range 0-107), a further local recurrence occurred in 18 cases and in 7 of them it was located in the same quadrant as the first recurrence. The median time to this new local event was 40 months. The incidence of contralateral breast carcinoma was 2.5%. Distant metastases were recorded in 2 patients. All patients had side effects that were limited to local moderate fibrosis. There were no severe wound healing problems.

Conclusions: For selected patients with an IBTR after initial treatment , a second excision followed by repeat radiotherapy to the site of recurrence by using ELIOT may be an acceptable alternative to the mastectomy.

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THE ROLE OF CHEMO-RADIATION IN INOPERABLE BREAST CANCER LOCO-REGIONAL RELAPSES

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Objectives: To evaluate feasibility, tolerance and efficacy of chemoradiotherapy in patients with chest wall or nodal recurrence from primary breast cancer.

Methods: Fifteen patients with non operable breast or lymph nodes local relapses underwent chemoradiation. Patients were treated with radiotherapy combined with chemotherapy mainly represented by daily Cisplatin. Adverse effects were scored by Common Terminology Criteria for Adverse Events v. 4.02. Treatment response was assessed at the time of maximal response, clinical or by imaging, after completation of chemoradiotherapy by RECIST criteria. Local control was determined from the time of the beginning of chemoradiation to local progression and estimated by Kaplan-Meyer method.

Results: Median age was 72 years (range: 25-87). A total of 18 relapses were treated. Median time to relapse was 26 months (interquartile range:10-55 months) and sites of recurrence were as follows: chest wall (10 lesions, 55%) and regional lymph nodes (8 lesions, 45%). The mean size of lesions was 4.3 + 2.8 cm. One patient had previously received radiation therapy on the same site. Median radiation dose delivered was 59.4 Gy (range: 34.2-61.4). Twelve lesions (66.6%) were treated with photons and 6 lesions (33.3%) with electrons. Eleven lesions (61.1%) were treated with concurrent daily Cisplatin (6 mg/m2), 4 lesions (22.2 %) with oral Capecitabine, 3 lesions (16.6%) with other chemotherapy regimens. All

patients but one completed chemoradiation. In the patient undergoing radiation retreatment no grade 3-4 acute skin toxicity was recorded. Grade 3-4 skin acute toxicity occurred in 5 patients (33.3 %). No late grade 3-4 skin toxicity were observed. The overall response rate was 66.6 %. Complete response was recorded in 6 cases (33.3%), partial response in 6 cases (33.3%). No patients progressed during chemoradiation. With a median follow-up of 15 months, local control at 1 years was 86 %, at 2 years was 57 % (median: 21 months). Response rate seems to be indipendent from the chemotherapy regimen adopted (p=NS).

Conclusions: Chemoradiotherapy represents a valid opportunity for local treatment of unresectable relapses of breast cancers and allows a good local control with a good profile of toxicity both acute and late.

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ADJUVANT LOCOREGIONAL RADIOTHERAPY IN ADVANCED BREAST CANCER PATIENTS AFTER NEOADJUVANT CHEMOTHERAPY AND SURGERY: A MONO-INSTITUTIONAL EXPERIENCE ON 50 PATIENTS

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Objectives: Neoadjuvant chemotherapy for advanced breast cancer has been shown to significantly change the pathological extent of the disease and to downstage primary tumor, increasing breast conserving surgery (BCS) in operable disease. We retrospectively analyzed the efficacy of postoperative locoregional radiotherapy in stage II to III breast cancer patients after neoadjuvant chemotherapy followed by BCS or mastectomy.

Materials and Methods: From July 2004 to march 2009 50 breast cancer patients were submitted to receive neoadjuvant chemotherapy with doxorubicin and docetaxel for 6 cycles. Hormone receptor positive patients underwent hormone therapy. DCE-MRI was performed at the baseline and before surgery. After neoadjuvant chemotherapy 40 patients underwent BCS (80%), while 10 patients were submitted to mastectomy; all patients underwent axillary lymph nodes dissection. Forty-four patients received conventional post-operative radiotherapy to the breast or to the chest wall. Patients with 4 or more pathological positive axillary lymph nodes underwent irradiation of the supra/infraclavicular fossa and/or of the axilla.

Results: Nineteen patients (38%) had a stage IIB disease, 31 patients had a a stage IIIA-C (62%); the median age was 51 yr (29 – 68). Seventeen patients (34.7%) received irradiation of the supra/infraclavicular fossa, 9 patients underwent irradiation of the axilla (18%). Locoregional relapse occurred in 4 patients (8%), while 12 patients had distant metastasis (24%). At a median follow-up of 63 months (39 – 115) the 5 years locoregional recurrence (LRR) rate was 10.7 % for all patients; the 5 years LRR for patients underwent regional lymph nodes irradiation was 6.3%, for patients who received only breast or thoracic wall irradiation was 13.6%. For all patients the 5 years overall survival was 79.2%.

Conclusions: the results of our retrospective analysis demonstrate the efficacy of adjuvant locoregional radiotherapy in advanced breast cancer patients after neoadjuvant chemotherapy and surgery. Moreover, despite the smallness of the sample size, in this subset of patients regional limph nodes irradiation seems to significantly reduce the risk of locoregional failure.

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BREAST CANCER AND ELETTROCHEMOTERAPY

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Introduction: Skin metastasis in breast cancer is an event that modifies the prognosis and worsens life quality in patients subjected to multiple treatment. A percentage of women treated because of breast cancer ranging from 10% to 35 % meets a locoregional relapse. Prognosis in patients that experience locoregional relapses seems to be worse than in those who don't, with a 52% of illness-free survival rate. A local-regional treatment with healing or palliative goal must always be taken into account for the high impact on life quality that such lesions provoke.

Materials and Methods: At our Unit, the IOV Breast Cancer Unit, a locoregional elettrochemotherapic treatment is executed on patients with skin relapses after breast cancer, whereas further surgical or radio therapy can't be carried on and drug treatments are little effective. ECT is the result of the combination of two effects: electroporation of cell membranes and administration of chemotherapic drugs. Electroporation is based on local application of short intense electric impulses that makes the cell membranes reversibly permeable. The most suitable drugs to ECT are bleomicine and cisplatino whose toxicity grows reversibly when combined with electroporation. Thus local efficacy of chemotherapic drug is strengthened where cells have been electropermeabilized through electric impulses, without hitting tissues that haven't been exposed to electric impulses. The protocol includes the CLINIPORATORTM equipment for ECT. We treated 25 patients that are between 39 and 85 years old. Lymph nodes involvement was present in the 68% of patients.Relapses appeared again after mastectomy in the 92 % of cases. The 24 % of patients had only skin relapse while 76 % of patients had also metastasis. The 60 % of patients was executing treatments associated with chemotherapy and the 80% treatments associated with hormontherapy. The treated lesions appear as singular or multiple nodules and can have either whole or ulcerated skin; in the latter the therapy goal is aemosthatic as well.

Results: The IOV Breast Cancer Unit has treated 25 patients: control and decrease of both pain and skin ten-

sion feeling were obtained in all patients. We treated a total amount of 380 single nodules; 8 patients presented confluent lesions and 6 presented ulcerated lesions One patient experienced skin de-pigmentation of the treated area. Response in patients with initial skin lesions was excellent and associated with disappearance of smaller nodules and decrease of wider lesions volume; an initial ulceration following the treatment resulted in patients with confluent lesions at ulcerating stage. The initial ulceration later decreased, eschars appeared and were removed during medications. Aemosthasys associated with final eschars resulted in patients with ulcerated lesions

Conclusions: Electrochemotherapic treatment of locoregional relapse in breast cancer is absolutely well tolerated by patients. Goals of such a treatment are twofolds: on one hand, we try to obtain stable clinical conditions and acceptable pain control in patients with advanced stage cancers, particularly when patients present skin localization only. On the other hand, we aim to local control in patients with still local illness though not responsive to any other treatment.

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MULTIMODAL THERAPY IN INFLAMMATORY BREAST CANCER MANAGEMENT: THE FLORENCE UNIVERSITY EXPERIENCE

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Aims: Inflammatory breast cancer (IBC) is a rare clinicpathologic entity characterized by rapid progression and aggressive behavior. It accounts for approximately 1–6% of total breast malignancies. The therapeutic approach to IBC should be multimodal, involving systemic therapy, surgery and radiotherapy (RT). The goal of primary systemic treatment is to downstage tumor to allow surgery. The aim of our analysis is to assessed the pattern of care of patients affected by IBC treated in Our Institute.

Materials and Methods: Using the institutional database, we retrospectively identified 61 consecutives patients with an histologically-proven IBC, treated between 1989 and 2011 with multimodal integrated therapies. Demographic and clinical variables were abstracted from the medical records.

Results: Median age at diagnosis was 54.5 years (range 29-96). Hormone receptors status (ER/PgR) was negative in 28 case (45.9%); Ki-67 expression >20% and positive c-erbB2 (score 2+ with FISH amplified and score 3+) was assessed respectively in 36 (59.0%) and 19 (31.1%) cases. Invasive ductal carcinoma accounted for 82% of cases (50 patients). Nodal involvement was pathologically staged as N1 in 20 patients (32.8%), N2 in 10 (16.4%) and N3 in 22 patients (36.1%). Radical mastectomy was performed in 54 cases (88.5%), in association with axillary nodal dissection. Forty-two patients (68.9%) underwent RT as adjuvant treatment: radiation was delivered exclusively to the chest wall in 11 patients (18.0%); to the chest wall plus supraclavicular region in 24 patients (39.3%). The dose of radiation to the chest wall and draining lymphatics ranged from 50 up to 74 Gy. In patients who underwent preoperative (n=39, 63.9%), or exclusive (n=2, 3.3%) CT, schedules consisted of anthracycline-taxane doublet in 20 patients (32.8%), anthracycline-based in 19 patients (31.1%), trastuzumab was administered in one case (1.6%). At the completion of the treatment course, complete and partial clinical response was obtained respectively in 2 (3.3%) and 25 (32,8%) cases; stable disease was observed in 11 patients (18%). At a median follow-up of 6.5 years (range 0.8-15), we recorded 16 local recurrences (26.2%) and 37 distant metastases (60.7%).

Conclusions: IBC is a rare and aggressive form of BC; therefore prospective trials are a difficult goal to obtain in order to get high levels of evidence. Multimodality treatment is compulsory to achieve satisfactory results in term of LC and survival.

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ORGANS AT RISK DOSE ASSESSMENT AND LEFT ANTERIOR DESCENDENT (LAD) CORONARY ARTERY DOSE SPARING IN LEFT BREAST IRRADIATION

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Left anterior descendent (LAD) coronary artery is a clinically relevant heart structure to be preserved during left breast irradiation, especially when other cardiac risk factors are present, such as age, further morbidity causes, and chemotherapy.In our work, we show that LAD coronary artery dose is maintained below 40 Gy in left breast radiotherapy using 3D conformal radiation(CR) techniques. We accept radiation treatment plans that keep the LAD coronary artery maximum dose below 40 Gy without compromising target coverage(at least 95% of the target volume covered by 95% of the prescribed dose).Since the imaging modality mostly used in radiation treatment planning(CT) is not able to clearly resolve this cardiac subvolume, the LAD coronary artery can neither be contoured nor be directly dose assessed. Thus, considering the treatment beam geometrical positions and the organ anatomy, we assume that the maximum dose to the LAD coronary artery is not higher than the maximum dose to the heart. When using the two wedged tangential field technique, the maximum dose to the heart can reach high values. Thus, we use the 3D CR technique most suitable to decrease the heart dose. When the two wedged tangential fields are not able to lower the heart maximum dose to the required value, we set up a multi-field (MF) technique, which consists in the irradiation of the target by the two wedged tangential fields and an additional number of fields. Typically, these additional fields

could be slightly more angled (5-10degrees) than the closest tangential field, or wedge-reversed, or not coplanar, or could irradiate only a part of the target volume for shielding the OAR(s). The prescribed dose is 47.25Gy (225cGy in 21 fractions) boosted with 9.00 or 4.5 Gy (225cGy in 2 or 4 fractions). Preliminary results for 13 patients recently treated with the MF technique for left breast tumour, are shown in Table1. The maximum dose to the heart was well below or slightly above the set limit, with the highest obtained value being 40.89 Gy and the percentage heart volume receiving more than 40 Gy never higher than 0.01%.

Table 1.

	Left lung	Heart	Right breast	
Age (years)	**n. of fields**	**V25 (%)**	**V30 (%)**	**D max**
(Gy)	**V10 (%)**	**V20 (%)**	**Mean dose (Gy)**	**D**
4cm (Gy)*				
77	4	0.12	0.06	
40.89	18.52	13.39	6.97	
0.61				
55	6	8.66	6.64	
38.17	25.56	17.48	8.00	
4.91				
53	6	5.07	3.30	
40.22	22.91	18.45	8.45	
1.29				
65	6	9.19	7.93	
39.03	11.71	6.86	3.97	
2.11				
50	2	1.94	0.63	
35.68	13.18	7.97	4.41	
1.68				
68	6	0.27	0.12	
40.75	9.83	5.20	3.74	
1.95				
65	6	0.16	0.02	
38.82	23.26	17.82	8.50	
0.65				
40	4	0.11	0.01	
30.96	24.45	17.04	8.60	
1.75				
51	4	0.14	0.05	
38.78	12.40	8.17	5.29	
2.17				
58	4	2.67	2.04	
40.21	11.07	7.75	4.45	
1.91				
76	4	0.00	0.00	
19.24	10.91	7.19	4.55	
1.39				
53	3	0.00	0.00	
15.33	19.10	14.69	7.63	
1.31				
53	4	0.34	0.12	
39.08	23.35	13.82	7.34	
1.71				

** The dose to the right breast was measured at the distance of 4 cm from the sternal point.*

Further relevant OARs were also investigated such the ipsilateral lung (V10,V20,mean dose) and the controlateral breast (dose measured at 4 cm from the sternal point). As compared to the two wedged tangential field technique, the MF technique allows better heart region dose sparing and good radiation protection to the patient, maintaining the OARs dose below the set limits

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MANAGEMENT OF LOCOREGIONAL RECURRENCE OF BREAST CANCER

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Backgrounds: The locoregional recurrence of breast cancer is not always sign of distant metastases, and a substantial proportion of cases are cured by salvage therapy. Patients with locoregional recurrence should not be treated with palliative intent as if they have visceral metastases. For patients who suffer from isolated chest wall recurrence after mastectomy, a surgical approach is recommended.

Methods: From January 2000 through December 2010, 17 adults with recurrence of chest wall breast cancer were submitted to RT after surgical resection. Prescription dose to the planning treatment volume (PTV) was 60 Gy at 2 Gy/fraction in patients with positive margins and 50 Gy at 2 Gy/fraction in patients with negative margins. Technically photon beams were used for the first 40-50 Gy and an electron beam was used as a boost. Seventeen patients (median age 64 years) were identified. Complete excision was achieved in 6 of 17 patients (30%) and no prior radiotherapy (RT) was done. Median follow-up was 62 months.

Results: Univariate analysis were performed for local control (LCR) and overall survival (OS). Actuarial overall five-year survival was 60%. The main prognostic factors for survival was the complete resection. In support of this, we observed that the trend in overall survival in patients with positive margins was lower than those undergoing a complete resection, even if the data is not statistically significant (p=0.9). Adjuvant radiotherapy and complete excision was associated with reduced local recurrence. The acute side effects of radiation therapy were two patients with G2 skin erythema, nine patients with G1 and six patients with G0 (RTOG scale). No cardiac and pulmonary late toxicity were found.

Conclusions: The complete resection was the main prognostic factor for local control and potentially on overall survival. RT is the treatment of choice in the management of chest wall recurrence breast cancer patients treated with mastectomy.

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ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF OCCULT BREAST CANCER PRESENTING AS AXILLARY NODAL METASTASES

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Purpose: The optimal treatment of axillary lymph node metastases from occult breast cancer is still controversial. The aim of this retrospective study is to evaluate outcome of patients with occult primary breast cancer and the role of radiation therapy.

Materials and Methods: We retrospectively analyzed 24 patients affected by axillary nodal metastases with histological diagnosis of breast cancer without clinical or radiological (mammography, ultrasound and sometimes MRI) evidence of breast primary, treated between 1991 and 2011 in our Radiation Therapy Departments in Florence. Median follow-up was 7 years (range 1-15). Staging was negative for distant metastases in all patients. All the patients received axillary dissection, in 8 cases was performed also a blind lumpectomy. Mastectomy was only used for recurrence. 79% received ipsilateral breast radiotherapy (19 pts) and the median dose to the whole breast was 58 Gy (in conventional fractionation). 5 patients did not receive any radiation treatment. In 23 patients (93%) was administered systemic therapy (56% chemotherapy, 69% hormonal therapy).

Results: We found 16% of breast failures (4/24 pts) and 20% of distant metastases (5/24) as first event. Among breast recurrence, we observed 5% of failures in patients who received radiation therapy (1/19 pts), *versus* 60% in those who did not (3/5 pts). Overall, we observed local or distant failure in 9 patients (38%): 26% in the radiation group (5/19 pts) and 80% in patients not irradiated (4/5 pts).

Conclusions: In this subset of patients with axillary nodal metastases from occult breast primary (Tx N+ M0) we found a trend towards reduced ipsilateral breast recurrence and even an increase in survival for patients who received radiotherapy, compared with those who did not, with the advantage of breast conservation. Larger or prospective studies are needed to validate these findings.

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DOSIMETRIC PREDICTORS OF NAUSEA IN PATIENTS TREATED WITH RADIOTHERAPY FOR BREAST CANCER

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Purpose: to assess dosimetric predictors for treatment-related nausea in patients undergoing adjuvant radiotherapy for breast cancer.

Materials and Methods: 74 consecutive patients treated with postoperative radiotherapy for breast cancer were considered. Seventy patients were treated with intensity modulated radiation therapy (IMRT) using a simultaneous integrated boost approach on the surgical bed; in four patients 3D conformal radiotherapy with two tangent fields was used. Sixty-four patients underwent breast conserving surgery: high-risk patients received 64.4 Gy on surgical bed and 50.4 Gy on the whole breast in 28 fractions, while patients deemed to be at low-risk received 60 Gy and 50 Gy in 25 fractions, respectively. Patients who underwent radical mastectomy were treated to 50 Gy. Regional nodes were included in the target volume in patients with metastatic axillary lymphnodes. None of the patients received concomitant chemotherapy. No attempt was made at planning to limit gastric dose. Patients were seen weekly during treatment and nausea was prospectively scored according to CTCAE 4.0. Peak nausea grade 1+ at any point during treatment was considered the endpoint. The stomach was retrospectively contoured as an organ at risk by a single observer, blindly to toxicity data; for each patient, the mean dose and the absolute cumulative dose volume histogram were extracted. The absolute volume of the stomach receiving at least x Gy (Vx) was compared between patients with and without endpoint with the Mann Whitney U test.

Results: Twenty-six patients (35%) developed nausea, grade 1 in 16 patients and grade 2 in 10 patients. Median time to symptom onset was the second week of treatment (range 1-5). The median mean dose to the stomach was 3 Gy (range 0.1-12.3). Compared to patients without nausea, on average, patients with nausea had a significantly worse gastric DVH in the V1-V3 range with the largest difference at V2 (p=0.005), and a higher mean dose (p=0.04). V2 and mean D were highly correlated (Spearman's rho=0.772, p<0.0001). According to a ROC analysis, the best cut-off value for V2 was 138.1 cc; patients with V2 > 138.1 cc at planning had a 68.8% risk of developing nausea while it was only 25.8% for patients with V2 < 138.1 cc.

Conclusions: Nausea during radiotherapy for breast cancer is correlated to the dose to the stomach and here we provide novel dose objectives for (IMRT) planning.

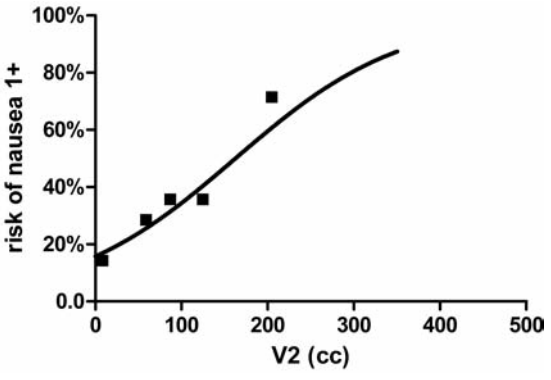

Figure.

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RISK OF ORO-PHARYNGEAL MYCOSIS DURING RT FOR H&N CANCER: MIGHT THE SEX PLAY A ROLE AS PROGNOSTIC FACTOR? PARTIAL RESULTS OF MIR (MYCOSIS IN RADIOTHERAPY) STUDY

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Aims: Oro-Pharyngeal Mycosis (OPM) may appear during treatment for different cancers. For H&N patients acute toxicity (mucositis, dysphagia, dysgeusia and pain) may be worsened by superimposed mycosis. Studio MIR (Mycosis In Radiotherapy) analysed several prognostic factors for OPM, including sex.

Materials and Methods: After approval of the ethic committee of any participating center, 12 italian centers recruited 410 patients candidate to curative treatment for Head and Neck cancer with chemo-radiation or exclusive radiotherapy. After informed consent, an exhaustive research of several factors, disease and treatment t parameters was carried out including acute side effects, smoking and drinking habits even during treatment. Appearance of mycosis was reported with radiation timing (before, during or never) and according to a clinical classification. All adults with H&N cancer undergoing curative RT or CT/RT without prior antimycotic treatment were included.

Results: Oropharyngeal mycosis was diagnosed in 221/410 patients, in 20 was present before and in 201 appeared during radiation treatment. Gender shows a predominance of Male (82.9%) with M/F ratio of 4.85. The incidence of OPM (Table 1) is 68.6% for female (roughly 3 out of four) and 50.9% for male (2 out of four), p(Pearson)=0.0069 and p(exact test of Fisher)=0.0082. With further analyses, all factors and treatment parameters were matched against sex, and we discovered that women have significant differences for: reduced salivation before RT (p=0.0013), worse salivation (p<0.0000), mucositis (p=0.0001) and dysphagia (p<0.0000) maximal acute toxicity, but less women continue to smoke during RT (p=0.0126). No significant differences were seen for Surgery, Chemotherapy, RT total dose, Salivary glands volume, Mucositis and Dysphagia before RT, Day Hospital, Inpatient admission, PMN, Alcohol during RT, Delay in Overall Treatment Time, Body Mass Index before and after RT. With actuarial analysis as shown in Figure 1, we saw that the cumulative hazard probability of OPM during RT course is always greater and earlier for Female (Mantel Cox, p=0.0193).

Conclusions: From our data female sex, even if less prevalent in H&N cancer, seems at higher risk for OPM. Possible explanations are probably related to impaired salivation.

Table 1. Sex and Oropharyngeal Mycosis (OPM) during radio/chemotherapy for H&N cancer.

Factor	Parameters	OPM No	OPM Yes	Prevalence	p (Pearson)	p (Fisher)
Sex	Female	22 *11.6%*	48 *21.7%*	*17.1%*		
	Male	167 *88.4%*	173 *78.3%*	*82.9%*	**0.0069**	**0.0082**

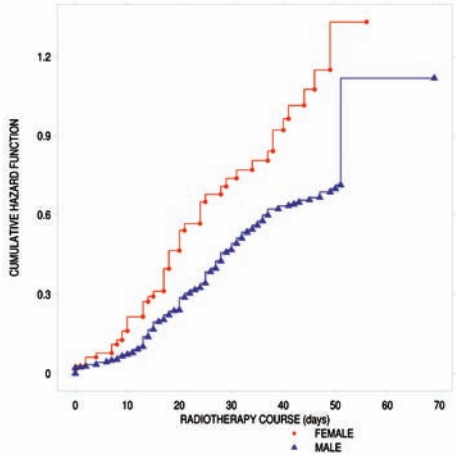

Figure 1. Sex and risk of orophar. Mycosis during RT for H&N cancer.

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ETHICS IN RADIOTHERAPY TECHNOLOGY: NEED FOR NEW TOOLS

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Aims: Radiotherapy is a well established cancer treatment which has significantly progressed over last decades due to the technology improvements. It is able to offer clear benefits to patients in terms of survival and local control rates, organ preservation, effective pallia-

tion and quality of life. Radiotherapy has some specificities, including the multidisciplinary presence of a large team of professionals, (radiation oncologists, technicians, medical physicists and nurses), the length of the treatments, usually requiring repeated daily fractions, delivered in some weeks and the relevance of expensive equipment. Many questions arise about the need that quality assurance activities should have ethical review and whether some of these activities should be classed as research tools.

Materials and Methods: For the optimization of external beam radiotherapy some questions should be answered: What level of accuracy is currently needed in radiotherapy practice? Is high technology indicated for every cancer treatment? How can be improved the quality control in radiotherapy? How can be optimized the volumes contouring? What can be applied to minimize the risk of health tissues damage? How do the waiting lists impact on tumor curability?

Results: In most cases the procedural complexity may lead to new risks for patients undergoing treatments. This risk imposes the need to develop a perspective strategy for the assessment and risk management. In practice, it means that a preliminary verify and a very high level of accuracy should be striven for at all the steps of the treatment chain, from the very first valuation of the patient and his insertion in the waiting list to the follow up time. The opinion of the radiation oncologist concerning the use of technology and their attitude toward the involved ethical problems are the central topics of this study.

Conclusions: Radiotherapy has presented considerable progress due to the introduction and diffusion of new technologies that allow the best conformations of radiation dose to the target volume, while ensuring better protection of normal tissues. Many problems arise in the current practice, due to indications, procedure optimization and treatment delivery. These issues must therefore become topics of future research and national dialogue, because the answers to these questions are necessary for the improvement in cancer care.

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RISK ANALYSIS WITH FAILURE MODE AND EFFECTSANALYSIS (FMEA) MODEL IN INTRAOPERATIVE RADIATION THERAPY (IORT) DELIVERED BY A MOBILE LINEAR ACCELERATOR

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Purpose: To review Intraoperative Radiation Therapy (IORT) process in our center applying Failure Mode and Effects Analysis (FMEA) as recommended by the TG100 Report of the American Association of Medical Physicist in Medicine (AAPM) and to improve patients safety.

Materials and Methods: The FMEA analysis provides a systematic method for finding vulnerabilities in a process before they result in an error. Three steps were identified: 1) process study with involved phases and activities; 2) hazard analysis with identification of possible failure modes and their effects, calculating for each failure mode the risk probality number (RPN) by the product of three scores (severity, frequency and detectibility of that failure, each on a scale of 1 to 10); 3) planning additional safety measures scored for effectiveness (1 to 10) and feasibility (1 to 10). The RPN scores can span a range of 1 to 1000, decisions are made based on the RPN values. The RPN value less than 125 was considered of little concern of risk.

Results: Critical failure modes were identified as incorrect data entry at treatment console and underestimation of CTV extension, resulting in wrong dose distribution and CTV underdose. Several safety solutions were proposed, including *in vivo* dosimetry

Conclusions: FMEA is a widely-used tool for improving safety and can be easily adapted for use in IORT (Ciocca et al., IJROBP,2012). The impact of this tool is under study.

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FMEA APPLICATION TO PREVENT CLINICAL RISK IN RADIOTHERAPY

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Aims: FMEA (Failure mode and effects analysis) is a previsional technique, widely used in health care, to evaluate process safety. Purpose of our work was the implementation of FMEA technique in the analysis of the process: “Radiotherapy Treatment” to identify possible errors and the consequent effects and to apply improvement suggestions of risk reduction.

Materials and Methods: In 2010, at Radiotherapy Structure, a working group was set up. The group was multiprofessional to include all available knowledge and ability. The group was made up by 3 radiation oncologists, including the structure Director, one medical physicist and two radiology technicians, working in radiotherapy. During the first meeting, the structure Director described the fundamentals of the FMEA technique to the whole team and invited all to identify one or more critical processes that would become the study’s scope. The process chosen for the analysis was “radiotherapy treatment”, *i.e.* the flow for the patient since the moment when the first radiotherapy session is performed, till the treatment’s end. During the following meetings, which were held fortnightly, the different phases for the study of the risk analysis process were applied.

Results: The different process phases, requiring containment actions, were identified and ranked, based on

severity and occurrence probability. For each activity where a possible adverse event was identified, the containment factors already included in the organisation were listed. Each event was rated from 1 to 5 according to severity, probability of occurrence and probability of the failure going undetected, taking into account available containment actions and the operating environment. The risk index was obtained by multiplying the score of the three parameters. The activities with a risk index of 24, or higher, were further analysed (7 activities). The activities were: 1) lack of notes for electron treatments for head and neck cancer, 2) wrong phase sequence planning after treatment stop, 3) exchange of patients at the waiting room call, 4) lack of EPID control, 5) missing control request for the EPID by the technician, 6) collision between the Linac gantry and the patient, 7) lack of planning for the visits during therapy. Containment actions were identified for each of these activities. Therefore the risk index was revised for the 7 activities was expected to fall well below the threshold of 24. The containment actins were, respectively: 1) reductions in the usage of phases with electrons, 2)planning of one phase at a time, 3) delivery of identification badge, sporting name, surname and treatment sheet number, to show before each session, 4) annotation by the radiation oncologist of all verifications to repeat, 5) double check by the technicians that the EPID control was requested, 6) test of all fields during the first session, with added explanation notes, 7) planning on an electronic calendar of the visits during the therapy. At the end, a meeting with all personnel was held where the work was explained and the new risk containment procedures were presented, together with the tasks for each of the professional roles involved in the process.

Conclusions: All identified containment actions were introduced by December 2011. At the end of 2012 their efficacy will be measured, by re-evaluation of all indexes based on the occurrences during the year.

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DEFINING PATIENT-SPECIFIC RECTAL AND BLADDER DOSE CONSTRAINTS FOR STEREOTACTIC BODY RADIATION THERAPY (SBRT) OF THE PROSTATE: AN EVIDENCE-BASED METHOD

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Purpose: Developing treatment plans for prostate cancer patients undergoing SBRT is often challenging due to the close proximity of critical organs such as bladder and rectum. Currently,standardized dose constraints relating dose-volume histogram parameters with threshold toxicity for hypofractionated high-dose regimen are not available in the literature and dosimetric objectives might be relaxed or improved depending on patient anatomy. Determining whether optimal radiation dose distribution has been achieved for an SBRT prostate treatment is a subjective process that depends on physician and planner experience. The purpose of this study was to develop a simple evidence-based method for evaluating achievable and patient-specific dose constraints for bladder and rectum to guide both the treatment planning optimisation process and plan quality evaluation.

Materials and Methods: In a recent paper(1), a new method for a quantitative assessment of volumes geometry in radiotherapy planning was suggested. To account for patient anatomy,this work suggests to quantify the proximity of the organs at risk(OARs) to the target volume adopting the expansion-intersection volume(EIV). This parameter represent the intersection volume between the OARs expanded by 5mm and the target volume,and increases with increasing extension and proximity of these OARs to the target. For each developed SBRT treatment plan, once the target coverage goal is achieved and the plan quality is deemed acceptable by at least one experienced physician and physicist,the volumes of bladder and rectum receiving 75% of the prescription dose(V75)as well as the EIV have to be collected. After a sufficient number of cases are recruited, data can be analysed.

Results: Analysis of collected data results in a linear correlation between EIV and V75 of bladder and rectum, confirming that rectum and bladder V75 increase with increasing extension and proximity of these OARs to the target. This correlation enables to easily develop a SBRT technique-specific linear algorithm to define patient-specific dose objectives that should be achieved for future treatment plans.

Conclusions: We have developed a method to define patient-specific dose constraints for the optimization of SBRT treatment plans.This technique-specific information can be used during the planning stage both to orient the plan optimization process and to facilitate the evaluation of the plan quality and consistency.

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P177

PROLONGATION OF OVERALL TREATMENT TIME DURING RADIOTHERAPY OF DIFFERENT TUMOR SITES: A SINGLE CENTER CASE REPORT

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Purpose: Unplanned treatment interruptions and the prolongation of overall treatment time (OTT)can have a detrimental effect on the irradiated patients outcome.In this case report we evaluate the difference between planned and registered OTT of a different tumor sites.

Materials and Methods: A total of 3936 patients (pts) were treated between 1990 and 2010 for breast, prostate, lung, head and neck (H&N) and pelvic malignancies with radiacal or adjuvant intent; palliative or symptomatic treatments were excluded. For all pts (treated with a single fraction of 1.8 to 2 Gy administered five times per week) we registered the total dose,the number of fractions and the treatment's duration(in days); than for each group we evaluated the difference between the mean planned OTT and the mean duration of the treatment.

Results: The gap between mean planned and registered OTT is about 10% for all of the groups. Causes of prolongation of OTT could be various(holydays, machine breakdowns, toxicity and others),but we can't identify them in our computerized record. Moreover tis case report don't correlate the prolongation of OTT with the therapeutic outcome. (Table 1)

Conclusions: This is a simple picture of an unselected case report of pts treated at a single institution. Our results shows a moderate gap between planned and observed OTT. In our center,according with a codified internal protocol, we add a fraction on Saturday if unplanned break caused by machine breakdown exceeds two consecutive days;we don't operate a compensation for other causes (*e.g.* holydays, toxicity). If the break has occurred late in the schedule, we sometimes deliver one or more extra fractions.

Table 1.

Site	Pts	Sex (M/F)	Total dose	Dose/F (Gy)	Number of Fs	OTT(days) planned	OTT(days) observed	Difference (days)
Breast (no boost)	902	0/902	50 Gy	2	25	35	39	**4**
Breast (+ boost)	1597	0/1597	60 Gy	2	30	42	47	**5**
Pelvis	219	67/152	45 Gy	1.8	25	35	38	**3**
Prostate	184	184/0	76 Gy	2	38	53	58	**5**
Lung	76	66/10	61.2 Gy	1.8	34	48	51	**3**
H&N (no CT)	741	494/247	58.7 Gy (mean)	1.8 – 2	31	43	46.5	**3.5**
H&N (+ CT)	217	145/72	63.7 Gy (mean)	1.8 – 2	33.5	47	50	**3**

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ANALYSIS AND RISK MANAGEMENT IN RADIOTHERAPY

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Purpose: The analysis of clinical risk represents one of the dimensions of the Quality. In compliance with the ISO program it was started to optimize a particular stage of cancer treatment at the Marco Polo's in Rome. It was then considered a risk during a phase of Radiation Oncology treatment according to the technique of FMEA (Failure Mode and Effect Analysis) that is a quantitative analysis of what might happen if there were a defect, omission, error, with the aim of identifying possible actions to improvement some actions by a interdisciplinary team of doctors, physicists and technicians. The purpose of the methods of analysis was to identify shortcomings in the system that may contribute to the occurrence of an adverse event and to identify and to design the appropriate protective barriers.

Materials and Methods: There were five different phases of FMEA method: 1) Identification of the critical process: use of appropriate systems of patient immobilization; 2) Study of the process; 3) Risk Analysis; 4) Definition and implementation of containment plans: risk based priority has been called the containment plan aims to reduce and/or eliminate the risk by acting on the causes that give rise to risk and appropriate containment measures; 5) Monitoring results.

Results: On the basis of the data obtained, it has been drawn a grid on which have been reported in the phases of the radiation treatment and the IR values more significant. The phase of the correct positioning of the system of immobilization of the patient on the clinical bed of treatment was the most important from the point of view of the score obtained by FMEA method. It was provided an action of improving the introduction of a checklist in order to assess the correct choice as well as the introduction of a photograph to be attached to patient reports.

Conclusions: The FMEA technique, despite its complexity, is the most important phase for culture of safety and it offers to professionals the opportunity to learn more detailed aspects of care perceived in their relevance. It also allows the implementation of improvement plans consistent with the critical issues relevant to patient safety. This control model of clinical risk had the aim of preventing the occurrence of an error and how it happened. It also wanted to investigate adverse events to identify the causes that were wrong.

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THE MANAGEMENT OF RADIATION TREATMENT ERROR THROUGH INCIDENT REPORTING: OUR EXPERIENCE

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Purpose: Radiation treatment for cancer is susceptible to clinical incidents resulting from human errors and equipment failures. A systematic approach to collecting and processing incidents is required to manage patient risks. We describe the application of an incident learning system in the management of error in radiation treatment

Materials and Methods: Actually the Radiotherapy Center as well as the entire Cosenza Hospital employs an incident reporting system based on signal card inside a regional project. The Hospital agency was also active in developing breafing on guidelines and encouraged information collection systems in a cooperation project of referees for risk management (one referee for each Operative Unit Center of the Hospital) to prevent shortages of staff. In case of severe error we perform an analysis RCA to study the causes of the accident. Analyzing internal incident occurred in October 2006 we reviewed the entire process of radiotherapy treatment and have found many errors due to a lack of procedures and respective responsibility, so we improved the operative procedures used in the department and personal responsibility (signature every step) of each member of radiotherapy staff to implement the safety of treatment.

Results: Dose prescription and dose calculation are the most critical phases of the entire process (possible severe error), but an other critical circumstance was the presence of voluntary staff and the made haste to treatment every patient. By this error, various directives issued by the European Union are implemented in our Center. Actually we have a completely networked system of electronic data transfer. In the process of radiotherapy the radiation oncologists, medical physicists, and radiation technologists are equally involved according respective responsibility (see ISTISAN papers). In case of public enquire we also request a legal framework to help us in the legal management of such incidents.

Conclusions: Human errors occur during the various stages of the complex process of radiation therapy. If uncorrected, these could lead to substantial dose errors to patients. The implementation of a quality assurance checking program can substantially reduce these human errors but never totally eliminate them.

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EVALUATION OF THE BENEFITS OF THE TREATMENT WITH LACTOBACILLUS BREVIS CD#2 TO PREVENT THE DEVELOPMENT OF SEVERE ORAL MUCOSITIS IN PATIENTS UNDERGOING CHEMORADIATION THERAPY FOR HEAD AND NECK CANCER

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Purpose: Oral mucositis is a common acute complication in patients undergoing chemoradiation therapy for head and neck cancer, that would affect patients' quality of life. Mucositis is an inflammatory process of the oral mucosa. Lactobacillus Brevis helps to maintain the balance of microflora of the oral cavity. Our purpose is to evaluate the benefits of the treatment with Lactobacillus brevis CD#2 to prevent the development of oral mucositis.

Patients and Methods: Since May 2011 to May 2012, 14 patients were treated with CD#2 (range 1cp x3/die – 1 cp x6/die) from the first day of the radiation treatment for head and neck cancer. The primary sites of disease were 3 oropharynx, 5 larynx, 3 oral cavity, 2 nasopharynx and 1 maxillary sinus. Ten patients were treated with a chemoradiation therapy and 4 with an exclusive radiotherapy. Seven patients were treated with a 2D technique, 1 with a 3DCRT, 1 with IMRT step and shoot and 5 with a VMAT technique. Eight patient received also an antimycotic drug with a precautional intent according to an internal protocol. All patients were evaluated weekly during the treatment to record the acute toxicity using RTOG scale.

Results: Of the 14 patients only 2 interrupted their planned course of radiotherapy, 1 of them because of worsening of the clinical and cognitive condition, and the other because of a complete dysphagia. No patient presented a grade 3 or higher oral mucositis during the treatment, six (43%) patients presented a grade 2, seven (50%) a grade 1, and one (7%) didn't develop mucositis. Only the two patients that stopped the treatment with CD#2 before the seventh session of radiotherapy, because of intollerance, present also candidosis that required a change of the antimycotic drug. No patient needed any sort of medication during the radiotherapy.

Conclusions: Treatment with Lactobacillus brevis CD#2 is effective to prevent the development of severe oral mucositis, with an improvement of the patients' compliance to the radiation treatment. However, it is necessary a greater sample to better evaluate the real efficacy of this supportive care.

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APPLICATION OF FMECA (FAILURE MODE EFFECTS AND CRITICALITY ANALYSIS) TO THE RADIOTHERAPY PROCESS

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Purpose: Radiotherapy (RT) is a complex process involving different health professionals. The increasing use of newer technologies requires continuous changes of procedures and QA programs. For these reasons, RT is a potentially high-risk procedure and needs prospective and systematic approaches to identify more critical steps and the anticipation of the Failure Modes (FMs, what could go wrong), as proposed by FMECA method. The aim of this work is to present the results of the FMECA application to our RT department.

Materials and Methods: All the staff (radiation oncologists R.O., technicians and physicists) was trained on errors occurrences, risk management in healthcare and particularly in RT, and FMEA/FMECA methods by qualified experts skilled of risk analysis.A small group analysed the whole RT chain in detail and identified 3 critical phases, chosen for the high risk to the patient (pt) and because involved all different professional profiles: vir-

tual SIM, filling medical and treatment chart in Mosaiq R&V system and positioning-set up of the patient at the Linac. The staff was divided into 3 working groups; each analysed one of the identified phase, dividing it in steps and identifying its potential FMs, causes, effects, current controls and risk index. The criticality index is obtained by multiplying the estimated frequency of occurrence of the FM by the expected severity of the damage to the pt and the detectability; these parameters were evaluated by using scales 1-5.

Results: The top-ranked FMs were: wrong positioning of the pt during CT simulation, mismatch between tattoos made in SIM and landmarks on CT images, incomplete filling of treatment description pt set-up, tattoos and position supports in Mosaiq R&V, errors in treatment fields import in Mosaiq, errors in treatment fields scheduling (in particular, about sequence of different treatments) and problems in pt identification.

Conclusions: FMECA method is a valid tool to identify the vulnerabilities in a process before they occur and generate an error. In our experience, FMECA study was very well accepted by the operators and further increased the commitment towards pt safety, thanks to an improved understanding of clinical risk. The work will continue with the analysis of the planning process (not considered until now because not involving directly technicians) and with the realization of practical corrective actions to reduce the overall risk to the pt.

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HFMECA ANALYSIS METHOD APPLIED TO ACTIVITY FLOW OF OUR RADIOTHERAPY DEPARTMENT

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Purpose: The present work lies in the framework of the application of our Institutional Clinical Risk Management Plan: indeed ours has been among the first departments which answered to Clinical Governance strategic objectives. It reports about the actions performed during analytical laboratories held in our Radiotherapy Department, in collaboration with the Risk Management Department, whose main purposes were two: the FMECA analysis of Radiotherapy activity flow and the scheduling of the appropriate interventions in those activities related to a higher clinical risk.

Materials and Methods: FMECA, HFMECA and IDEF0 methodologies. Clinical risk reports of the Risk Management and Radiotherapy joint analysis laboratories.The whole Radiotherapy staffing was involved in FMECA process analysis.

Results: After a preliminary phase of collection of all protocols relating the procedures performed in our department, as well as the local practices, analytical laboratories were started in order to :1) define the object of the analysis, (*i.e.* the overall process of Radiotherapy); 2) individuate its main component sub-processes;3) decompose each sub-process in elemental activities; 4) assess the eventual failure modes, causes, effects and define for each one its own Occurrence(O), Detectability(D) and Severity(S) score on previously defined appropriate scales. For each failure mode, a Risk Priority Number=PxDxS was obtained. By ordering all assessed failure modes according their resulting RPN score, we obtained a criticality ranking. This way we could identify those activities requiring corrective actions (defenses, control barriers, safeguards) with higher priority, in order to reduce operational risks, as suggested by HFMECA.

Conclusions: The concomitant use of FMECA,HFMECA and IDEF0 tools allowed the production of logical-graphic schemes for each process component, while developing the radiotherapy activity flowchart. Indeed, while FMECA analysis allowed the progressive decomposition of the overall Radiotherapy process in individual constitutive activities, the construction of a cascade of IDEF0 diagrams, powered and supported the final endpoint, that is the determination of possible failures modes, their causes, their effects with the associated clinical risk in order to plan the corrective actions to address the most serious concerns.

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NEW TECHNOLOGIES IN RADIATION THERAPY INCREASE THE CLINICAL RISK. CRITICAL ANALYSIS OF "ENTERPRISE" RISK

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Introduction: The term "clinical risk" defines the possibility that a patient suffers damage or distress caused by involuntary access to health care. In health there are two types of risk: a risk of "enterprise" intrinsic to the technologies and a risk described as "pure risk" not related to the complexity of the system, unpredictable and unquantifiable. The development of modern accelerators has promoted the widespread development of 3-D conformational techniques, from these it is switched to the most advanced equipment capable of IMRT and IGRT treatments. Modern techniques allow to improve radiation therapy (*e.g.* homogeneous dose distribution, conformation of the dose, organs at risk preserving, organ motion control) but they can introduce an additional source of error and thus they can increase the clinical risk in its component of "enterprise risk". The aim of our study: to analyze the factors that contribute to defining the "degree of riskiness" in radiotherapy; point to possible solutions and corrective instruments.

Materials and Methods: We analyzed the documents found on the web related to "patient safety and clinical risk management" The documents have been reinterpreted depending on radiation therapy. The factors that contribute to defining the "degree of riskiness" in health care

were examined to determine which of them represent "risk factors" in radiotherapy. Documents relating to "quality assurance in radiotherapy" have been taken into account for providing possible solutions.

Discussion. The "clinical risk" refers to the possibility that a patient suffers damage due to health care and can be divided into two types of risk: risk of "enterprise" and "pure risk". If considered in its entirety, several factors combine to determine the "clinical risk". These factors can be generally divided into 4 groups that are also applicable to radiation therapy: 1) structural-technological factors, 2) organizational factors, managerial and working conditions, 3) human factors (individual and team), 4) characteristics of users, 5) external factors. When we go to decompose the clinical risk into its two components we find that: a) group 1 configures the "enterprise" risk itself; b) the remaining groups determine the "pure risk". Group 1 encloses specific risk factors: 1) characteristics of the building and plant health (design and maintenance); 2) security and logistics environments; 3) equipment and instruments (functioning, maintenance, renewal); 4) infrastructure, networks, digitization, automation. All these factors are applicable to radiotherapy and particularly to the modern radiation therapy, where the technological evolution goes hand in hand with automation. Since the business risk is closely linked with new technologies, programs of QA and maintenance of equipment, we seem to now the only and most suitable tools for prevention.

Conclusions: Modern radiation therapy and new technologies through the introduction of additional steps, increase the clinical risk of "enterprise" when compared to techniques obsolete. Programs of QA and maintenance of all equipment are necessary to monitor and prevent this component of the clinical risk.

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RISK ASSESSMENT OF INTRAOPERATIVE RADIATION THERAPY USING THE INTRABEAM SYSTEM

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Purpose: To assess the clinical risk of the Intraoperative Radiation Therapy (IORT) procedure with the Intrabeam system, applying the Failure Mode and Effects Analysis (FMEA).

Materials and Methods: The IORT procedure was divided in 7 subprocesses: 1) Selection of the spherical applicator, 2) Docking, 3) Skin retraction from the applicator, 4) Chest wall protection with polyurethane-tungsten impregnated sheets, 5) Apposition of the superficial polyurethane-tungsten impregnated sheets, 6) Dose prescription, 7) Radiation delivery. Potential failure modes and consequent failure effects were identified for each of the 7 sub processes. The hazard analysis was conducted for each subprocess according to FMEA. The clinical risk, also referred to as the criticality index (CI), is a quantitative measure to evaluate and assess a failure mode, and is the product of 3 scores: CI = S x O x D , where S is the Severity score, O is the Occurrence score, and D the Detection Score. A five-point scale was used for scoring each of these categories.

Results: The potential identified failure modes and their effects, and the relative CI follow: 1) Selection of the spherical applicator causing an over dose effect, CI = 24; Selection of the spherical applicator causing an under dose effect, CI = 30; 2) Incorrect docking, CI = 1; 3) Inadequate skin retraction from the applicator, CI = 36; 4) Missing the chest wall protection with polyurethane-tungsten impregnated sheets, CI = 9; 5) Missing the apposition of the superficial polyurethane-tungsten impregnated sheets, CI = 6; 6) Incorrect dose prescription causing an over dose effect, CI = 12; Incorrect dose prescription causing an under dose effect, CI = 15; 7) Dose delivery interruption, CI = 10.

Conclusions: Two subprocesses, "Selection of the spherical applicator" and "Skin retraction from the applicator", with a higher Criticality Index were identified. For such sub processes strategies to reduce the severity of the failure should be developed.

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IORT PROCEDURE ANALYSIS ACCORDING TO THE JOINT COMMISSION INTERNATIONAL ACCREDITATION SYSTEM

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Aims: The Department of Radiotherapy of Trieste has recently acquired a IORT dedicated accelerator, the Mobetron. In 2011 the University Hospital of Trieste received confirmation of Joint Commission International (JCI) accreditation for 2011-2014. The accreditation requires the drafting of the Procedure of every new technique that is introduced in the clinical practice, according to the manual instructions of JCI and the application of FMECA (Failure Mode, Effects and Criticality Analysis) prospective approach, in order to fully assess and manage the risks of accidental exposures deriving from the use of innovative methodologies. The aim of this study is to present the results of the Procedure elaborated by our Working Group and the application of FMECA prospective approach to IORT delivery.

Materials and Methods: A multidisciplinary Working Group was created, including different professional profiles; the Group was coordinated by a facilitator, a Medical Doctor of the Medical Direction of the Hospital, qualified in clinical risk management. The description of the Flow Chart of IORT, included in the Procedure text, which reported the sequence of all the process steps, made up the platform of the FMECA study. Each member of the Working Group was asked to identify the potential failure modes (FM) he/she could encounter in the process

steps concerning his/her specific activity. The risk analysis was completed by asking the members of the team to evaluate the Risk priority number (RPN) of each FM, obtained by multiplying the estimated frequency of occurrence (O) by the detectability (D) of the FM and the expected severity of the damage to the patient (S), using a 5-point scale for each parameter.

Results: The Flow Chart of IORT, was subdivided into 43 steps, and 39 criticalities were identified by the Working Group. They represented the issues prospectively investigated according to the FMECA method. An Excel worksheet was created, inserting in rows: process step, professional figures involved, failure mode, potential effects of failure, potential causes of failure, RPN and finally corrective actions. The highest scores regarded the misalignment of the perspex plate used to protect the underlying normal tissues (RPN= 60); the inadequate selection of the applicator in relation with the CTV extension (RPN= 40) and the inaccurate placement of the applicator in the tumour bed (RPN= 36). The introduction of appropriate corrective actions reduced the extent of the potential risks.

Conclusions: The FMECA technique has provided a prospective, systematic method for discovering potential failures in IORT procedure, evaluating not only their frequency but also their severity and detectability. It represents, therefore, an important tool to optimize patient safety right from the start of our clinical activity, and to improve risk management culture among all the professionals involved in the Working Group.

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PEOPLE MAKE HEALTHCARE

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Purpose: This work proposes a series of reflections on healthcare, examined in relation to the importance of human aspects in macrosystem and therefore humanization of factors that influence the results of a cure. The goal is necessary tools, or at least desirable, for a peaceful exercise of the medical profession, also seen by the patient, in a context of heavy reliance on organizational growth and human potential.

Materials and Methods: Our work explains the meaning of quality of life, and of welfare for people and how to evaluate it. Analyzing the meaning of the term "welfare" and its perception to the recognition of the social value that this holds, the collective responsibility, emphasizing the centrality of the individual but by virtue of a social action that amplifies exponentially good staff in the common good. The importance and the countless benefits from the personal construction of professional liability associated with employment status of "health", which enhances the relationship between the organization and workers, colleagues themselves participating in an intermodel shared care, bringing advantages to end users. The operator activates the capacity, or somehow develops in response to environmental requirements are the support base of his profession.

Results: Being able to listen to the patient, free from bias or prejudice, to help in the understanding and management of their problem so that we would refocus and find the resources needed to combat it is the main activity report required in our business, namely the health and counseling patient empowerment. Also needed are the means of effective communication, "strategic", so as to implement a concrete relationship help that contextualizes the communication flow.

Conclusions: This work intended to carry out the reflections on the activity of healthcare workers and the importance of relational aspects of health-related issue, with reference to the organizational system by privileging the relationship between staff and patients. It is considered desirable for continuing education of professionals who can implement the communication and interpersonal skills in order to make the organization more functional and responsive to the needs of both professionals and patients.

CHIRURGIA E RADIOCHIRURGIA A CONFRONTO NEL TRATTAMENTO DELLA PATOLOGIA NON ONCOLOGICA E DEI TUMORI BENIGNI EXTRA-ASSIALI

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LOW DOSE CYBERKNIFE RADIOSURGERY FOR TRIGEMINAL NEVRALGIA(TN): THE EXPERIENCE OF THE DIAGNOSTIC CENTER OF MILAN

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Aims: Idiopathic TN is the most common type of facial pain nevralgia.Treatment options include medicines, surgery and complementary approach. In the year 2002 at the Stanford University the treatment of Cyberknife Radiosurgery for NT was first developed and afterwords performed with a protocol of low dose. The aim of this study is to evaluate the results in term of efficacy and safety in patients treated with low dose cyberknife radiosurgery for TN.

Methods: From 2005 to date we have treated 245 patients for idiopathic NT. This review have considered 45patients from 4.2010 to 12.2011 who have received a median dose of 55Gy (range going 50Gy to 60Gy). the dose was prescribed to a 6 mm of the retrogasserian trigeminal nerve. The median dose of prescription was to the 80% and maximum dose was not exceed 75GY. It was used a 5 mm collimator. All patients underwent volumetric MRI (Fiesta sequences) and Ct scans and the target was obtained providing the fusion images. Patients were evaluated for the level of pain control according to the Boulder-Stanford Pain scale and the occurance of hypostesia. The BNI facial hypostesia scale and scoring system was used. The median of follow-up period was 15.8 mounths (6.6-25.4).

Results: Results at six mounths after treatment, patients-reported outcomes were: excellent in 12 patients

(26.7%), good in 17 patients(37.8%), not improvement in 4 patients (8%). After 1 year the analysis of 38 patients was: excellent in 11 patients (28.9%), good in 13 patients (34.2%), not improvement in 5 patients (13%). The median time to pain relif was one mounth. Post treatment numbness occurred in 8 patients (18.2%)

Conclusions: low dose Cyberknife radiosurgery for NT results effective and safe providing a valid option without undergo invasive procedures A major time of follow up is needed to define long term results and to suggest the optimal features of the CK treatment also according to the results already reported in the literature

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EXTERNAL BEAM RADIOTHERAPY FOR PITUITARY ADENOMAS: UNIVERSITY OF FLORENCE EXPERIENCE

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Purpose: To evaluate therapeutic outcome and side effects of radiotherapy in pituitary adenomas as sole or combined treatment.

Materials and Methods: Retrospective analysis of 37 patients (14 male, 23 female) irradiated for pituitary adenoma from 1989 to 2011 was performed. Mean age was 51.8 years (25-83 years). Regular follow-up (mean follow up 2.4 years range : 2 months- 9.4years) included radiodiagnostical [computed tomography (CT), magnetic resonance imaging (MRI), x-ray], endocrinological, and ophthalmological examinations. Ten patients suffered from nonfunctional pituitary adenoma, 6 patients suffered from growth-hormone producing adenomas, 6 had prolactinomas, and 15 patients had adrenocorticotropic hormone (ACTH) producing pituitary adenomas. In 22 patients surgery was followed by radiotherapy in case of suspected remaining tumor (invasive growth of the adenoma, assessment of the surgeon, pathologic CT after surgery, persisting hormonal overproduction). Twelve patients were treated for recurrence of disease after surgery and 3 patients received radiation as primary treatment. Total doses from 44-54 Gy (mean: 48 Gy) were given with single doses of 1.8-2 Gy.

Results: Tumor control was achieved in 34 patients (94.9%). In three patients, recurrence of disease was diagnosed in the mean 2.9 years (8-74 months) after radiotherapy. Dose higher than 45 Gy correlated with tumor control. Ninety-six percent of the patients with hormonally active pituitary adenomas had a benefit from radiotherapy in means of complete termination (37%) or at least reduction (60%) of hormonal overproduction. Thirteen patients had a hypopituitarism prior radiotherapy; 7 patients (18.9%) after radiotherapy developed partial or complete hypopituitarism. No patients suffered reduction of visual acuity.

Conclusions: We conclude that radiotherapy of pituitary adenomas, using fractionated external beam radiotherapy, is effective and safe. To achieve optimal tumor control doses of 44-54 Gy should be applied.

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LINAC-BASED RADIOSURGERY FOR CEREBRAL ARTERIOVENOUS MALFORMATIONS: LONG-TERM RESULTS IN 81 PATIENTS

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Purpose: Intracranial arteriovenous malformations (AVMs) are vessel abnormalities consisting in arteries directly and pathologically connected to the venous drainage. Treatment of choice is complete excision, particularly for small AVMs (<10cc) located in superficial and non eloquent areas of the brain. Instead radiosurgery (SRS) is used for <10cc centrally located AVMs, or for inoperable ones. Endovascular embolization can be used for large AVMs to decrease the initial size, improving conditions for subsequent surgery or SRS. Target of SRS is AVMs obliteration, prevention of bleeding and neurological symptoms.

Materials and Methods: From January 2002 to May 2012 we treated 117 patients (pts). 81 pts with a follow-up >24 months were analyzed. Median age was 38 years (range,8-78), female/male ratio 36/45, median volume 2.05cc (range,0.10-64.70), median dose 20Gy (range,12-24). SRS-based AVM score (RBAS)* was <1, 1-1.5, 1.6-2, and >2 in 29,19,19, and 14 pts, respectively. Treatment was delivered using a 5-MV linear accelerator fitted with a dynamic micro-multileaf and invasive head fixation. Multimodal imaging with magnetic resonance (MRI) and angiography was used for target definition and dose was prescribed at isocentre. Follow-up was done with MRI and/or angiography.

Results: Outcome resulted excellent (obliteration without neurological symptoms) in 38 pts (47%), good (obliteration with minimal neurological symptoms) in 4 pts (5%), stable in 35 pts (43%), poor in 4 pts (5%). Of these last pts, 3 died, 2 for stroke and 1 for unrelated causes, 3, 8 and 36 months after SRS, respectively. There was a good compliance without acute toxicity. Regarding late toxicity, 2 pts (2%) had radionecrosis, 3 pts (4%) new or worsened seizures controlled by therapy and 2 pts (2%) a re-bleeding requiring surgery. Obliteration rate at 2, 3 and 4 years was 47%, 52% and 56%, respectively. Increase of obliteration rate with follow-up length resulted statistically significant (p=0.05). Excellent outcome was significantly conditioned by RBAS: 80% in <1, 48% in 1-1.5, 27% in 1.6-2 and 6% in >2 (p=0.038). Conclusions: Linac-based SRS for cerebral AVMs was feasible and well tolerated. Obliteration rate increased with follow-up length and outcome was linked to RBAS.

*RBAS = (0,1 x AVM volume[cc]) + (0,02 x patient age[years]) + (0,3 x AVM location);0=frontal, temporal; 1=parietal, occipital, intraventricular, corpus callosum, cerebellar; 2=basal ganglia, thalamic, brainstem.

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TRIGEMINAL NEURALGIA: RADIOSURGERY *VS* HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY BY DEDICATED LINEAR ACCELERATOR. RESULTS IN 45 PATIENTS

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Radiosurgery (RS) at 40 Gy and hypofractionated stereotactic radiotherapy (HSRT) were performed respectively in 23 and 22 patients for the treatment of trigeminal neuralgia. RS and HSRT were performed by a dedicated Linear Accelerator (LINAC); invasive frame or relocatable stereotactic frame with thermoplastic masker and byte were used for patient positioning in case of RS or HSRT respectively. Treatments were performed delivering 40 Gy in a single fraction (RS) and the equivalent radiobiological fractionated dose (72 Gy in 6 fractions for HSRT). The target (retrogasserian cisternal portion of the trigeminal nerve) was identified by fusion of CT images with T2 weighted MRI of 1 mm of thickness, and the radiant dose was delivered by cylindrical collimator of 10 mm diameter. Results were evaluated using BNI pain scale during follow-up time averaging 3,9 years. All the volume of the target was included in the isodose of 95%. After RS, Class 1, Class II, Class IIIa, Class IIIb, and Class V results were observed respectively in 10, 9, 2, 1 and 1 patients; 2 (8,7%) facial numbness, 2 (8,7%) recurrences occurred. Following HSRT in 22 patients, Class 1, Class II, Class IIIa and Class IIIb results were achieved in 8, 8, 4 and 2 patients respectively; six (27,5%) recurrences occurred, in absence of complications. RS and HSRT resulted an effective and safe therapy in the treatment of trigeminal neuralgia. RS allowed better results concerning pain relief and rate of recurrence, while HRST presented no side effects, in particular no facial numbness.

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EFFICACY OF RADIATION THERAPY IN THE TREATMENT OF MENINGIOMAS: A 12 YEAR EXPERIENCE OF THREE CENTERS

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Purpose: 0Meningiomas are the most common primary brain tumors in adults. Surgical resection is curative when complete removal of a benign meningioma is possible. Incompletely resected tumors and high-grade lesions are frequently treated with fractionated radiotherapy or stereotactic radiosurgery. When it is not possible to perform a resection, highly conformal techniques are mandatory.

Patients and Methods: 136 patients with meningiomas were treated with 3DCRT, fSRT (Intensity Modulated Arc Therapy-IMAT), SRS and Tomotherapy between 1998 and 2010. Patients received RT either as primary treatment (n = 96), or after incomplete resection (n = 28) or recurrence (n = 12). 39 patients were treated with a single isocenter with 3DCRT, 65 with multiple converging arcs (3-9) with a dynamic micro-multileaf collimator (leaf width at isocenter 5 mm) and 33 with SRS circular collimators. Amplitude and dose-rate modulation were used in 34 patients treated between 2001 and 2010. GTV was defined as the contrast enhancing area, CTV was considered equivalent to GTV and PTV encompassed the GTV with a 2 mm margin. MRI followed by image co-registration and fusion with CT was used for planning in 81 patients while CT only was used in 55. The mean radiation dose in fractionated RT was 54 Gy/30 fr, in SRS was 15 Gy at isocenter. Evaluation of treatment plans was done using indexes of target coverage, dose conformality and homogeneity and outcome measurements. F-up examinations, including MRI, were performed at 6 month intervals for the first 3 years and yearly thereafter. Median f-up was 72 months (range 14-136).

Results: Patients treated with modulated techniques had better target coverage and conformality with higher target dose heterogeneity; doses to optic nerve, chiasm, and brain stem were lower and NTCPs were better with arc modulation. Pre-existing neurologic symptoms were present in 38 patients, were improved in 25 (65.7%), unchanged in 11 (28.9%), worsened in 2; no patient developed new symptoms. Tumour shrinkage was observed in 23 patients (16.9%) while volume remained unchanged in 110 (80.8%) and increased in 3 (2.2%). OS at 5 years was 98.5% and PFS was 96.3%. No patient developed treatment-related oedema or other toxicities.

Conclusions: 3D-CRT, SRS, fSRT (IMAT) and tomotherapy are a safe and effective treatment for meningiomas. Particularly arc modulation and tomotherapy increases conformality and reduces the dose to critical structures in the base of skull meningiomas.

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CYBERKNIFE RADIOSURGERY FOR 110 BENIGN MENINGIOMAS, MONOISTITUTIONAL EXPERIENCE

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Introduction: Present the results obtained with an image-guided radiosurgery system in a series of 110 benign intracranial meningiomas.

Methods: In this series we have included lesions unsuitable for surgery and/or remnants after partial surgical removal. Twenty-eight tumors were in supratentorial area, 45 were in contact with anterior optic pathways

(cavernous sinus,petrous bone or clivus); 27 were parasagittal and 12 were in the posterior fossa. Tumor volumes varied from 1.5cc to 20.5cc (median volume, 6.7cc) and radiation doses ranged from 12 to 61Gy (mean, 16Gy). Treatment isodoses varied from 62 to 100% (median isodoses 77%). We used 25Gy in 5 fractions for the perioptic meningiomas (in about 35% of the similar cases) and the single session for the meningiomas located in the posterior fossa, in parasagittal and supratentorial area (in about 50-80% of the similar cases). In 45 patients with larger lesions and/or located closed to critical structures, the dose was delivered in 2 to 15 daily fractions.

Results: The follow-up periods ranged from 1 to 60 months. The tumor volume decreased in 23 patients, it was unchanged in 82 patients, and it increased in 5 patients. No patients underwent repeated radiosurgery, and 5 ones underwent operations. One hundred patients were clinically stable. In 5 patients, neurological deterioration was observed with new cranial deficits in 2 patients, worsened diplopia in 2 and visual field reduction in 1.

Conclusions: The introduction of the CyberKnife extended the indication in 45 patients who could not have been treated by single-session radiosurgical techniques for volume and site. The procedure proved to be safe.

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FRACTIONATIONATED STEREOTACTIC IRRADIATION WITH 18-21GY IN 3 FRACTIONS FOR ACOUSTIC NEUROMAS

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Introduction: Stereotactic radiosurgery has proven effective in the treatment of acoustic neuromas. Prior reports using single-stage radiosurgery have shown excellent tumor control, but only 50-73% of patients maintain hearing at pretreatment levels. The use of CyberKnife (Accuray, Inc., Sunnyvale, CA) image-guided radiosurgery permits to treat acoustic neuroma with a staged approach. This approach minimizes injury of adjacent cranial nerves. In this retrospective study, we report our experience with staged radiosurgery for acoustic neuromas.

Methods: Since july 2007, the CyberKnife has been used to treat more than 50 patients with acoustic neuroma. Among the patients treated, the median tumor volume was 4.1cc (range, 0.2-25.5cc), the median total marginal dose has been 18Gy (range,18-21Gy) using a marginal dose of 6-7Gy for fraction. All patient underwent MRI and CT scan for treatment planning. The GTV was the target volume considered for treatment, and included the enhancing mass extending in the meatus and cerebellopontine angle. Audiograms and magnetic resonance imaging were obtained at 6-months intervals after treatment for the first 2 years and then annually thereafter.

Results: Eighty percent of patients maintained serviceable hearing at the last follow-up, and no patient had lost hearing after treatment whereas they had lost it before treatment. Dmax to the brainstem was 1622 ± 279 cGy, the D1% was < 1500 cGy. Dmax to the trigeminal nerve was 1491 cGy, Dmax to the cochlea was 1222 cGy. Six patients had serviceable hearing (Gardner-Robinson Class 1-2), only three treated tumor progressed after radiosurgery; 25 decreased in size and 22 tumors were stable. No patients had new trigeminal dysfunction and permanent injury to facial nerve.

Conclusions: Staged treatment regimen may improve hearing preservation in acoustic neuroma patients undergoing stereotactic radiosurgery.

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FRACTIONATED STEREOTACTIC RADIATION THERAPY (FSRT) FOLLOWING LIMITED SURGERY IN CHILDHOOD CRANIOPHARYNGIOMA

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Surgery and radiotherapy (RT) are the treatment for craniopharyngioma: because of its proximal location to critical structures it remains one of the most challenging intracranial tumours. Due to the long life expectancy, any therapy should aim to minimise long term side effects. Between October 1997 and December 2011, 30 children (median age 9 years-range: 5-18) with craniopharyngioma were treated with limited surgery and FSRT. Twenty two patients received FSRT as first line therapy and 5 at progression at 8, 12, 18, 33 and 43 months after surgery. Two of them, at the recurrence had a further debulking. Two patients were treated with FSRT for tumour re-growth 43 and 60 months after an initial surgery and conventional external RT. One patient had 90yttrium intracavitary irradiation 76 months before FSRT. Surgery consisted of a sub-total resection in 25 patients, by craniothomy in 20, by trans-sphenoidal approach in 5. Five patients had drainage of cyst by endoscopic approach. Extent of surgery was determined by the neurosurgical report combined with early post-operative contrast enhanced MRI. Gill-Thomas-Cosman, Boston Children's Hospital or Tarbell-Loeffler relocatable frames were used for treatments planning and delivery, assuming an overall accuracy of 1.5 mm. Treatment was based on CT and MR imaging, matched by the Radionics image fusion program. All received a total dose up to 54 Gy with conventional fractionation. At a median follow-up of 9 years (range: 6 -175 months), survival rate is 100%. Two children had re-growth after 16 and 98 months, 8 showed complete response, 15 partial response, and 5 remained stable. In 6 patients vision improved, 1 experienced visual deterioration. After SFRT pituitary function further deteriorated in 7 patients while improved in 4. Nine had hypothalamic obesity post therapy, 1 presented moyamoya disease. We did not observe any severe toxicity to normal tissue or any radionecrosis. No secondary malignancies have been diagnosed. All these children but one were attending school regularly and conducting a normal life according to their age and sex. Considering the reduced toxicity of FSRT compared to conventional RT and the at least similar effectiveness, it seems FSRT should be preferred whenever possible. Because the effectiveness

of a less radical surgery combined with FSRT is at least comparable to that with radical resection, limited surgery followed by FSRT can be considered one of the treatment of choice.

ATTUALITÀ NEL TRATTAMENTO DEL PAZIENTE METASTATICO

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CRITICAL ASPECTS AND PARAMETER OPTIMIZATION FOR AN IMAGE GUIDANCE SYSTEM FOR ROBOTIC TREATMENT OF SPINAL AND PARASPINAL METASTASES

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Purpose: The Xsight-spine tracking system(Xssts)is the alignment method developed for the robotic Cyberknife(Accuray)which allows the detection,alignment and tracking of the spine for the treatment of vertebral and paravertebral lesions.The aims of this study are:the analysis and optimization of the radiological parameters and the ROI(Region of Interest)used for matching,as well as the optimization of the procedures for the initial alignment of a sample of patients with vertebral and paravertebral secondary lesions. Our study final purpose is to optimize both the accuracy of image fusion and treatment timing execution which is often protracted because of the involuntary movements of the patient. These could be considered a very critical factor for the treatments with the Cyberknife System.

Materials and Methods: Image guidance by Xssts is based on radiological image acquisition(90°), target localization, and alignment corrections. Sequences of radiological images are acquired at regular intervals continually repeated during treatment delivery. These images are matched with the corresponding DRR (digital reconstructed radiographs),generated by the TPS (treatment planning system), in order for the system to make a set-up correction and re-align beams with the target during treatment delivery intra fraction motion correction. Our series analyzed 30 patients: divided according to spine section. Patient positioning system is based on the use of precision positioning tools available, which are different for each spine sections.Some radiological parameters values (range:110-150kV,100-300mA and 80-125msec) have been considered as a possible correlation with the accuracy of matching between images acquired and DRR, expressed as number of false nodes. The number of false nodes was also analyzed as a function of the region of interest used for image and DRR matching. The number of interruptions occurred during treatment due to patient motions beyond the tolerance levels (10mm,1deg) has been also considered.

Results:The detected average N°of false nodes is 13% *versus* a maximum tolerance threshold of 50%, the average N° of interruptions during treatment is 2, due mainly to movements of the patient for pain. The average radiographic parameters are 120KV,200mA and 100msec.

Conclusions: Through this analysis we develop a protocol based on the reduction of false nodes. This may allow the Xssts to work in optimal conditions to obtain time reduction during patient positioning and treatment delivery.

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WHOLE BRAIN RADIOTHERAPY WITH ADJUVANT OR CONCOMITANT BOOST IN BRAIN METASTASIS: PRELIMINARY DOSIMETRIC COMPARISON BETWEEN HELICAL AND VOLUMETRIC TECHNIQUE

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Aims: To compare two highly sophisticated techniques (VMAT and Tomotherapy) and two different boost delivery modalities (adjuvant stereotactic boost –SRS- or simultaneous integrated boost –SIB- in the treatment of brain metastases (BM) in RPA classes I-II patients (pts).

Materials and Methods: Ten pts were treated with Tomotherapy® since June 2011 at Brescia University Radiation Oncology Dept., 5 of them with SRS after whole brain radiotherapy (WBRT) and 5 with SIB. MRI co-registration with TC planning was mandatory. Prescribed doses were 30 Gy/10 fr for WBRT, 15Gy/1fr for SRS and 30-45Gy/10fr for the SIB modality, respectively. For each patient, 4 treatment plans (VMAT SRS and SIB, Tomotherapy® SRS and SIB) were calculated and accepted if PTV boost volume was included in the 95% isodose and dose constraints of the organs at risk were respected. Homogeneity Index (HI), Conformal Index (CI), Conformal Number (CN) were calculated in order to compare the dosimetric differences of the plans obtained. Time of treatment delivery was also calculated.

Results: BM volume ranged 1.43 - 51.01 cc (mean 12.89 ± 6.37 cc) and 3 pts had two lesions. V95% resulted over 95% for PTV on average for all techniques, but target coverage was inferior for VMAT when two sites had to be treated. The HI resulted close to the ideal value of zero in all cases. CI, CN, treatment time mean values and range are reported in the Table 1.

Conclusions: This retrospective dosimetric comparison of 40 plans shows that Tomotherapy® obtains slightly better CI and CN values, when two BM are treated. Treatment times clearly favour V-MAT. HI index is excellent for both techniques. Dosimetric results should be substantiated by clinical results in a comparative effectiveness research and EBM perspective.

Table 1.

	CI mean (range)	CN mean (range)	Time treatment mean (range)
VMAT-SIB	2,36 (0.96-8.25)	0,37 (0.00-0.74)	210 (133-277)
VMAT-SRS	3,15 (1.06-6.67)	0,38 (0.06-0.51)	467 (375-578)
TOMO-SIB	2,11 (1.35-4.79)	0,36 (0.15-0.61)	440 (247-980)
TOMO-SRS	1,82 (1.00-5.57)	0,51 (0.19-0.80)	1598 (1051-2784)

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HYPOFRACTIONATED PALLIATIVE RADIOTHERAPY IN METASTATIC LUNG CANCER: EVALUATION OF CLINICAL OUTCOME

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Purpose: The aim of this study was to evaluate the clinical outcome of patients with metastatic lung cancer after palliative hypofractionated radiation therapy treatment at total dose of 30Gy.

Materials and Methods: Between January2011 and April2012 we have treated 18 patients with IV stage NSCLC and 1 patient with IV stage SCLC with hypofractionated palliative 3D conformal radiation therapy (3D-CRT). The median age was 66.5, range 53-79 years. A total dose of 30Gy in 10 daily fraction (3Gy/f) was delivered to mediastinum with two opposed fields (11pts) or multiple fields (8pts) of energy 6-20MV. The toxicity was evaluated during and after RT treatment (at least one month after the end of RT) with clinical examination. Pulmonary, esophageal, hematological and skin toxicity was evaluated according to RTOG toxicity scale, whereas the pain was evaluated using an internal questionnaire. The evaluation of clinical outcome was performed comparing the toxicity during and after hypofractionated radiotherapy treatment.

Results: The median follow-up was 4 months (range1-14). All patients completed the treatment without break.Two patients,who had G4 pulmonary toxicity during RT, had respectively G1 and G2 toxicity after RT;One patient had G3 pulmonary toxicity during and after RT; two patients, who had G2 pulmonary toxicity during RT, had respectively G1 and G0 toxicity after RT; 11 patients, who had G1 pulmonary toxicity during RT, 4 had G1 and 7 had G0 toxicity after RT; 3 patients had G0 pulmonary toxicity during and after RT. Any G4 and G3 esophageal toxicity was observed during and after RT.Four patients, who had G2 esophageal toxicity during RT,3 had G0 and one had G2 toxicity after RT; one patients,who had G1 esophageal toxicity during RT, had G0 toxicity after RT; 14 patients,who had G0 esophageal toxicity during RT, 13 had G0 and one had G1 toxicity after RT. Any G4, G3 and G2 hematological toxicity was observed during and after RT.Four patients had G1 hematological toxicity during and after RT and 15 patients had G0 hematological toxicity during and after RT.Skin toxicity was observed in two patients only during RT. The pain, which was present in 7 patients during RT course, has disappeared in 3 patients, was decreased in 3 cases and has persisted in one patient after treatment.

Conclusions: The results derived from comparing the observed toxicities showed that palliative hypofractionated radiation therapy is acceptable and feasible treatment for patients in stage IV lung cancer. Hypofractionated Radiotherapy decreases the symptoms of respiratory failure and pain with acceptable esophageal toxicity and optimal hematological toxicity.

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SHORT COURSE ACCELERATED RADIATION THERAPY (SHARON) IN PALLIATIVE TREATMENT OF ADVANCED HEAD AND NECK MALIGNANCIES: A PHASE I STUDY

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Aims: To define the maximum tolerated dose (MTD) of a conformal SHort course Accelerated RadiatiON therapy (SHARON) in the symptomatic treatment of patients with advanced head and neck cancer.

Patients and Methods: A phase I clinical trial was designed, escalating the dose in four steps: 14 Gy (3.5 Gy fraction), 16 Gy (4 Gy fraction), 18 Gy (4.5 Gy fraction) and 20 Gy (5 Gy fraction). Eligibility criteria included histologically proven of locally advanced cancer and/ or metastatic disease in the head and neck and ECOG performance status < 3. Treatment was delivered in two days with a twice daily fractionation and at least eight hour interval. Patients were treated in cohorts of 6 to 12 to define the MTD. The dose limiting toxicity (DLT) was defined as any acute toxicity > Grade 3, according to RTOG scale. Pain was recorded using a Visual Analogic Scale (VAS).

Results: Characteristics of the overall 25 enrolled patients were: M/F: 13/12; median age: 72 yrs (range: 40-96). The primary tumor sites were: head and neck (28%), skin (24%), lung (12%), breast (8%) and others. ECOG Performance Status was <3 in 23 patients (93%). Twenty patients (80%) had baseline symptoms. The most frequent baseline symptoms were pain (100%) with (20%) or without dysphagia. Grade 1-2 skin (24%) and mucosal or pharyngeal (32%) acute toxicities were recorded. One patient at the fourth dose level experienced DLT in term of Grade 3 mucosal acute toxicity. With a median follow-up time of 6 months (range, 3-12 months), G1 subcutaneous late toxicity has been observed in 1 patient. The overall symptom remission (complete plus partial remission) was 95% (CI 0.95: 68.6% - 99.9%). Two patients (8%) had complete pain relief, and 10 patients (40%) showed more than 30% VAS reduction.

Conclusions: Three-dimensional conformal short course accelerated radiotherapy in twice daily fractions for two consecutive days is well tolerated up to a total dose of 20 Gy. A phase II study has been planned to confirm the efficacy on symptom control and quality of life parameters.

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SHORT COURSE PALLIATIVE RADIOTHERAPY: DEFINITIVE RESULTS OF THE SHARON (SHORT COURSE ACCELERATED RADIATION THERAPY) PHASE I STUDIES

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Aims: Radiation treatment(RT) is able to control symptomatic conditions such as neurological disorders, dyspnea, mediastinal syndrome, dysphagia, bleeding and pain. Nevertheless, some studies revealed a lack of knowledge in the oncological community about the potential of palliative RT, as well as about the benefit of short palliative RT schedules. Aim of this study is to evaluate the feasibility of a SHort course Accelerated RadiatiON therapy (SHARON study) in the symptomatic treatment of patients with advanced disease from six different tumor sites.

Patients and Methods: A multi-arm phase I clinical trial was designed. Eligible patients had pathologically proven advanced and/or metastatic cancer and ECOG performance status ≤3. Six arms were defined according to tumor or metastases site: 1) brain metastases; 2) head and neck malignancies; 3) lung and/or mediastinal malignancies; 4) pelvic malignancies; 5) bone metastases from prostatic cancer; 6) complicated bone metastases. Within each group the dose was escalated in three or four levels. The dose and fractionation in the different levels and the Planning Target Volume definitions are shown in Table 1. Patients were treated in cohorts of 6 to 12 to define the maximum tolerated dose (MTD). The dose limiting toxicity (DLT) was defined as any acute toxicity ≥ grade 3, according to RTOG scale. Three-dimensional conformal radiation therapy was planned. Treatment was delivered in two days with a twice daily fractionation and at least eight hour interval. Information on pain, symptoms severity and quality of life parameters were recorded and compared before and 3 weeks after the treatment.

Results: Characteristics of the enrolled patients were: total number: 176 (M/F: 111/65); median age: 67 yrs (range: 23-96); performance status (ECOG) 0-1: 107 patients (60.7%); median follow-up: 7 months (range, 1-36 months). Patients' enrolment has been completed for all arms. Grade 1-2 were mainly recorded acute toxicities and the MTD was not reached in any study arm. A significant reduction of pain, as evaluated by VAS, was recorded (pre- treatment *vs* post- treatment mean VAS: 5.7 + 2.1 *vs* 2.3 + 2.4; p= 0.003). An improvement EGOG performance status was recorded in 23% of patients and 39% were stable.

Conclusions: 3D-conformal short course accelerated radiotherapy BID in two consecutive days is well tolerated at evaluated levels. A phase II study have been planned to confirm the promising data on symptoms control.

Table 1.

		Brain	H&N	Lung	Pelvis	Prostate Middle Half Body	Bone
Planning Target Volume		Whole brain plus 0.5 cm margin	GTV plus 1 cm margin	GTV plus 1 cm margin	GTV plus 1 cm margin	Pelvic bones + lumbar spine + femurs	Involved bone
Dose and fractionation	Dose level: 1°	12 Gy; 3.0 Gy/fx	14 Gy; 3.5 Gy/fx	16 Gy; 4.0 Gy/fx	14 Gy; 3.5 Gy/fx	13 Gy; 3.25 Gy/fx	16 Gy; 4.0 Gy/fx
	2°	14 Gy; 3.5 Gy/fx	16 Gy; 4.0 Gy/fx	18 Gy; 4.5 Gy/fx	16 Gy; 4.0 Gy/fx	14 Gy; 3.5 Gy/fx	18 Gy; 4.5 Gy/fx
	3°	16 Gy; 4.0 Gy/fx	18 Gy; 4.5 Gy/fx	20 Gy; 5.0 Gy/fx	18 Gy; 4.5 Gy/fx	15 Gy; 3.75 Gy/fx	20 Gy; 5.0 Gy/fx
	4°	18 Gy; 4.5 Gy/fx	20 Gy; 5.0 Gy/fx	/	/	/	/

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STEREOTACTIC BODY RADIATION THERAPY FOR LUNG METASTASES

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Introduction: Stereotactic body radiotherapy (SBRT) is an emerging non invasive technique for the treatment of oligometastatic cancer. The use of small numbers of large doses achieve high rates of local control. The aim of this study was to evaluate the efficacy and tolerability of SBRT for the treatment of lung metastases in a cohort of patients treated between 2007 and 2012 at our institution.

Materials and Methods: A total of 51 patients with oligometastatic lung tumor (single pulmonary nodules in 30 patients, 58.8%) were included in the study. SBRT was performed with a stereotactic body frame and a 3D-conformal technique. 31 patients received 23 Gy in 1 fraction, 44 a dose of 30 Gy in 1 fraction, 6 a dose of 42 Gy in 3 fractions, 3 a dose of 36 Gy in 3 fractions and 1 a dose of 25 Gy in 5 fractions. Primary tumor was lung cancer in 15.7% of patients, colorectal cancer in 35.3%, breast cancer in 13.7% and a variety of other origins in 35.3%. The primary endpoint was local control, secondary endpoints were survival and toxicity.

Results: After a median follow-up interval of 11 months (3-36), local control rates at 1 and 2 years were 79.8% and 73.2%, overall survival 69.1% and 32.6%, cancer-specific survival 77% and 36.2%, progression-free survival 47.8% and 5.5%. Median survival time 18 months, while median progression-free survival time 12 months. Toxicity profiles were good, with 3 case of grade II toxicity (pulmonary fibrosis).

Conclusions: SBRT is an effective and safe local treatment option for patients with lung metastases, although it remains investigational, longer follow-up to confirm results is required.

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SINGLE FRACTION RADIOSURGERY WITH VOLUMETRIC MODULATED ARC THERAPY (VMAT) FOR LIVER METASTASES: FEASIBILITY AND EARLY CLINICAL EXPERIENCE

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Aims: Radiosurgery is an emerging radiation technique for the treatment of liver metastases and primary liver tumors, with encouraging local control rates and the ability to spare normal liver tissue radiation toxicity. The aim of this study was to demonstrate the feasibility of linac-based radiosurgery for liver metastases in terms of plan quality, dosimetric accuracy and treatment efficiency. In addition, the early clinical results are reported.

Materials and Methods: Nine consecutive patients with liver lesions were treated using Volumetric Modulated Arc Therapy. Patients immobilization was performed by means of the stereotactic body frame (SBF, Elekta, Crawley, UK). Clinical volumes were defined on CT-scans, PET/CT and MRI. The CTV was defined as the gross tumor volume. The PTV was individually defined for each patient based on Internal Margin (IM) and Set-up Margin (SM) assessment. The IM was defined based on respiratory excursions in 3 dimensions. The SM was set at 3 mm. The OARs considered for all patients were the normal liver (liver minus CTV), spinal cord, esophagus, stomach, duodenum, small bowel and kidneys. VMAT plans were generated with ERGO++ TPS, with a single arc clockwise rotation. The dose calculation was performed using the pencil beam algorithm with inhomogeneity correction and a dose grid resolution of 2 mm. All patients were accrued at 26 Gy single fraction dose prescription. The prescription isodose surface (IDS) was selected as the greatest IDS fulfilling the two following criteria: 95% of PTV volume reached 100% of the prescription dose and 99% of PTV reached a minimum of 90% of prescription dose. Constraints for organs at risk were: healthy liver (700 cc < 15 Gy; V7Gy<50% and V12Gy<30%); stomach and duodenum (Dmax<12.4 Gy); spinal cord (Dmax<14 Gy); kidneys (V10.6Gy<2/3) and heart (Dmax<22Gy). Plans quality was evaluated by conformity index (CI), conformation number (CN) and gradient index (GI). VMAT delivery parameters were recorded in terms of MUs and beam-on time. All plans underwent dosimetric verification by means of ion-chambers array.

Results: All patients were treated with a single fraction dose of 26 Gy. Median PTV size was 54.7 cc (range:14.6-102.9 cc). The dose volume constraints for OARs were observed in all patients. Figure 1 shows the mean ± 1 SD dose-volume histogram for healthy liver for all patients. Median CI, CN and GI were 1.23 (range: 1.16-1.50), 0.81 (range: 0.66-0.87) and 3.6 (range: 2.6-4.3), respectively. The median beam-on time and MU number were 8.1 min (range:7.6-8.5 min) and 3010 MUs (range: 2789-3148 MUs), respectively. The average percentage of points passing the gamma test was greater than 95% for every arc (both on coronal and sagittal planes) with acceptance criteria of 3%-3mm, then every VMAT plan was considered clinically acceptable. Treatment was performed without interruptions in all patients. Overall

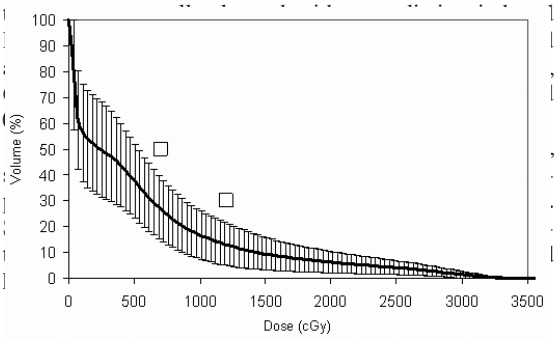

Figure 1.

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STEREOTACTIC RADIOSURGERY FOR PATIENTS WITH RADIORESISTANT BRAIN METASTASES

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Objectives: We evaluate the efficacy of stereotactic radiosurgery (SRS) for the treatment of patients with radioresistant brain metastases on the basis of histological examination.

Methods: We reviewed the medical records of 44 consecutive patients who underwent SRS for 80 brain metastases from radioresistant primaries. Tumor histologies included 17 renal cell carcinoma, 25 melanoma, and 2 sarcoma. Twenty-four patients had a solitary metastasis, and 20 patients had multiple metastases. The median target volume was 3.0 ml (0.1-21 ml) and the median prescribed dose was 18.0 Gy (14.0-22 Gy).

Results: The median overall survival time was 13.8 months after SRS. Longer survival time was associated with performance status, primary renal cell carcinoma, extracranial disease control, and RPA class (P less than 0.005). The median survival time was 20 months for patients in RPA Class I status and 10.7 months for patients in RPA Class II or III status. Multivariate analy-

sis showed RPA class (P less than 0.01) and histological diagnosis of primary tumor (P less than 0.05) to be independent predictors for overall survival. In 60% of the patients, distant brain failure (DBF) developed.

Conclusions: Well-selected patients with brain metastases from radioresistant primary tumors who undergo SRS survive longer than historical controls. RPA Class I status and primary renal cell carcinoma predict longer survival.

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HALF BODY IRRADIATION OF PATIENTS WITH MULTIPLE BONE METASTASES: A PHASE I-II TRIAL

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Aims: The primary aim of this study was to evaluate the effect of half-body irradiation (HBI) on pain in cancer patients with multiple bone metastases. The secondary aim was to evaluate side effects of the treatment.

Materials and Methods: From May 2003 to May 2012, 150 patients (M/F 60/90; median age: 64; range 30-91) presenting widespread symptomatic bone metastases and no previous history of large field radiotherapy were recruited. Pain score and dosage/frequency of analgesic consumption were recorded either baseline as in follow up. Pain intensity was measured by the validated visual analogue self-assessment scale (VAS). Moreover, pain intensity and analgesics consumption (Pain and Drug scores) were also recorded according to Salazar's scales (IJROBP 2001). HBI involved the lower half of the body (pelvic bones, the lumbar-sacral vertebrae and the upper third of femurs). The latest thoracic vertebrae (D10-D12) or the inferior limbs up to the ankles were included only if involved. Prostate cancer metastases received 3-Gy fractions for 5 days up to a total dose of 15 Gy. Skeletal metastases related to other primary tumors received 3-Gy fractions twice a day, 6–8 h apart, on 2 consecutive days, up to 12 Gy.

Results: All patients completed the treatment. After HBI, a significant reduction of pain, as evaluated by VAS, was recorded (pre- treatment *versus* post- treatment mean VAS: 6.5 *versus* 3.2, CI: 1.8-4.7; p=0.000). Moreover, 36 patients (24%) had complete pain relief and 32 patients (21%) showed more than a 30% VAS reduction. Overall response rate for pain was 45% (CI 0.95: 35.9% - 54.6%). In 129 patients Pain and Drug scores before and after treatment were valuable. Statistical analysis showed a significant reduction of Pain and Drug scores especially for patients with the highest scores before treatment (Chi squared test: p=0.000). In particular, 22 patients (17%) achieved Drug Score's reduction and 29 patients (22%) discontinued completely analgesic therapy. Thirty six percent of patients did not experienced treatment related complications at all. Acute toxicity was mild or moderate (transitory) in 61% of patients. As a whole, Grade 3 hematological or gastro-intestinal toxicities were registered in four patients (3%). No life-threatening toxicity (G4) was recorded. Thirty five patients (23%) presented pain flare's phenomenon.

Conclusions: HBI is safe and effective providing long lasting pain reduction in patients with multiple bone metastases.

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EXTRACRANIAL RADIOSURGERY WITH VOLUMETRIC MODULATED ARC THERAPY (VMAT): PRELIMINARY EVALUATION OF A FEASIBILITY TRIAL

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Aims: To report early clinical experience in stereotactic body radiosurgery (SBRS) delivered using volumetric intensity modulated arc therapy in patients with primary or metastatic tumours in various extra-cranial body sites.

Materials and Methods: Each enrolled subject was included in a different phase I study arm, depending on tumour site and disease stage (lung, liver, bone, advanced), and sequentially assigned to a particular dose level. Dosimetric results, acute toxicity, tumour response and early local control were investigated and reported.

Results: 54 lesions in 39 consecutive patients (M/F: 20/19 median age: 66; range 40-89) were treated. Of these, 9 were primary or metastatic lung tumours, 2 were primary pancreatic tumours, 10 were metastatic liver tumours, 19 were bone metastases and 14 were nodal metastasis. Dose prescription ranged from 12 to 26 Gy to the Planning Target Volume. Median follow-up was 9 months (2-20). No incidence of grade 2-4 acute and late toxicity (CTCAE 4.03) was recorded. Overall response rate based on CT/MRI was 79.6 % (CI 0.95: 63.7%-89.9%) with a complete response rate of 37% (CI 0.95: 22.2%-52.7%). Actuarial local control (defined as irradiated site progression freedom) was 87% at 12 months.

Conclusions: SBRS delivered by means of VMAT allowed to achieve required target coverage as well as to keep within normal tissue dose/volume constraints.

VMAT-SBRS resulted to be feasible with encouraging tumour response, local control rate and acute toxicity profile. The maximum tolerable dose has not yet been reached in any study arm.

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MULTICENTER EXPERIENCE IN PALLIATIVE RADIOTHERAPY OF BONE METASTASIS

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Summary: Radiation therapy is considered a standard treatment when pain, risk of pathologic fracture and spinal cord compression is present. Radiation therapy is one of the most effective therapeutic modality in the palliation of bone metastases. The ASTRO 2011 Guidelines on palliative radiotherapy of bone metastases claimed that various fractionation schemes can provide an equivalent response to pain control, although longer treatment has the advantage of a lower incidence of retreatment on the same site. The aim of our study was to evaluate, in a multicenter experience of radiotherapy of bone metastases, the differences in requirements and their impact on patients in relation to primary tumor type and quality of life.

Materials and Methods: In the year 2011 were made in 5 UUOO Radiotherapy of Naples, 457 radiation treatments for bone metastases. We distinguished the treatments based on the primary tumor and the fractionation scheme. Those with single fraction were 173 and we did a monitoring of the pain, pre and post-RT, dividing the score (scale NRS) in three groups (<5, 5-7, 8-10). We evaluated the P.S. with Karnofsky Performance Status (KPS) in 3 groups [Poor (10-40), Moderate (50-70), Good (80-100)] and the analgesic therapy. This has resulted in an estimate of mortality and response to treatment in order to verify that in tumors with a longer natural history was confirmed equivalence between single fraction and other fractionation schemes. Same evaluation was made for all types of fractionation in metastases from cancer of the breast (190 treatments).

Results: The most represented treatments were from primary breast cancer with 41.6% (190 treatments), lung 22.7% (104 treatments) and prostate cancer by 7% (32 treatments). The schemes used were the single fraction 8Gy (38.7%), followed by 30Gy in 10 fractions (37.2%). In treatments with single fraction, we recorded in metastases from breast and prostate cancer mortality, respectively 20% and 10%, *vs* 38% in patients with primary lung cancer. In all cases there was an improvement in pain symptoms in post-RT detected with increase of patients who reported pain <5 (NRS): 64% *vs*. 7.5% in breast cancer, 63.2% *vs* 0% in lung cancer, 60% *vs* 10% in prostate cancer. The KPS 80-100 post-RT was 59% *vs* 22% pre-RT in breast cancer, the 52.7% *vs* 50% in lung cancer and 50% *vs* 50% in prostate cancer. In the different schemes used in metastatic breast cancer, the KPS 80-100 post-RT has reached a rate of 59% in a single fraction, a percentage of 70.6% in the 20 Gy, a percentage of 70.6% in the 30 Gy, and 100 % in the 40 Gy.

Discussion: Our study confirms that radiotherapy is the most effective treatments in the palliation of bone metastases. In accordance with the guidelines, there was the equivalence in pain control of the different treatment schemes, but showed the role of radiotherapy in improving the P.S. of patients with primary breast cancer, in particular those treated with treatment schedules longer, by 30 and 20 Gy where the percentage of patients with KPS 80-100 was 70.6%, against 59% in the single fraction.

Conclusions: All types of fractionation schemes provide palliation of pain, it is also true that in patients with a longer life expectancy and a pre-RT-KPS of 10-40 a more conventional fractionation guarantees an increased performance status and a better quality of life.

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THREE YEARS' EXPERIENCE IN LUNG TUMOURS STEREOTACTIC BODY RADIOTHERAPY/ RADIOSURGERY (SBRT/SBRS)

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Scope: Radiosurgery is largely approved in the clinical course of oncologic patients, when affected by primitive lung tumours or few (1-3) lung metastases from other sites. A joint program to set the standards and efficacy of Stereotactic Body Radio-Therapy & Radiosurgery (SBRT-SBRS) treatments started in 2008, in Foggia and Salerno University Hospitals.

Materials and Methods: These Radiotherapy centers are very similar in their structure, and irradiate 1400 patients/year, with 4 Elekta Linacs. Patients had Karnofsky Status > 80, primitive/metastatic lung tumors, diameter < 5 cm and were unsuitable for surgery. On the beginning, patients were treated with 3-6 fractions (Stereotactic Body Radiotherapy - SBRT), while in 2008 it was decided to use also a single fraction (Radiosurgery - SBRS) like other centers in Germany and Japan, for lesions that were 2 cm afar from mediastinum. We used a BRAINLAB Micromultileaf; Radiological Physics Center (RPC) at the MD Anderson Cancer Center, Houston,Texas, made the external monitoring of photon beams dosimetry.

Results: We have treated 35 patients with a minimum follow-up of 6 months (range: 6-36 months; mean: 15 months). The CTVs varied from 1.37 to 27.48 ccm. The CTV - PTV margin expansion was 5-8 mm in antero-posterior and latero-lateral direction and 10-13 mm in cranio-caudal direction. Patients were irradiated with 9-19 coplanar or 8-12 non-coplanar fields. Radiation dose was always prescribed to the peripheral isodose of 80%.

Five metastatic lesions received 36-37.5 Gy in 3 fractions, 4 primitive tumours received 50Gy in 5 fractions, 3 lesions in the immediate proximity of mediastinal vessels (<3 cm) received 42 Gy in 6 fractions. Otherwise, 19 patients were treated with a single fraction (26 Gy in 11 cases - 27 Gy in 6 cases and 18 Gy in the remaining 3 cases. Moreover SBRT or SBRS was used as boost technique to treat 4 patients, 3 T3N1 cancer and 1 sarcoma metastasis, diameter 5 cm. 32/35 lesions were controlled, until now (91% local control). There were no acute complications, while only 1 patient had a late complication (mild pleural effusion, after 1 year). CT examination revealed radiological signs of radiotherapy pneumonitis after 6-8 months. Two patients went to surgery and the histological examination revealed no tumour in the >100 Gy (BED 10) treated volume. 1 patient died after 33 months for other reasons, with lung tumour controlled.

Conclusions: In our experience SBRT/SBRS is a safe technique to treat lung tumours.

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WHOLE BRAIN RADIATION THERAPY COMBINATED WITH RADIOIMMUNOTHERAPY WITH 131I-L19SIP IN PATIENTS WITH MULTIPLE BRAIN METASTASES FROM SOLID TUMORS: PRELIMINARY RESULTS IN OUR CENTRE

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Objectives: The Whole Brain Radiotherapy (WBRT) is the standard treatment for multiple metastases. The L19SIP is a human antibody's part binding to domain B of fibronectin, a marker of neoangiogenesis. A multicenter Phase II study about Radioimmunotherapy (RIT) with131I-labeled L19SIP in combination with WBRT in patients (pts) with brain metastases from solid tumours is in progress. The aim of this study is to value the therapeutic effect of131I-L19SIP combined with WBRT. The primary objective is to investigate the brain lesions uptake of131I-L19SIP or124I-L19SIP and the safety of combined treatment. The secondary objective is to determine the intracranial, extracranial and total response rate, the overall survival and the clinical performance index.

Materials and Methods: From October 2009 to May 2012,we enrolled14pts(9M,5F,40-76yrs),with multiple brain metastases(of which at least1measurable according to RECIST1.1), unfit for surgical excision or stereotactic radiosurgery, with ECOG PS <3, naive to monoclonal antibodies therapy. The baseline diagnostic evaluation was performed with PET/CT FDG and contrast-enhanced MRI and/or CT brain. All pts received WBRT (30Gy:300 cGy/die in10fz) and underwent a"diagnostic phase"with administration of124I-L19SIPiv (in1pt131I-L19SIP). The intracerebral uptake of I-L19SIP was investigated withPET/CT in sequential time (4,24,48 and 72 hours pi). Pts eligible for RIT must have a gradient between at least 1 lesion and healthy brain tissue(T/B)>4. These pts received a single therapeutic dose of131I-L19SIP with 4.1GBq/m2. Then TC or RM and SPECT images were acquired at least two times between day 1and10. Clinical examinations and blood tests are performed every week for6weeks(observation period)and then every8-12weeks for12 months. The response is valuated using the RECIST criteria with CT and MR scans compared to baseline imaging and eventually with addition of PET/CT.

Results: 12/14pts enrolled were eligible for RIT:9were treated with131I-L19SIP (dose:6740 347 MBq), 3 were excluded for disease progression during WBRT and 2 were not candidates (T/B<4). The dose of RIT boost delivered to brain lesions,as calculated by dosimetry with 124I-L19SIP, ranged from3.4 to 29.5Gy.The treatment was well tolerated (neutropenia G4 in only 1pt). The evaluation response (available in8/9pts) at4-6weeks after treatment was:partial response in 3pts, stable disease in3 pts and progression in 2pts.

Conclusions: Our preliminary results suggest that the RIT with L19SIP is well tolerated. Enrolment of more pts is necessary to value RIT efficacy.

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RESULTS OF SBRT FOR 216 CONSECUTIVE OLIGOMETASTATIC PATIENTS TREATED WITH CURATIVE INTENT

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Purpose: It has been hypothesized that the oligometastatic state can represent a phase of neoplastic disease in which ablative therapies may lead to good local control and offer a cure in some patients (pts). We analyzed the SBRT results in terms of local control (LC), OS and toxicity for oligometastatic patients.

Materials and Methods: In this study, 216 patients (70 female, 146 male) were enrolled and 383 lesions were treated. The number of metastatic sites (in no more than two organs) was 1 and 2 in respectively 127 and 66 patients, between 3 and 5 in 23 patients. All lesions were contemporary treated with curative intent by SBRT. Primary tumor was lung cancer in 77 cases, CRC in 52, breast in 16, others in 71. Primary tumor was controlled in all patients. SBRT was delivered by 6MV LINAC with multiple arcs in one up to 3 fractions. Before each fraction, isocenter position was verified by CBCT. Dose was prescribed to coverage or to 70% isodose. BED10 was generally equal to or greater than 100Gy for liver, lung and adrenal metastases, and however, never down 60Gy for other sites. PTV volume ranged between 1.3cc and 130cc (median 27.6cc). For 152 patients, Active Breathing Coordinator was used for taking in account respiratory organ motion and for 57 patients internal gold markers were inserted as target surrogate. Results were evaluated by multiphasic CT scan every three months during the first year and then every six months. Moreover

for some patients and always in suspect recurrences, Pet FdgF18 was performed. Toxicity was evaluated by CTCAE score v4.

Results: With median follow up of 18 months (range 2-84 months), 163 patients (75%) are still alive (median not reached) and out of these, 30 pts are NED. OS and DSS (Kaplan-Meier) are respectively 37% and 42% at 5 years (yr). LC is 72% at 5yr. 12 recurrences in field out of a total of 33, were retreated by SBRT. Gastrointestinal G2 toxicity was observed in 12 pts, while in two cases gastrointestinal ulceration medically recovered was occurred.

Conclusions: In our experience, with careful selection of patients in true oligometastatic state, SBRT appears as useful and safe treatment modality, that can lead not only to high rate of LC (72% at 5yr), but also to high rate of disease specific survival (42% at 5yr) with mild and transitory toxicity.

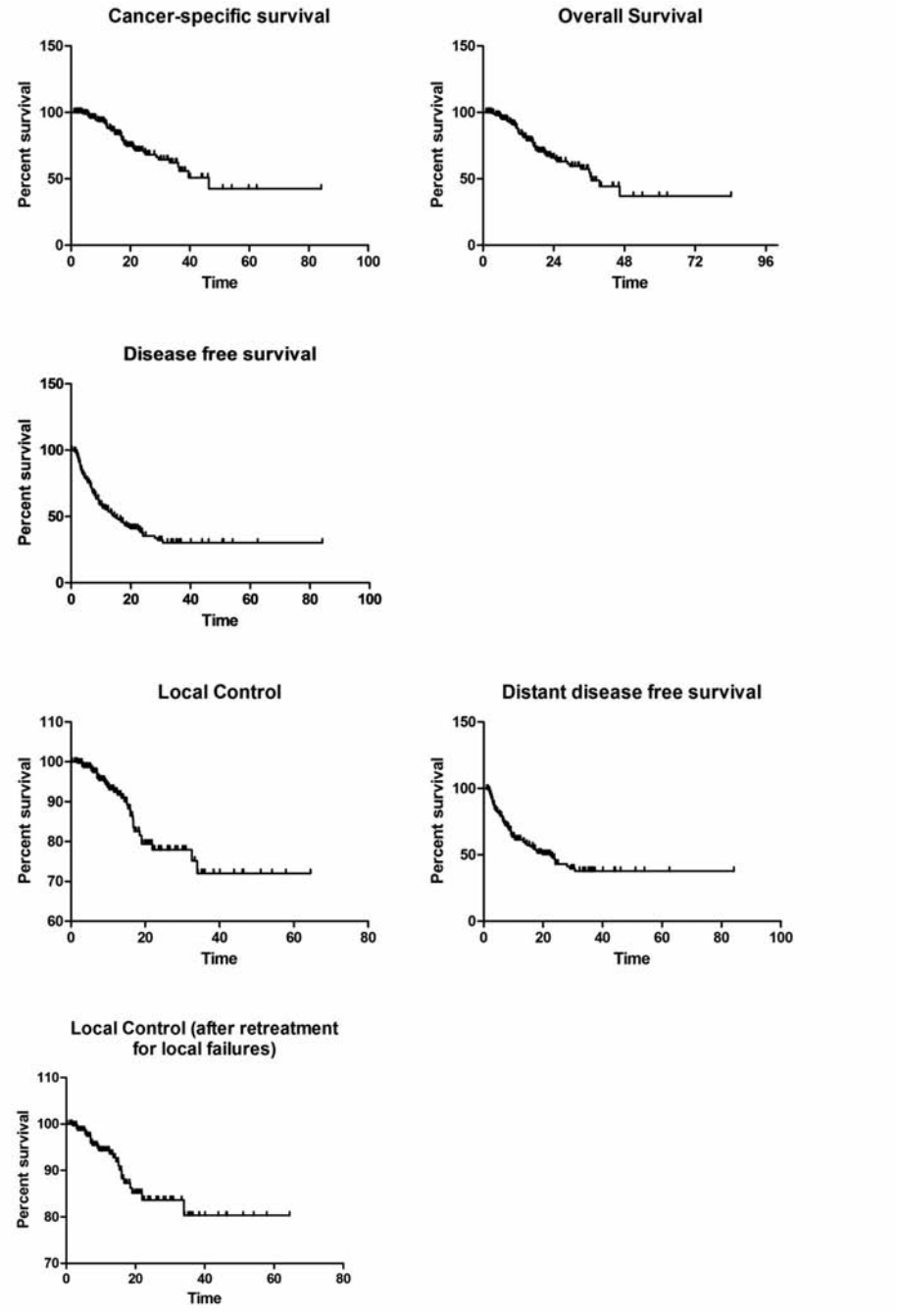

Figure.

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PALLIATIVE RADIOTHERAPY: THE EFFECTS ON PAIN AND ACTIVITY OF DAILY LIVING IN METASTATIC CANCER PATIENTS

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Aims: To evaluate Quality of life (QoL) terms of pain relief and activity of the daily living in metastatic cancer patients treated with palliative radiotherapy (RT).

Methods: Patients with metastases treated by palliative RT (total dose of 20-30 Gy, 4-3 Gy/die respectively) were enrolled. To assess the QoL, the Barthel Index (BI) and the numeric scale of pain was administered before and after RT. BI test was used to assess the "functional activity" of each patient in the daily living: movement, eating, self-care, bathing, clothing etc. The numeric pain scale was graded form 0 (no pain) to 10 (hardest pain).

Results: Seventy pts were evaluated (43 patients were male and 27 female) with a median age of 71 years old (range 21-80). Sixty-two percent of patients were treated for bones metastases, while 33% of patients for brain metastases. When we analyzed the BI before and after RT, we observed an improvement in the autonomy for 16 patients (23%) and stability in 52 patients (74%). Pain relief was obtained in 50 patients (71.4%) and 18 patients (26%) experienced a stable pain scale. The only two patients, who experienced progression disease during RT, registered a worsening of pain and BI.

Conclusions: Palliative radiotherapy is useful in the pain control but also to improve the autonomy of patients in the daily activities without damage in QoL.

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SINGLE DOSE LOWER HALF-BODY IRRADIATION (HBI) WITH TOMOTHERAPY FOR MULTIPLE PAINFUL PELVIC BONE METASTASES IN BREAST CANCER PATIENTS: FEASIBILITY, TOXICITY, AND COST-EFFECTIVENESS

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Purpose: To assess the feasibility of single dose lower HBI with Tomotherapy in patients affected by metastatic breast cancer in terms of acute toxicity and delay in chemotherapy (CT) administration. Cost/effectiveness analysis of this therapeutic approach.

Materials and Methods: From June 2011 to April 2012, 11 breast cancer patients affected by multiple painful bone metastases to the pelvis were enrolled in this prospective trial. The tumor subtypes were the following: 4 luminal A, 5 luminal B, 1 HER2 +, and 1 triple negative. Six patients were receiving CT, and 5 only hormonal therapy. The PTV included the whole pelvic bones, including L4-L5 and the bilateral femoral shafts. Radiation consisted in 8 Gy in one fraction, delivered with Tomotherapy to the 90% of the PTV. Patients were administered steroids preventively. Pain was assessed by the visual analogic scale (VAS). Toxicity was scored using the CTCAE v3.0. Quality of life was scored by the EORTC QLQ-C30 questionnaire, that was administered to all patients before and 21 days after the radiation course. For cost/effectiveness analysis a comparison with a 5 daily fractions of 3 Gy given in 2 anterior-posterior opposing fields (AP/PA) was done. This schedule was considered the best schedule for delivering HBI according to the International Atomic Energy Agency randomized trial reported by Salazar et al.

Results: Median follow-up was of 6 months (range, 2–10 months). All but two patients had a pelvic pain relief. Five patients interrupted the analgesic drugs consumption. Toxicity was acceptable: 2 Grade 3 haematological toxicities were registered (transitory anaemia and leukopenia). Grade 2 toxicities were the following: haematological = 5, fatigue = 3, fever = 1, nausea = 1, diarrhoea = 1. No patient was hospitalized. Two of the 6 patients had a 14 and 30 days delay in CT administration, due to G2 diarrhoea and G3 leukopenia, respectively. Eight patients answered to the QLQ-C30 questionnaires, and an improved quality of life was documented in 6 cases. Single fraction Tomotherapy resulted in an increased cost of about €400 if compared with the 5 fractions AP/PA treatment procedure.

Conclusions: Lower HBI delivered with single dose Tomotherapy resulted in a well-tolerated regimen, without significant delay in CT schedule. Pain relief and toxicity experienced were consistent with the literature data for fractionated HBI. The higher cost provided advantages regarding logistics and patient comfort.

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STEREOTACTIC BODY RADIOTHERAPY FOR LIVER METASTASES: PHASE I-II STUDY

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Purpose: We report the results of a phase I-II trial exploring feasibility and the efficacy of stereotactic body radiotherapy (SBRT) for treatment of liver metastases.

Patients and Methods: Patients with liver metastases that were inoperable or medically unsuitable for resection, and who were not candidates for standard therapies, were eligible for this study for SBRT. The ExacTract positioning platform (BrainLAB) was used for immobilization during the initial simulation and subsequent treatments. This system consists of a vacuum cushion for initial positioning, and external body fiducial markers monitored by infrared cameras. The gross tumor volume (GTV) included contrast-enhancing disease visible on contrast enhanced CT scan or MRI fused with the planning CT for more accurate delineation of the gross target volume. The clinical target volume was 1 cm around the GTV. A nonuniform expansion for the planning target volume was based on individual patients tumor motion (minimum 5 mm). At the beginning prescription dose was 30 Gy in three fractions. Subsequently, given the lack of

serious side effects, has been prescribed a dose of 36 Gy (12 Gy/fr). Dose was prescribed to the 80% isodose line. Clinical response was evaluate 3 weeks after the end radiotherapy by CT scan and thereafter with PET/TC 18 FDG.

Results: Fourteen patients with inoperable colo-rectal (n= 5), or other (n=11) liver metastases were treated. Four of these had extrahepatic disease. Median tumor diameter was 2.5 cm. With median follow-up of 17 months, in 15 evaluable lesions, 8 had a sustained objective response according to RECIST (2 partial response, 13.3%; 6 complete response, 40%). three patients had progressive disease at first reevaluation. The median time to maximal response was 4 months (1-13 months). Local control at 1 year was 72%; local control was improved, in smaller tumors (< 2,5 cm; p<0,06) and higher delivered dose (> 30 Gy; p= 0,02). Thirteen patients developed recurrences. The first site of recurrence was the treated tumor in 4 patients; two of these had both hepatic and extrahepatic progression; 3 had massive hepatic recurrences. Six patients had isolated extra-hepatic recurrences. Two grade 3 liver enzyme changes occurred, but no RILD or other grade 3 to 5 liver toxicity was seen.

Conclusions: Hypofractionated SBRT provides good local control with minimal side effects in selected patients with limited hepatic metastases.

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EFFICACIA E TOLLERANZA DELLA RADIOTERAPIA STEREOTASSICA GUIDATA DALLE IMMAGINI NEI PAZIENTI CON METASTASI OSSEE

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Purpose: Several reports have shown that high dose, stereotactic body radiotherapy(SBRT)for bone metastases is effective in improving tumor control compared with lower doses. Technological advances allow to increase radiation-induced cell-killing and accuracy in radiation delivery. These new strategies have been successfully exploited for palliative purposes such as pain relief and functional recovery. We report our preliminary experience on SBRT in patients with bone metastases in terms of efficacy and tolerability.

Materials and Methods: Between April 2011 and April 2012, 82 consecutive patients with a total of 92 lesions were treated with SBRT. Treatment was delivered with an Elekta Synergy linear accelerator or with Cyberknife robotic radiotherapy.The dose was prescribed to the 70-90% isodose line to encompass the PTV; the prescribed doses ranged from 24 to 36 Gy in 1 to 3 fractions. Patients had to have a performance status of 0-2 and an expected survival of at least 6 months. Acute and late toxicity were evaluated according to RTOG and EORTC–RTOG scale respectively. Pain assessment was performed according to visual analogue scale(VAS)and pain/drug score. Patients had to be examined at 4-8 weeks after treatment and at 3 months'interval thereafter. Local response was scored as complete or partial response, stable disease or failure on the basis of imaging/metabolic evaluation no prior than 2 months after treatment (RECIST criteria). Median follow-up was 5 months.

Results: Of the 92 lesions treated, 67 (72.8%) were spinal. Of the non spinal lesions (25=27.2%), the most frequent site of disease was the sacrum in 12 cases (13%). The most represented primary tumor was breast in 35 patients (42.7%), prostate in 21 patients (25.6%) and renal cancer in 14 cases(17.1%). The 6-months actuarial local control rate for all treated lesions was 56%.When SBRT was prescribed for palliative purposes,improved results after treatment were shown in the majority of patients (67=71,6%) in terms of pain relief and functional recovery. A moderate decrease of VAS was reported at 3 months in evaluable patients compared to baseline, pre-SBRT values (mean decrease value: 2.8); not significant for pain and drug scores. Treatment was generally well tolerated: the most common acute >G2 adverse acute event was gastro-intestinal toxicity in 17 patients(20.7%). No severe toxicity was seen.

Conclusions: Our results support the use of high dose stereotactic radiotherapy as an effective and safe strategy for bone metastases in selected patients. Sustained local control and pain relief are achievable. Further studies are required in order to better define the role of SBRT in the treatment algorithm for specific neoplasms.

P213

PRELIMINARY RESULTS OF WHOLE-BRAIN HIPPOCAMPAL-SPARING RADIOTHERAPY

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Purpose: The Whole Brain Irradiation (WBI) involves neurocognitive damage, particularly in patients in advanced age and/or undergoing chemotherapy. Treatment techniques that spare the hippocampus while maintaining an effective treatment of the residual brain parenchyma seems necessary. In this study, we compared the results in terms of dose distribution and hippocampal sparing using IMRT step&shoot, IMAT by dynamic arc therapy *vs* 3D CRT.

Materials and Methods: Intensity-modulated radiotherapy (IMRT) treatment plans and dynamic arc therapy were generated for a prescription dose of 30 Gy in 10 fractions and imposing as constraint for hippocampus a maximum dose of 12.5 Gy and V9Gy <40% and a maximum dose of the eye 7Gy. Dosimetric evaluation relating to plans of radiotherapy IMRT step&shoot and arc dynamic therapy were compared. Imaging acquisition: Patients underwent a contrast and noncontrast CT scan of the entire head region with 3mm slice thickness using a mask for immobilization.

Planning: The treatment plans were optimized with TPS Xio (CMS Software, Elekta Group), the standard technique consists of two opposing lateral fields shaped throughout the brain. The solution provides instead IMRT

9 fields. The arc treatment consists of three arcs all shielded on the hippocampus and two latero-lateral fixed fields.

Treatment delivery: The used energy was 6 MV with LINAC (Clinac DHX Varian Medical Systems) with multileaf millennium integrated system with 120 leafs with a thickness of 5 mm at the isocenter. Patient positioning was verified by EPID portal images. The following treatment planning parameters were used to evaluate the treatment plans: Target Coverage (TC), V95% and V107% for the PTV and Mean dose and maximum dose (D1%) for OARS; Homogeneity Index (HI); Compliance Index (CI 95%). Finally the number of MU per fraction and the times of beam on, relative to the individual techniques, were analyzed.

Results: The 3D-CRT implies a better coverage (V95% = 99.3%) and a greater homogeneity of dose to the target (HI = 0.08) in comparison to the IMRT techniques (V95% = 67.5%, HI = 0,52) and dynamic arc therapy (V95% = 71%, HI = 0.51). Instead the latter saves more the hippocampus. The UM medium is 320 ± 0.5 in 3D-CRT, 1651 ± 0.8 in IMRT and 661 ± 0.5 in arc-dynamic therapy. The total average time of delivery of the plane (excluding the time of set-up and imaging pre-treatment, that is common to all three techniques) was 2min for 3D-CRT, 25min for IMRT and 12min for arc-therapy.

Conclusions: The techniques used, both IMRT and arc dynamic therapy, have been successfully able to spare the hippocampus and maintaining an effective treatment. IMRT deliveries time is longer than the arc therapy. The two techniques are, however, a viable alternative to machines "dedicated", such as tomotherapy.

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HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY FOR TREATMENT OF BRAIN METASTASES: OUR EXPERICENCE

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Introduction and Aims: Brain metastases are the most common form of brain cancer and the primary tumors most likely to metastasize to the brain are located in the lung, breast, skin (melanoma), colon-rectum, and kidney. It is known that the prognosis for patients with brain metastases from any histology is poor overall, with a median survival of 4-7 months following treatment with whole-brain radiotherapy (WBRT). Several studies have showed improvement in local control with the addition of hypofractionated stereotactic radiotherapy (HSRT) to WBRT when compared to WBRT alone. Our retrospective analysis evaluated the efficacy of various dose fractionations using HSRT in the treatment of brain metastases.

Patients and Methods: We analyzed 38 patients with 47 brain metastases treated with HSRT at the Radiotherapy Department of Foggia from January 2008 to June 2011. Of the 47 lesions, 36 lesions were treated with WBRT plus HSRT and 11 lesions were treated with HSRT alone as definitive treatment. The primary cancer was lung for 52.6% of patients and breast for 34.2% of patients. Other patients had skin (one patient), kidney (one patient), stomach (one patient) and ovary (one patient) primary tumour. The median lesion size was 1.15 cm. The median prescribed dose was 28.35 Gy (range, 18.8 Gy-36.6 Gy) with a median of 5 fractions (range, 3 fractions-6 fractions) with a minimum of 80% isodose line to the Planning Target Volume. During follow-up patients were seen at least 4 weeks after HSRT and were evaluated with MRI and a physical examination. Each lesion was measured and graded using the criteria of MacDonald with the following categories: complete remission indicated the disappearance of all enhancing lesions on MRI, partial remission indicated evidence of a >50% reduction in the dimension of the tumor on MRI, progressive disease indicated a >25% increase in size, and stable disease indicated all other responses. Moreover, overall survival was obtained and calculated as time between the end of radiotherapy treatment and time of death or last control.

Results: After HSRT treatment of 47 brain lesions, 5 lesions demonstrated complete responses, 16 lesions demonstrated partial responses, 18 lesions demonstrated stable disease, and 6 lesions demonstrated progressive disease while 2 patients died before MRI execution. There was no difference in results depending on different dose fractionations. The median overall survival time was 12 months.

Conclusions: Although much progress has been made in the last years with new technologies and new radiotherapy equipment, prognosis of metastatic patients continues to be poor. Management of brain metastases continues to evolve over time and proposed management goals will not only aim to increase overall survival and brain disease-free survival, but also to improve quality of life of this group of patients.

P215
LUNG METASTASES TREATED WITH HYPOFRACTIONATED STEREOTACTIC BODY RADIOTHERAPY: OUR EXPERIENCE

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Introduction and Aims: Metastatic disease to the lung is common and excluding primary lung cancers, which do metastasize to either lung, the most common tumours involving the lungs are breast cancer, gastrointestinal tumours, kidney cancer, melanoma, sarcomas, lymphomas and leukaemia. In most cases, management of metastatic cancer to the lung relies on systemic treatment for the primary malignancy and on rare occasion it can be cured by resection of lung metastases or with Hypofractionated Stereotactic Body Radiotherapy (HSBRT). Our study aims to analyze the use and the effect on local control, survival, and toxicity of HSBRT for pulmonary metastases.

Patients and Methods: We analyzed twenty-four

patients with solitary lung metastases treated with HSBRT at the Radiotherapy Department of Foggia from January 2008 to December 2011. The primary cancer was breast for 50% of patients, colorectal cancer for 25% of patients, gynaecological cancer for 16.7% of patients, kidney for one patient and larynx for one patient. All patients underwent a Computed Tomography (CT) and a Positron Emission Tomography (PET) before any treatment and they all received both radiotherapy and chemotherapy. The median lesion size was 3 cm and the median Standard Uptake Value (SUV) of lesions was 12. The median prescribed dose was 39.5 Gy with a median of 5 fractions (range, 3 fractions-6 fractions) with a minimum of 80% isodose line to the Planning Target Volume. During follow-up patients were seen at least 4 weeks after HSBRT and were evaluated with CT and PET. Each lesion size and each lesion SUV was measured after HSBRT. Acute and late toxicity was evaluated. Overall survival was obtained and calculated as time between the end of radiotherapy treatment and time of death or last control.

Results: After HSBRT 54.2% of lesions demonstrated complete responses since they were not visible at CT and PET, 20.8% of lesions demonstrated a reduction in size and/or in SUV, 16.6% of lesions demonstrated stable disease, and 8.3% of lesions demonstrated progressive disease. No acute and no late toxicity was observed. The median overall survival time was 32 months.

Conclusions: This analysis suggests that Hypofractionated Stereotactic Body Radiotherapy is a feasible, well-tolerated and safe technique and it could be considered as a valid option for treatment of solitary lung metastases.

P216
HYBRIDARC APPLICATION IN THE TREATMENT OF LUNG METASTASIS

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Purpose: The aim of this work is to evaluate the possibility of the application of HybridArc (HA) technique (BrainLAB) for stereotactic body radiotherapy (SBRT). For dosimetric verification it was used a two-dimensional ion chamber array (MatriXX, IBA). The HA technique is a combination of enhanced Dynamic Conformal Arcs (eDCAs) and Intensity-Modulated RadioTherapy (IMRT) treatments: a number of IMRT beams are added to each eDCA in order to further optimize the target dose conformity while minimizing exposure to normal tissue and dose to organs at risk (OARs).

Materials and Methods: HA plans were made using iPlan RT Dose 4.5. In order to evaluate the dosimetric merits of the application of this technique to SBRT treatments, patients with the PTV in the vicinity of the OARs, who might have had a clinical advantage of using this treatment modality, were chosen. For these patients, two different treatment plans were processed: one with Dynamic Conformal Arcs (DCAs) and the second with HA. To demonstrate the quality of HA delivery for the stereotactic treatments considered here, DVH analysis for DCA technique was presented together with HA. Comparison of the dose distributions measured through MatriXX with those calculated in iPlan RT Dose for all HA plans was performed using a gamma analysis.

Results: From 26.10.2011 to 23.05.2012 a total of 11 patients with lung metastasis were analyzed. The comparison of DVHs shows that HA stereotactic treatments are excellent compared to those made with DCAs, probably due to the presence of IMRT beams that better conform the dose to PTV, ensuring consistently greater sparing of OARs. In particular, we found that it produced better target dose homogeneity and substantial saving of surrounding organs. In fact, in all cases we investigated, dose to spinal cord was considerably lower with HA compared to DCAs treatments. Comparison of MatriXX measurements to dose calculation with Pencil Beam (PB) algorithm gives good agreement both for HA plans and for DCA treatments. However gamma criterion fails in the low-dose regions, especially at larger distances from the target.

Conclusions: In this work, HA is investigated to be able to safely apply in clinical practice. HA technique is demonstrated to be technically feasible; it offers a new and efficient means for SBRT treatments. Further studies such as optimization of the treatment technique and Monte Carlo dosimetric implementation are currently under way at our center.

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RANDOMIZED DOUBLE ARM TRIAL FOR PAIN PALLIATION IN PATIENTS WITH BONE METASTASES: EBRT *VERSUS* MRGFUS. ANALYSIS OF TREATMENT RESPONSE BY USING VISUAL ANALOG PAIN SCORE AND FUNCTIONAL MAGNETIC RESONANCE

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Aims: To investigate and compare the response to EBRT and MRgFUS treatments of painful bone metastases using Visual Analog Pain Score (VAS) and diffusion-weighted (DW) magnetic resonance (MR) imaging with apparent diffusion coefficient (ADC).

Materials and Methods: We enrolled 36 consecutive patients (female:15 male:21; mean age:60,3) with painful bone metastases in a prospective, double arm, randomized study. 18 patients underwent EBRT and 18 patients underwent MRgFUS treatment, using ExAblate 2100 system (InSightec). Pain palliation was evaluated by visual analog pain score (VAS). All patients underwent ce-MRI (3T) before treatment and at 1, 2, and 3 months afterward. MRI protocol included DWI sequences with five b factors (0–800 sec/mm2) and ADC maps. The average ADC values for each lesion were analyzed in pre- and post-treatment.

Results: No treatment-related adverse events were

noted in both arms. Statistically significant differences among baseline, follow-up VAS values and drugs intake for both EBRT and MRgFUS patients were detected. DWI showed substantial increase in ADC values after treatment for both EBRT (pre:1313,3±424,3 mm /sec; post:1777,9±386,3) and MRgFUS (pre:1080,6±269 mm /sec; post: 1577,5±311,6); there were no statistically significant differences in ADC values between EBRT and MRgFUS. Progressive decrease in VAS values was positively correlated to an increase in ADC values for both treatment modalities.

Conclusions: EBRT is actually the gold standard for pain treatment and to improve quality of life in patient with bone metastases, but MRgFUS is a new, promising noninvasive approach.

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RAPID PALLIATIVE-SYMPTOMATIC IRRADIATION USING HELICAL TOMOTHERAPY: ANALYSIS OF WORKFLOW AND CLINICAL FEASIBILITY

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Aims: To establish the workflow, define the procedures and evaluate the clinical benefit of rapid palliative irradiation with helical tomotherapy (StatRT) in a retrospective series of symptomatic metastatic patients (pts)

Materials and Methods: Between March 2009 and April 2012 fifteen pts with symptomatic metastasis were accrued. Average pts age was 68 years (range: 48-95 yrs). Twelve pts received StatRT for bone metastasis,1 pt for rectal bleeding,1 for lung lesion and 1 for adrenal gland lesion. Twelve pts were treated at 1 single site while in 2 pts RT was delivered to 2 sites in a single treatment session. Four cases were re-treatments to previously irradiated sites. After patient positioning on the treatment couch, irradiation was delivered using a Megavoltage CT (MVCT) with superior/inferior borders encompassing the intended treatment volume to define on-line contouring of CTV and PTV. IMRT plans were created and optimized to the PTV*s*. Time for each treatment phase (set-up, MVCT, contouring, plan calculation and irradiation delivery) has been registered and each patient compliance evaluated by an arbitrary index score (1=good, 2=fair, 3=poor). A dosimetry comparison between conventional 3D-CRT and TOMO plans was also performed by evaluating Conformity Index (CI) and OARs and PTV dose distribution.

Results: Mean overall treatment time for the 15 treated pts was 103.5 min. (range: 48-180 min), with longer time in pts with lower compliance score (3 pts) and multiple lesions (2 pts). The comparison of rival plans has shown an improvement of PTV CI (0.034 +/- 0.021 *vs*. 0.026 +/- 0.014), a decrease of dose to OARs (Average Dmax spinal cord: 11 Gy Gy *vs*. 9.3 Gy) and a better PTV coverage (V95Dp: 91% *vs* 99%) in favour of TOMO. During the analysis period we observed a reduction in total treatment time which was directly proportional to the progressive improvement of technical performance by the staff and to satisfactory patient compliance, which can probably lead to an average machine occupation time lower than 1 hour per patient

Conclusions: The results of our analysis indicate that StatRT may be considered in compliant patients who need urgent palliation of symptomatic metastasis, especially in those requiring re-treatments, with CI and OARs dose gain. Further studies in larger patient series seem warranted in order to more accurately define organizational procedures and the costs/benefits ratio of this treatment modality, particularly in pts with poor compliance

P219
SBRT FOR LIVER METASTASES: RESULTS ON 173 TREATED LESIONS

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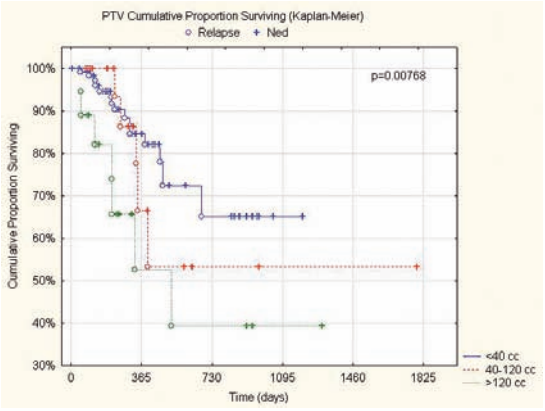
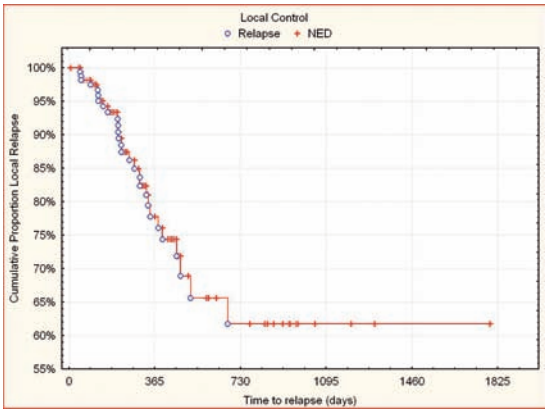
The liver is a common site of metastatic spread for solid tumor and often represents the only site of metastases. Some patients , however are not fit to surgery or other ablative strategies (*e.g*. RFA and PEI). The purpose of this study is to assess efficacy of SBRT to achieve local control and its relationship with primary tumor,delivered dose and treatment delivery modalities. 100 Patients (pts) (173 lesions) were treated by SBRT for liver metastases (primary was colon in 59, breast in 18 , lung in 7 and others in 16). Inclusion criteria were: no more than 5 metastases and no more than 6cm in diameter. GTV was countered using CT data sets acquired at different respiratory phases to obtain an ITV in 17/100 pts and in 83/100 pts using Active Breathing Coordinator (ABC) to achieve a reduction of respiratory displacements. In 66 pts gold fiducials markers as target surrogate were implanted. Target mean volume was 65.7 cc (range 0.3-365 cc) and mean number of treated lesion was 1.7 (range1-5). Mean dose in three Fx was 35Gy (range 25-48Gy) prescribed to isocenter in 65/173 lesions and to the 67-70% isodose in 108 lesions. Treatment was delivered through multiple coplanar and no-coplanar arcs and dmlc by 6 MV LINAC. Isocenter position was verified using CBCT co-registered to planning CT on diaphragm profile or gold fiducials. Local Control (CL), defined as no tumor regrowth in the irradiated volume, was evaluated by multiphasic CT at 2, 6, 12 months and every 6 months successively. Toxicity was evaluated according to CTCAE.

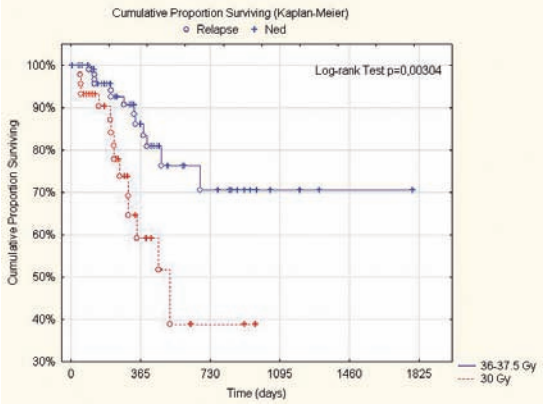
Results: Median follow up was 15 months (range2-63 months). The rate of LC at 6, 12, 24 months was 92.8%, 78%, 62% respectively. On univariate analysis, the use of ABC system (p=0.0169), implanted fiducials (p=0.0006), low lesion volume (p=0.00768), higher delivered dose (p=0.00304) were correlated with better LC. No correlation was observed with tumor type, although there was a

positive trend for breast metastases. G1 toxicity in 12/100 patients and G2 (ulceration medically recovered) in 4 patients was observed.

Conclusions: In our experience, SBRT for liver metastasis , as ablative treatment, lead to high rate of LC that appears, in our results, to be stable after two years (62%). The use of breath control and target surrogates improve LC rates. These results and low toxicity suggest the SBRT as a safe and effective treatment that can be offered to patients not suitable for other ablative therapies.







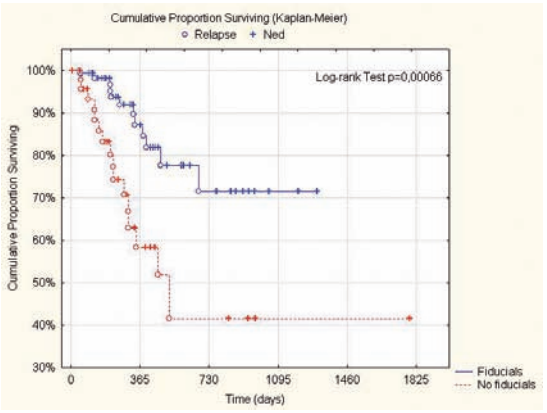


Figure.

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LUNG METASTASES IN OLIGOMETASTATIC PATIENTS: A NEW STEREOTACTIC BODY RADIOTHERAPY (SBRT) APPROACH USING VOLUMETRIC MODULATED ARC THERAPY (VMAT) WITH FLATTENING FILTER FREE (FFF) BEAMS

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Purpose: Data on the use of stereotactic body radiation therapy (SBRT) in oligometastatic patients are emerging and the early results on local control are promising. Aim of this study was to evaluate results and toxicity of SBRT using VMAT-FFF in lung metastatic patients from different primary tumors.

Materials and Methods: One hundred forty-five consecutive patients treated between October 2010 to September 2011 were included. The most common primary cancers were lung and colon-rectal. One hundred sixty-seven SBRT were performed. All patients had oligometastatic disease. Dose prescription was 48 Gy in 4 consecutive fractions for peripheral lesions with maximum diameter < 3 cm, 60 Gy in 6 consecutive fractions for central lesions and 32 Gy in 4 consecutive fractions for lesions with maximum diameter between 3 and 5 cm or in case of multiple lesions in the same lung. Clinical outcome was evaluated by CT scan and CT-PET. The incidence of pneumonitis was graded according to the NCI CTCAE v3.0 scale.

Results: Median follow-up was 9 months (range 3-14). Response was recorded in 134/167 lesions (80%). At the last follow up 132/155 of patients (85%) were alive. No pulmonary toxicity of grade 2 or greater was recorded. No chest pain toxicity occurred. Removal of the flattening filter (FF) increased the dose rate. The median beam-on time (BOT) was reduced by 75% passing from about 8 minutes (with FF modality) to 2 minutes (with FFF modality).

Conclusions: SBRT is a feasible, safe and effective local treatment option for pulmonary metastases in patients unsuitable for surgery. VMAT technique improved target coverage while minimizing higher dose to normal tissue with respect to coplanar beam arrangements. Furthermore, the BOT was significantly reduced in FFF modality with a subsequent increase of patient comfort and reduction of intra-fraction motion. In our experience SBRT with VMAT-FFF resulted in a good radiological response though a longer follow-up is needed to assess the effective outcome incidence and to select patients with better prognosis.

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NEW TREATMENT FOR BRAIN METASTASES: SIMULTANEOUS BOOST AND WHOLE-BRAIN RADIOTHERAPY WITH VOLUMETRIC MODULATED ARC THERAPY

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Purpose: To access treatment toxity and patients' survival after Volumetric Modulated Arc Therapy (VMAT), a novel rotational Intensity Modulated RadioTherapy (IMRT) technique, with Simultaneus in-field Boost (SIB) for patients with brain metastases. In the Department of Radiation Oncology at V. Fazzi Hospital, we use VMAT®. This technique allows delivery of both a standard radiation dose to the whole brain as well as a higher radiation dose to the brain metastases at the same time (simultaneous integrated boost, SIB).

Materials and Methods: Between November 2010 and March 2012, 13 patients with 1-3 brain metastases were treated with SIB-IMRT in our Department of Radiation Oncology (maximum diameter of largest metastasis ≤ 3 cm, KPS ≥ 70, RPA < III). Mean age was 61 ± 7.5 years. Patients were neurologically stable. Extracranial disease well-controlled (6-month estimated median life expectancy). Patients will undergo contrast-enhanced TC scan of the brain for radiotherapy planning purposes. The macroscopic (gross) tumor volume (GTV) was drawn on the MRI images. The prescription isodose line was generally 3 mm larger than the GTV. Patients will be treated with WBRT/SIB using VMAT, delivering a total of 30 Gy in 10 fractions to the whole brain and SIB doses to brain metastases were 40 Gy to lesions >or= 2.0 cm and 50 Gy to lesions <2.0 cm in diameter, delivered once daily on working days. Following therapy completion, patients will be seen every 3 months for the 1st year, then every 6 months thereafter. At each clinic visit, clinicians or study investigators will monitor for toxicity from therapy, document neurologic symptoms and signs and performance status. Patients will have MRI brain at 3 months and 1 year, and every 6 months after the first year. Each lesion was measured for local tumor response and graded using the criteria of MacDonald et al.

Results: The median follow-up interval was 9 months (range, 2 months- 16 months). The median overall survival time was 11 months, and 3 of patients died of disease progression. The 6-month overall survival was 91%. After SIB-IMRT treatment of 19 brain lesions, 14 lesions demonstrated complete responses, 3 lesions demonstrated partial responses, 2 lesion demonstrated stable disease. Actuarial local tumor control rates at 6 months and 1 year were 93.9% and 82%, respectively. Ten patients did not have any adverse events >grade1. The majority of common adverse events were grade 2 headaches (4 patients), grade 2 motor neuropathy (2 patients), and grade 2 lethargy (2 patient). One patient developed a grade 3 headache 5 months after receiving SIB-IMRT.

Conclusions: The delivery of 40/50 Gy in 10 fractions to 1 - 3 BM using VMAT provides a high level of tumor control with minimal toxicity no significant toxicity. Therefore, we believe there is a need for a larger prospective study to establish dosing guidelines for SIB-IMRT and to pave the way for a randomized trial to compare SRS/STS plus WBRT with this approach.

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MULTIDISCIPLINARY TREATMENT OF METASTATIC PATIENT

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Introduction: During the last years, the number of metastatic patients increased, due to the improvement of integrated therapies of the tumors and overall survival. Treatment of metastatic disease needs multidisciplinary and interdisciplinary approach. Hormonotherapy, immunotherapy, chemotherapy and radiotherapy have target effects about single tumor and lower adverse effects. Surgery is less invasive and radiotherapy save healthy tissue.

Purpose: The aim of this study is the choice of adapted treatment, shared from other specialists, that has benefit for the patients and gives them better quality of life, personal autonomy, reduction of pain, the functional impotence and the reduction of fracture risk in bone metastasis, of coma and intracranial hypertension, of lymphoedema and tromboembolia and ulcers, in lymphonodal metastasis.

Materials and Methods: Between May 2011 and May 2012, 220 patients are given treatment by Marco Polo Clinic in Rome. Mean characteristics of patients were: bone metastasis 100 pz brain metastasis 75 pz lymphonodal metastasis 25 pz soft tissue metastasis 20 pz. Median age 60 yrs (range 35-94) M: F 1:1 Main primary sites were: lung 40%, breast 30%, genital urinary 20 % other

20 %.Schedule fractions was: brain metastasis: 3 Gy x 10 fractions 90% 4 Gy x 5 fractions 5% 6 Gy x 4 fractions two days week 5% bone metastasis: 3 Gy x 10 fractions 40% 4 Gy x 5 fractions 35% 8 Gy single fraction 25% lymphonodal metastasis: 3 Gy x 10 fractions 40% 5 Gy x 5 fractions 20 % 4 Gy x 5 fractions 40 %

Results: Most patients showed overall survival (mean 3 months - 4 years), improvement life, a return to work, pain reduction, the reestablishment functionality arts and a decrease risk of adverse effects. The best results are showed in patients undergo established and decompression surgery, in patients got chemotherapy, biphosfonate(bone metastasis), physiotherapy, supportive and pain care, corticosteroid and mannitol (brain, metastasis).

Conclusions: An adaptive fractionation, age, medical conditions, concomitant disease of the patients, stage of neoplasia, number ,localizations and dimensions of metastasis, approach medical multidisciplinary are very important for overall survival, improvement life and pain reductions.

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INTENSITY MODULATED RADIOTHERAPY WITH DYNAMIC ARC (VMAT) TO TREAT MULTIPLE BRAIN METASTASES WITH SIMULTANEOUS BOOST (SIB) SPARING HIPPOCAMPUS

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Purpose: Brain metastases occurred in 20-40% of cancer patients. The Whole Brain Irradiation (WBI) is the most common treatment, but clinical studies demonstrate the superiority of surgery or radiosurgery in terms of control of the disease, when applicable. However, there are sufficient data in the literature that show long-term serious and permanent toxic effects, including cognitive deterioration and cerebellar dysfunction, WBI related. It is important to search a radiotherapic technique that ensures, as SRS, a local control of evident lesions, a prophylaxis of cancer progression in other cerebral site sparing dose to hippocampal region. To this aim, we studied the possibility to perform a treatment with VMAT delivering a Simultaneous Integrated Boost (SIB) to gross metastatic diseases to improve intracranial tumor control, decreasing the dose absorbed by hippocampus.

Materials and Methods: 5 patients with multiple brain metastases (nmin=2, nmax=3) were selected for our study. The countouring was performed using contrast-enhanced CT dataset with a 2-mm slice thickness. The organs at risk included the eyes, the optic nerve and hippocampi. The PTV of metastasis was used as the target volume for the boost. The prescription to the whole brain was 34Gy in 15 fractions, the prescribed dose of simultaneous boost to the brain metastasis was 40.5Gy.The mean dose to the hippocampi was <10Gy. Treatment plans were optimized with TPS Monaco (Elekta, Crawly). Treatments were delivered using 6MV photons on Elekta SynergyS linear accelerator (Elekta, Crawly) with Beam Modulator. Plans were evaluated on homogeneity index (HI), target coverage (TC), conformity number (CN), maximum dose to prescription dose ratio (MDPD) and prescription isodose to target volume ratio (PITV).

Results: Mean values for brain metastases were HI=0.110±0.004, CN=0.554±0.002, MDPD=1.060±0.050 and PITV=0.985±0.034. For the whole brain TC and HI were 0.958±0.16 and 0.280±0.023 respectively. The mean hippocampal dose was 10.34±2.2Gy.

Conclusions: in our experience, VMAT technique appears useful to delivery a ''prophylactic'' dose to whole brain parenchyma and to reach eradicative doses to metastates sparing hippocampus. These useful dose distributions, obtainable with VMAT, permit to offer a good solution for patients with limited number of brain metastases not amenable to surgery or radio surgery. But this technique involves long time of treatment.

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RADIOTHERAPY FOR BONE METASTASES. HAS BISPHOSPHONATES DECREASED THE INCIDENCE OF TREATMENTS FOR BREAST AND PROSTATE CARCINOMA WITH SKELETAL METASTASES? AN ANALYSIS OF DATA FROM 2004 TO 2011 IN THREE SICILIAN RADIATION DEPARTMENTS

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Purpose: To evaluate the need of irradiation for bone metastases from breast and prostatic carcinoma in the era of bisphosphonates. A retrospective analysis.

Patients and Methods: All patients treated for bone metastases, from 2004 to 2011, in three Sicilian radiation departments (Policlinico of Messina, Taormina Hospital, REM Radioterapia Catania), were collected. Among these, metastases from breast and prostatic carcinoma were analyzed according to year of irradiation.

Results: A total of 2164 bone metastases patients were treated, 642 had metastatic breast cancer and 332 had metastatic prostate carcinoma. According to the year of treatment, we observed a median of 268 (range 243-305) total patients treated for bone metastases; a median of 79 (range 73-93) breast cancer patients; a median of 37,5 (range 35-57) prostate carcinoma patients. Table 1 resumes the complete results.

Conclusions: During the last ten years epidemiological data demostrate a costant increment both of incidence and prevalence of breast and prostate cancers in Sicily. Theoretically these incrementes should result in an higher

need of radiation therapy for bone metastases from these cancers. Our data seems to demonstrate that there is an homogeneous distributions of patients treated during the period of observation in the three radiation departments participating at this study. The lack of differences could be linked to the actual extensive use of bisphosphonates in clinical practice at the time of first diagnosis of skeletal metastases both in breast and prostate cancer patients. A larger analysis including more radiation departments should be performed to validate our hypothesis.

Table 1.

Year	Total pts* with BM°	Breast cancer pts	Prostate cancer pts
2004	243	88	36
2005	272	73	35
2006	262	73	47
2007	246	82	35
2008	273	75	35
2009	264	93	57
2010	305	76	48
2011	299	82	39

** pts: patients; ° BM: Bone Metastases*

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PALLIATIVE ROLE OF HYPOFRACTIONATION RADIOTHERAPY SCHEDULE IN RECTAL CANCER PATIENTS

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Aims: To evaluate the palliative role of an hypofractionation radiotherapy schedule in elderly or metastatic rectal cancer patients unfit for chemoradiation.

Methods: Inclusion criteria were symptomatic disease in elderly or metastatic rectal cancer patients unfit for chemoradiation or surgery. The clinical target volume 1 (CTV1) included the gross tumor volume (GTV, both primary tumor and enlarged pelvic nodes) and the corresponding mesorectum plus 2 cm cranio-caudally. The CTV2 included the CTV1 plus the entire mesorectum, the entire pre-sacral space and the internal iliac nodes. The planning target volume (PTV) was the CTV plus 0.8 cm margin in all directions. Conformal three-dimensional radiotherapy was planned using the Masterplan-Oncentra treatment planning system 4.0. A four field box technique was used. Radiation dose delivered to PTV2 was 20 Gy (4 Gy/fraction) concomitant with a boost dose of 1 Gy to the PTV1 up to a dose of 25 Gy in five sessions. Symptom palliation, acute toxicity and colostomy free survival were evaluated.

Results: From March 2003 to December 2011 23 consecutive patients (17M, 6F; median age 76, range 51-97) were treated. Ten patients (43.5%) had poor performance status and relevant co-morbidities, while 13 patients (56.5%) patients had metastatic and/or recurrent disease. One or more initial presenting symptoms were recorded as follow: pain (7 patients; 30.4%), bleeding (13 patients; 56.5%), tenesmus or stenosis related symptoms (16 patients; 69.5%). All patients completed the prescribed treatment. Only 2 patients (8.7%) presented a grade 3 (RTOG Scale) acute gastrointestinal toxicity. No grade 4 acute toxicity was registered. Symptom response was valuable in 17 patients (73.9%): 13 (76.5 %) achieved a symptom palliation and 4 (23.5%) had stable condition at 1-month follow up after treatment. The median follow-up was 11 months (range 1-58 months). Actuarial 2 year colostomy free survival and overall survival rate were 74.1% and 49.4%, respectively.

Conclusions: A short course radiotherapy with hypofractionation schedule is well tolerated representing an effective palliation treatment in patients with symptomatic rectal cancer unfit for chemoradiation or surgery. The quality of life of these patients may be improved by reducing the indications for colostomy.

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COMBINATION OF THERMAL ABLATION AND/OR CEMENTOPLASTY TREATMENT PLUS ADIATION THERAPY FOR PALLIATION OF NEOPLASTIC BONE METASTASIS. OUR EXPERIENCE WITH 63 TREATED LESIONS IN 46 PATIENTS

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Purpose: The aim of this study is to report the safety and efficacy of combined thermal ablation and/or cementoplasty plus Radiation therapy in treating painful and stabilization of bone metastases.

Materials and Methods: Were selected 46 patients (59 % female and 41% male), treated in our Centre between December 2006 and December 2011; these patients received combined treatment: thermal ablation and/or cementoplasty plus Radiation Therapy. Primary malignancies included: 53 % breast, 24% lung , 4% prostate gland , 2% multiple myelomas, 2% renal cell , 2% colon, 2% parotid gland, 2% pancreas, 2% bladder and 2% hepatocarcinoma. One patient (2%) presented simultaneous lung and thyroid cancer. Patients ranged in age from 44 years to 84 years (mean years 63,3) at the treatment time. The total number of treatments was 63. Sixty-eight vertebrae (41% thoracic , 27% lumbar), 24% pelvis bone , 6% femurs and 2% shoulders were treated. The average of treatments' for each patient was 1,3 (range 4-1). Seventy percent of Intervention Radiology treatment were cementoplasty , 27% thermal ablation and 3% was combined, both treatments. The fractionation schemes of dose for radiation therapy adopted were 30 Gy in 10 fractions (20%) 20 Gy in 5 (68%) , 8 Gy in 1 (10%). Only one patient received

6 Gy because was re treatment. Pain levels pre- and post-procedure (as assessed using the Visual Analog Scale).

Results: 8% of treatments showed complications : cement leaks into the needle track occurred in 2 cases (3%). Cement leaks into spinal canal , disc spaces and radicular nerve occurred in 1 patient each one (5 %). However the vast majority of cement leaks were entirely asymptomatic. Radiation therapy was well tolerated in all patients. The mean pre-procedure and post-procedure pain, as measured by the Visual Analog Scale (VAS), was 7,5 (range 10-5 SD=1,12) and 2,3 (range 0-8 SD=1,34) respectively.

Conclusions: according to our experience, Radiation therapy and Intervention radiology is not mutually exclusive; rather, they should be considered complimentary procedures. Thermal Ablation and/or Percutaneous Injection of acrylic cement was found to be safe, practical and effective in the palliative treatment of painful neoplastic lesions and offers an adjuvant therapy to radiotherapy by providing additional stabilization and pain relief with minimal risk of complication. A multidisciplinary approach to patient selection and management is essential.

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PATIENT- AND DISEASE-RELATED PROGNOSTIC FACTORS IN PALLIATIVE WHOLE BRAIN CONFORMAL RADIOTHERAPY: OUR EXPERIENCE

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Aims: To report the outcomes of whole brain conformal radiotherapy (WBRT) in patients with newly diagnosed of multiple brain metastases from solid tumors not suitable for selection in radiosurgery in a single institution. As secondary end-point, to evaluate the presence of potential prognostic factors useful for clinical identification of a better prognostic patients subgroup.

Materials and Methods: From January 2010 to April 2012 we enrolled 40 patients affected by brain metastasis submitted to whole brain conformal radiotherapy (3D-CRT), with a total dose of 30 Gy/3 - 2.5 Gy die, delivered into 10-12 fractions, respectively. Steroid therapy was administrated in all patients during the treatment. The median age was 66 years with a range from 34 to 79 years. Outcomes of interest included survival, local brain tumor control defined as stable disease or partial response, adverse effects and neurological function during and after radiotherapy. Informations about age, Karnofsky performance status (KPS), number of brain metastases, presence/absence of edema and necrosis and histology of primary tumor were collected as potential prognostic factors. Univariate and multivariate analyses were performed.

Results: With a median follow-up of 5 months, median survival was 6 months, with a range between 1–20 months. At 6 and 20 months follow-up the survival with local brain tumor control was 47 % and 17 %, respectively. 44.4 % of patients had no adverse effects during RT while 28 % showed symptomatic hypertension intracranial syndrome and neurological dysfunctions. After WBRT, the most frequents adverse events were headache and dizziness (25% of incidence in both cases) whereas 25% of patients treated showed no symptomatic effects. Only 2 patients interrupted definitively steroid therapy after WBRT. In this cohort of patients, multivariate analysis demonstrated that a overall survival was related with a favourable KPS at diagnosis of brain metastatic disease (KPS > 60-70), with the number of brain metastases < 5 ($p = 0.08$) and with the absence of radiologic necrosis inside metastatic lesions. Taking into account the small number of patients, we observed that breast cancer, adenocarcinoma and small cell lung cancer primary tumors seems to be correlated with a better mean survival (9 and 6 months). Furthermore, our analysis showed no correlation between age and radiologic presence/absence of edema with overall survival. Finally, in 8% of patients we observed an hair regrowth after WBRT, but this clinical feature was not correlate with dosimetric parameters because the dose to the scalp was in a range between 28-31 Gy in all treated patients.

Conclusions: WBRT with standard schedule is still an effective and actual treatment in patients with multiple brain metastases. In according to literature data, KPS, number of metastases, absence of necrotic lesions and histology seem to characterize a subgroup of patients with favorable prognosis.

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INITIAL EXPERIENCE OF STEREOTACTIC FRACTIONATED RADIOTHERAPY IN THE PALLIATIVE TREATMENT OF CHORIO RETINAL METASTASIS

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Purpose: To initially evaluate feasibility and safety of radiation treatment with stereotactic technique (IMRT or Dynamic Arc Therapy) for palliation of chorio retinal metastases.

Materials and Methods: From October 2009 we treated seven patients with chorio retinal metastasis (5 females and 2 males). Mean age was 58 years (39-74). Primary tumor were: 4 breast adenocarcinoma, 2 lung adenocarcinoma and 1 urothelial carcinoma. All patients have widespread visceral and/or bone metastasis. Two patients were treated after radiosurgical treatment for the appearance of brain metastasis. All patients underwent eyes examination, fluorescein angiography, eco B-scan and MRI as local staging procedure. Five patients had bilateral chorio retinal metastasis and two pts monolateral in the right eye. Two pts were pretreated with photodinamic therapy and Laser therapy. The irradiation procedure included the moulding of custom Klarity® mask; the use of a repositionable stereotactic Leksell-type localization system; CT simulation without contrast media with 1.5 mm slice and

volumetric coregistration and fusion with volumetric 2 mm slice MRI with gadolinium contrast media. Treatment planning was performed on BrainLab iPlan®. Dynamic arc or Step and Shoot IMRT technique with 6 MV x-rays collimated with BrainLab microMultileaf collimator were used. Prescribed dose to PTV including choroid and retina with 2 mm margin was 34-36 Gy in 2.0 or 2.4 Gy per fraction in 2 pts and 20-24 Gy in 3-5 Gy per fraction in other 2 pts. Biologically Effective Dose (BED) calculated for tolerance was 60-68 Gy2.

Results: At three months we observed, after evaluaton, PR in 2 pts, SD in 4 pts and PD in 1 pt. Four patients died from disease progression in other metastatic sites with median survival of 12 months (4-18) free from progression in the chorio retinal sites.

Conclusions: Stereotactic Fractionated Radiotherapy of chorio retinal metastasis showed to be feasible and safe with full compliance by patients and virtually no observed toxicity. Therefore we are extending this experience to more patients in order to escalate the dose and reduce the number of fractions.

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RADIOTHERAPY IN OLIGOMETASTATIC DISEASE

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Backgrounds: Hellmann in 1995 defined the concept of "oligometastatic" as the patient at "an intermediate phase of metastatic disease that presents a potential for disease control with the ablation of the few metastases".Such patients usually have a better prognosis and the local treatment of metastases may play a significant role on the future development of their disease leading to a sort of "chronic" state. Radiation therapy is certainly the most frequently used local treatment with the greatest potential in these situations. Modern techniques of high-shape beam (3DCRT, IMRT, SRT, SBRT) and new technologies (TomoTherapy, CyberKnife) available today allow us to administer high doses per fraction with minimal irradiation of normal tissues by reducing the side effects not only acute but also late, which must be taken into account in these patients that are possible long-term survivors. Is still to be defined how justified is the use of new technologies (cost and resource-consuming) in palliative care in terms of clinical and organizational appropriateness.

Materials and Methods: In the year 2011, we treated 217 metastatic patients, 170 for bone metastases and 47 for brain metastases. Using the definition of oligometastatic disease as the presence of 1-5 mestatases in no more than two organs, 53 patients could be classified as oligometastatic. Of these, 38 were treated for bone metastases, some of them in more than one site for a total of 50 treatments, and 15 for brain metastases. Treatments were performed on bone metastases with conformal techniques (3DCRT) in 70% of cases (35 treatments) and with 2D technique in the remaining 30% (2 with a single fraction). Treatments of brain metastases (WBRT) were carried out in most cases with 2D technique (67%).

Results: Patients treated on bone metastases showed pain reduction in 95% of cases with complete disappearance of the same in 67%. Acute and late toxicity was negligible.

Conclusions: some experiences show better clnical results in oligometastatic disease with the use of advanced radiation techniques (eg. RTOG 9508 study). Moreover to date there are no data showing a clinical advantage of "high tech" compared to conventional equipment, in front of the clear dosimetric advantage. Certainly 3DCRT represents the most appropriate technique for palliative treatments allowing in most cases to deliver ipofractionated doses with low toxicity. Advanced technologies may be useful in specific situations or in retreatments.

P230
COMPLICATED BONE METASTASES: HAS 8GY IN SINGLE FRACTION ANY ROLE?

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Aims: To evaluate a single fraction of 8 Gy in terms of short-term side effects and benefits in patients with complicated bone metastases.

Patients and Methods: Twelve patients with complicated bone metastases were entered in this study. Patients recorded pain severity using both Patients Pain Intensity Scale (PPI) and Numerical Rating Scale (NRS); analgesic requirements and breakthrough pain (BP) were evaluated before treatment, at 2 weeks and at 8 and 16 weeks after radiotherapy. Pain relief was the primary endpoint with short-term side-effects as second one.

Results: From January 2012 to April 2012, 12 patients were enrolled. Before radiotherapy the median PPI and NRS score was respectively 4 (range 2-5) and 80 (range 60-90); patients reported a median of 4 daily incident BP. All had a standard pre-medication with hydration, dexamethasone and antiemetics. An isocentric conformated technique with IGRT was used and the dose was delivered using a Lin.Ac. Elekta-Synergy. Up-to-date two patients died for progressive disease respectively 2 and 9 weeks after therapy; in a patient the follow-up is less than 16 weeks. At 8 weeks, in 11 patients, median PPI of 3 (range 1-4) with a median NRS of 50 (range 40-70) were observed; at 16 weeks, in 8 patients a median PPI of 2 (range 1-3) with a median NRS of 50 (range 10-70) were reported. After treatment, no patients had pathological fracture or increase in symptoms from epidural spinal cord compression. Analgesic use decreased with a reported median incident BP of 1. No grade 2 or more toxicities were observed. In a patient retreatment was delivered after 17 weeks.

Conclusions: A single fraction of 8 Gy seems to be safe and effective in the palliation of complicated bone metastases. These data need to be validated in a larger study.

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RETROSPECTIVE ANALYSIS OF 244 PATIENTS WITH METASTATIC LIVER LESIONS TREATED WITH STEREOTACTIC BODY RADIOTHERAPY

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Purpose: To evaluate the efficacy and tolerability of high-dose stereotactic body radiation therapy (SBRT) for the treatment of patients with hepatic metastases.

Patients and Methods: Two hundred and forty-four patients with lesions were treated with SBRT. These patients had one to four lesions with an average diameter of about 39.7 mm. Radiation therapy was administered in between 3 and 7 fractions. The dose was increased in a secure manner from 21 Gy to 56 Gy. Lesions were evaluated using the RECIST criteria and PET and/or TC exams every three months. The analysis of retrospective data to determine the percentages of local control and overall survival was performed using the Kaplan-Meier method, the difference between overall survival and local control curves was studied with the long rank test. Acute toxicity was evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results: Median follow-up was 373 days, at latest 193 patients had died, none due to SBRT. 7 were lost during the follow-up and 44 were alive. Local progression occurred in only 14 patients with a median time of about three hundred and fifty days after SBRT. The local control rates at one year, two years and three years after SBRT were respectively 92.8%, 79.1% and 66.9% (Figure 1). Overall survival at one year, two years, three years was found to be respectively 57.0%, 37.5% and 25.0% with 6.3% of patients surviving 2185 days after radiation therapy (Figure 2). Only 19 patients had acute toxicity (7.8%) of grade G1 and G2. No late toxicity was observed.

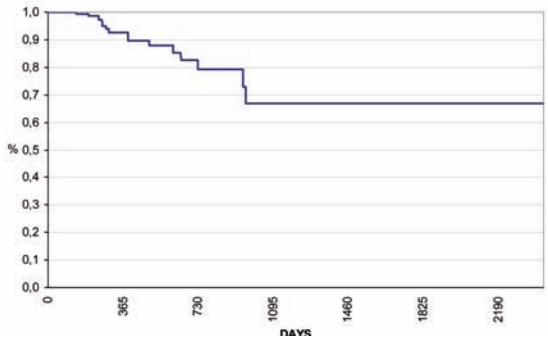

Figure 1. Local control.

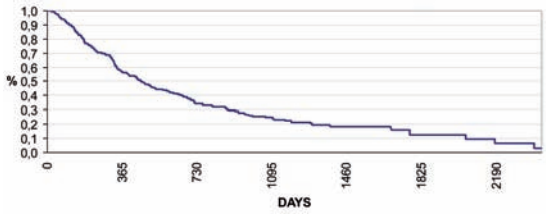

Figure 2. Overall survival.

Conclusion - Retrospective analysis of the data shows that stereotactic body radiation therapy with high-dose fractions on liver metastases is a safe and well tolerate therapy.

P232

PALLIATIVE RADIOTHERAPY 8 GY SINGLE FRACTION TAILORED TO LIFE EXPECTANCY IN SYMPTOMATIC PLURIMETASTATIC PATIENTS: OUR EXPERIENCE.

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Aims: About 30%to 50% of patients (pts) are referred to Radiation Therapy Departments to be treated for palliation and hypofractionated radiotherapy is widely used. Fractionation schedules should be chosen according to patient's life expectancy: single fraction radiotherapy (SFR) is generally used to treat pts with bone pain uncontrolled by analgesics and poor prognosis. The purpose of this retrospective study is to investigate the adequacy of pts selection according to six months life expectancy for 8 Gy single fraction radiotherapy (SFR) in the management of symptomatic bone metastasis.

Materials and Methods: From November 2002 to December 2011, 266 pts with painful bone metastasis [prevailing primary cancer types were lung (27%), breast (24%), gastro-intestinal tract (12%), prostate (8%), genito-urinary tract (8%), multiple myeloma (6%), head-neck (4%), others (11%)] referred for palliation to our observation were treated with 8 Gy single fraction radiotherapy. Patients selection for 8 Gy hypofractionation was done according to Performance Status, primary histology, age, number of metastatic sites, site of metastasis. Twenty-nine pts received radiation therapy on more than one target in different times; 18 pts received radiotherapy on more than one target at the same time; 5 pts were retreated with SFR on the same bone target. Patients were followed after radiation treatment completion to evaluate 6 month survival that represents the primary endpoint.

Results: Patients treated with SFR were divided in three groups according to survival: group A) pts who died before 6 months; group B) pts surviving over 6 months; group C) patients lost at follow up (censored pts). Patients treated with SFR from 2002-2003 to 2011 (widely delivered in subjects with worse prognosis at diagnosis) are 2.7% of all the referred pts (range: 0.8% - 3.9%) and they are quite constant in the last four years (2.6% - 3.1%). The number of pts who died before 6 months from SFR (A group) is increased from 2002-2006 (49% of uncensored pts) to 2007-2011 (67% of uncensored pts). In the B group (long survivors) the number of pts decreased from 2002/3-2006 (51.% of uncensored pts) to 2007-2011 (33% of uncensored pts). The censored data (C group) reduced from 2002-2006 (23% of all pts treated with SFR) to 2007-2011 (10%); data are summarized in Table 1.

Table 1.

Year	Not Censored patients			Censored patients	Patients treated with 8Gy	Tot. patients
	A group	B group		C group	observed	
	Death before 180 days	Death after 180 days	Total	%	in the year	
2002-2003	1	3				
7	11	0.8				
1405						
2004	13	7				
9	29	1.6				
950						
2005	12	21				
3	36	3.8				
941						
2006	18	15				
8	41	3.9				
1055						
2007	11	17				
6	34	3.4				
998						
2008	15	7				
1	23	2.2				
1019						
2009	22	9				
3	34	3.1				
1102						
2010	18	7				
2	27	2.3				
1185						
2011	23	3				
5	31	2.6				
1189						
	133	89				
44	266	2.7				
9844						

Conclusions: survival results of the A group demonstrated our improvement in pts selection and the adequacy of the chosen hypofractionation schedule to the predicted survival, providing to plurimetastatic symptomatic pts an effective survival-time-adapted palliation. Few pts (1.9% of all pts treated) required a retreatment on the same bone target for residual or recurrent pain demonstrating the correct use of SFR in the management of plurimetastatic symptomatic pts. SFR is still not widely used (2.7% of all referred pts) also if recent randomized studies reported that a SFR regimen is safe and effective in terms of pain relief also in patients with a more favorable prognosis. The censored data, although significantly reduced during the years, show our current limit in the management of follow up for those pts after radiotherapy completion: the use of integrated database systems may ameliorate data collection from all pts treated with SFR.

P233

IS STEREOTACTIC ABLATIVE RADIATION THERAPY AN ATTRACTIVE OPTION FOR UNRESECTABLE LIVER METASTASES? PRELIMINARY RESULTS FROM A PHASE II TRIAL

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Objectives: To evaluate the feasibility of high-dose stereotactic body radiation therapy (SBRT) in the treatment of unresectable liver metastases originating from solid tumours.

Materials and Methods: Patients with one to three unresectable liver metastases with maximum individual tumour diameters less than 6 cm, a Karnofsky Performance Status of at least 70 and life expectancy more than 6 months were enrolled and treated by SBRT on a phase II clinical trial. The prescription dose was 75Gy in 3 consecutive fractions of 25Gy each, prescribed to the mean PTV. Whenever this is not achievable for organ at risk tolerance, the mean CTV received homogeneous full prescription dose of 75 Gy, and the margin between CTV and PTV could receive an underdose corresponding to the critical structure tolerance dose level. SBRT was administered using the volumetric modulated arc technique (VMAT) , with photon 10 MV FFF (Filter Flattening Free-dose rate of 2400 MU/min). The primary end point was in–field local control, evaluated using the modified RECIST criteria. Secondary end points were toxicity, assessed according to CTCAE v3.0, and survival.

Results: Between 2/2010 and 8/2011, 57 patients with 70 lesions were enrolled in this trial. Among them, 40% had stable extrahepatic disease at study entry. The most frequent primary sites were colorectal and breast cancer; 80% of patients had one lesion, 16% and 4% had 2 and 3 lesions, respectively. Fifty-nine lesions (84%)

were treated with a full dose of 75Gy. The dose was dropped down for 11 lesions to fulfill the dose constraints. Mean beam on time was 2.9±1.5 min (range 1.9-6.2 min). Among 50 assessable patients, after a median of 6 months (range 1.5-19 months) in–field local response rate was 96.5%. None of the patients experienced grade 3 or higher acute toxicity. G2 acute toxicity, mainly gastrointestinal, occurred in 7 patients (14%). No radiation induced liver disease (RILD) was detected. Given the short length of follow up, no data on late toxicity are currently available.

Conclusions: Our findings suggest that SBRT for unresectable liver metastases is associated with a high rate of local control and a low incidence of acute toxicity, and can be considered as an effective, safe, and noninvasive therapeutic option in this setting. Whether these promising results will translate into better clinical long-term outcome requires additional follow up.

P234

RITA PROJECT (HYPOFRACTIONATED RADIOTHERAPY AND ANALGESIC THERAPY): INITIAL EXPERIENCE OF A MANAGEMENT CARE APPROACH DEDICATED TO METASTATIC PATIENTS AT HUMANITAS CANCER CENTER

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Backgrounds and Aims: Pain is the most common, most feared, and most debilitating symptom for cancer patients in metastatic stage and it plays a crucial role in their quality of life. Pain is reported in almost 2/3 of patients with advanced cancer and increases as patients approach death.

The aim of "RITA" (hypofractionated radiotherapy and analgesic therapy) project is to highlight the advantages of a fast access to a palliative radiotherapy department, thanks to a multidisciplinary approach dedicated to symptoms management.

Materials and Methods: In April 2012 RITA, a Radiotherapy management care approach dedicated to symptomatic patient, started its activity in the department of Radiotherapy and Radiosurgery of Humanitas Cancer Center, Milan. It involves a multidisciplinary team with a radiation oncologist with expertise in palliative medicine and palliative care, pain management specialist, an anesthetist, and a dedicated nurse. When a patient is eligible for radiotherapy, treatment starts within 24-48 hours. We evaluated patients included in this project from April to May 2012.

Results: In the period of analysis, in the RITA project were included and treated 20 cancer patients: 15/20 for bone metastases (dose prescription: 12 p. 30 Gy /10 fr, 2 p. 20 Gy/5 fr, 1p. 8 Gy /1 fr), 3/20 for brain metastases (30 Gy/10 fr) , 1/20 for abdominal metastases (32 Gy/12 fr). In all patients a better compliance to radiation treatment, no request for additional visits for symptoms management and a significant improvement in quality of life and psychological status, both of patients and their families were noticed.

Conclusions: Despite the RITA short activity time, we can suggest that a multidisciplinary approach to symptomatic patients and the contribution of radiation oncologists with expertise in palliative care improve therapeutic strategies and quality of life reducing also the timing of action and the health care costs. More experience will enable us to better define the preliminary results.

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NEWS IN THE TREATMENT OF BONE METASTATIC PATIENTS

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Introduction: Radiotherapy provides successful palliation of painful bone metastasis that is time efficient and has been associated with very few side effects. In the last three years, in our department we had the same widespread variation that exists in the worldwide practice patterns for palliative radiation dose fractionation schedules.

Purpose: The aim of this analysis is to analyze the evolution of RT in the treatment of bone metastases.

Patients and Methods: From January to March 2012, 34 patients were submitted to palliative radiotherapy on painful bone metastases in a single 8Gy fraction schedule. They were 53% (18) females and 47% (16) males, and the mean age was 69,4 years (median 74 years, 36-84). Mean follow up was 94 days, median 91 (range 59- 135 days). We classified patients according to: primary disease (20,6% gastro-intestinal; 32,3% breast; 20,7% lungs; 11,8% prostate; 2,9% thyroid; 2,9% gynecology; 5,9 % occult and 2,9% melanoma) and part of body treated (35,3% pelvis; 8,9% upper limbs; 2,9% lower limbs; 50% spinal column; 2,9% skull). Mean ECOG was 3,24 (median 3, 5-0), the average daily consumption of morphine pre-RT was 75,2 (mg) (median 55, 0-300) and the mean VAS pre-RT was 6,85 (median 8, 2-10). All the treatments were made with LINAC: 90% with 6MV photon energy and 10% with 6- 20 MeV electrons (for superficial lesions, f. e. sternum, ribs and skull). The follow up was made at 1 month from the end of the treatment and we analyzed the evolution of Visual Analogue Scale (VAS) and of the consumption of morphine for each patient. We knew the evolution of pain after radiotherapy of 27 patients.

Results: 27/34 (79,4%) patients had improvement in pain symptoms: of these, 6/27 (22,2%) had total pain relief (VAS 0), and 21/27 (77,8%) had a reduction of VAS of about 1,19. 25/34 (73,5%) patients are alive and 9/34 (26,5%) patients are dead. The mean VAS post-RT was 4,52 (median 5, 0-10) and the mean daily consumption of morphine post RT was 67,6 mg (median 55, range 0-300), so, the difference between VAS pre and post RT was 2,33 and the difference between consumption of morphine pre and post RT was 7,6 mg. Despite the small sample analyzed, through the t student test, we found a statistically

significant difference between VAS pre and post RT (t student=2,76 > 1,677 for p<0,05 and degrees freedom= 48), but not between consumption of morphine pre and post RT (t student =0,33 < 1,677). After RT, 8 patients have stopped taking any medication, they take only analgesic as needed, and the other ones continue to take strong narcotics with better control of pain.

Conclusions: Our study confirms that single fraction regimen provides pain relief and allows patients to use lower quantity of narcotics. Benefits of this fraction regimen has been: better compliance of patients to the treatment (specially patients with poor performance status), reduction of the waiting times and the use of the equipment for radical treatments. Our patients had a good control of pain and a better quality of life.

P236
HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY FOR PATIENTS WITH BRAIN METASTASES. A MONOINSTITUTIONAL RETROSPECTIVE ANALYSIS

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Introduction: Hypofractionated stereotactic radiotherapy (HSRT), combines precision of the stereotactic approach with the radiobiological advantage of fractionation. Our casuistry on pts with BM treated with HSRT was retrospectively revised.

Methods and Materials: Between 2001 and 2008, 246 pts with 361 BM underwent stereotactic radiotherapy without whole brain irradiation (WBRT); of those, 217 with 327 BM received radiosurgery and 29 pts with 34 BM underwent HSRT. Male/female ratio was 19/10, median age was 66 years (range,40-86). Karnofsky performance status ranged from 50 to 100 (median 90) and median recursive partitioning analysis class was 2 (range,1-3). Tumour histologies were non small cell lung cancer in 15 (52%) pts, breast in 3 (10%), kidney in 3 (10%), colon in 3 (10%), and other tumours in 5 (18%) pts, respectively. Fifteen (52%) pts had a controlled primary tumour, while 14 (48%) a local or systemic progression of disease. Median number of BM treated per patient was 1 (range,1-3), with a median diameter of 32mm (range,0.3-5.4), and a volume ranging from 0.3 to 79.9cc (median 18). Dose was prescribed at isocentre, with minimum accepted dose ≥90%. Location and volume of tumors conditioned the choice of fractionation: 21 (62%) lesions, received an accelerated dose-schedule of 5 x 6Gy (10, 30%), 6 x 5Gy (7, 20%) and 5 x 7Gy (4, 12%); remaining 13 (38%) lesions were treated with a moderate hypofractionated regimen of 10 x 3Gy. Local control was achieved if tumor regressed or was stable.

Results: Median follow-up was 4 months (range,2-48). Local control was obtained in 94% of the lesions: complete remission in 3 (9%), partial remission in 12 (35%), no change in 17 (50%) and progression in 2 (6%) BM, respectively. Median duration of response was 4 months (range,2-42). Of 9 (31%) pts who relapsed, 4 (14%) had an "in-field", 5 (17%) an "out-field" and 1 (3%) both an "in-field" and "out-field" recurrences. Salvage brain treatment was administered in 6 (21%) pts: 3 (9%) underwent radiosurgery, 2 (7%) WBRT and 1 (3%) a new HSRT. No more than grade II acute toxicity was registered. In 12 (41%) pts, there was skin erythema with alopecia fully reversible in all cases. Median survival time was 5 months, 1- and 2-year actuarial survivals were 38 ±9% and 14 ±6%, respectively.

Conclusions: HSRT resulted safe and effective. Local control was high even without upfront WBRT. The low toxicity registered, allowed us to treat pts with higher HSRT (5 x 7-9Gy).

DIAGNOSTICA PER IMMAGINI MORFOLOGICA E FUNZIONALE NELLA STADIAZIONE, TERAPIA E FOLLOW-UP DEI SARCOMI DELLE PARTI MOLLI

P237
POSTOPERATIVE RADIOTHERAPY FOR SOFT TISSUE SARCOMAS: A SINGLE INSTITUTION REPORT ON 12 CASES.

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Backgrounds: Soft tissue sarcomas represent a heterogeneous group of tumors with variable risk of local recurrence and distant metastasis. Conformal radiotherapy (CRT) is an option both as preoperative and as post-operative treatment. In this retrospective study, to define the rate of acute and late toxicity of the radiation treatment, we analyzed the data of patients with resected soft tissue sarcomas bearing high risk of local relapse due either to grading 3 or to positive resection margins treated with postoperative radiotherapy (PORT).

Patients and Methods: From 2002 to 2012 12 patients with histologically proven high risk soft tissue sarcomas were treated with PORT at our institution. Median age was 56 years (range 29-71). Sites of disease were superior limb in 3 patients, inferior limb in 6 patients and trunk in 3 patients. Four patients had liposarcoma, 4 patients had rhabdomyosarcoma, 3 fibrohistiocytic tumors and 1 synovial sarcoma. Three of 13 patients had positive resection margins. On the whole, 2 patients (17%) had tumor stage I, 7 patients (58%) II and 3 patients (25 %) III. Three patients received neoadjuvant chemotherapy and 1 adjuvant chemotherapy. The radiation therapy was administered with conformal technique and a median dose of 55 Gy (range 50 – 60) with conventional fractionation.

Results: All patients completed the radiation treatment. At a median follow up of 41.5 months (range 15-72) 4 patients were dead (3 patients for relapsing disease

and 1 for unrelated cause). Acute toxicity (erythema and pain) was registred in 67 % of patients, while late toxicity (mainly chronic pain) was registered in 42% of patients.

Conclusions: Our data suggest that postoperative radiation therapy for soft tissue sarcomas results in a good local control rate. Attention has to be made to the possible late effects of the treatment that are mainly in relation to the site of disease.

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SOFT TISSUE SARCOMA TREATED WITH POSTOPERATIVE PULSED-DOSE-RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY

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Purpose: This is a retrospective rewiew of our experience in order to evaluate local control, overall survival, disease free survival, metastasis free survival and late toxicity of adjuvant pulsed-dose rate brachytherapy (BRT-PDR) and external beam radiotherapy (EBRT) in soft tissue sarcoma (STS) patients

Materials and Methods: Between 1/00 and 1/11 a total of 310 medical records of pts with primary high-grade STS of extremities and trunk underwent surgery combined with RT (BRT-PDR and EBRT) were reviewed. Patients were stratified into three groups according to the type of surgery: the first group (66 pts), the second group (85 pts) and the third group (159 pts) underwent RT after the first surgical resection, after excision of relapse andafter excision of scare, respectively. The BRT-PDR dose was 20 Gy.The EBRT mean dose was 46 Gy. Histologically, the most common tumors were fusate cell sarcoma (18%), synovial sarcoma (14%), fusate polymorphic cells sarcoma (13%).The median age was 51 years (range: 12-86 years).The median follow up was 40 months (range: 2-130). Overall survival were calculeted using Kaplan-Meier estimates. Differences between variables were tested using the X2 method. Comparison of survival curves was performed using the Mantel-Cox test. Indipendent prognostic factors were identified using Cox's stepwise regression analysis. Late toxicity was evaluated according to Common Terminology Criteria for Aderse Events.

Results: The 5-year Kaplan-Meier estimate for overall survival was 80%. Sixty-one pts (20%) developed distant mets, and 238 pts (80%) did not develop distant mets. The predictors of worsening 5-year survival rate were: metastases, advanced stage of desease and local recurrence. The subgroup with mets showed a significantly lower survival than the subgroup without (P< 0.001). The stage of deasease reduced the overall survival significantly (P= 0.003) as well as the presence of local recurrence (P=0.001). Other prognostic factors such as location, type of surgical and surgical margin type did not have a significant impact on overall survival (P=0,871; P=0.610; P=0,572). Local control for the whole group was 92%. Desease-free survival and desease free metastases for all pts was 75% and 80% respectively. About 90% of pts did not develop any toxicity for all adverse events examined.

Conclusions: Our study shows that combination of PDR-BRT and EBRT is a valid adjuvant strategy for STS with a low rate of toxicity.

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NEW TENDENCIES IN NEOADJUVANT RADIOTHERAPY OF SOFT TISSUE SARCOMA: A CASE REPORT

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Backgrounds: Highly conformal image-guided radiotherapy (IGRT) improves the radiation dose delivered to tumor targets, minimizing radiation to normal tissue by reducing the planning target volume (PTV). The technique permits the simultaneous delivery of different doses at different volumes.

Purpose: To evaluate the feasibility of dose-escalation IGRT in neoadjuvant therapy of soft tissue sarcoma, delineating CT-scan gross tumor volume (GTV) and clinical target volume (CTV) (Figure 1 and Figure 2).

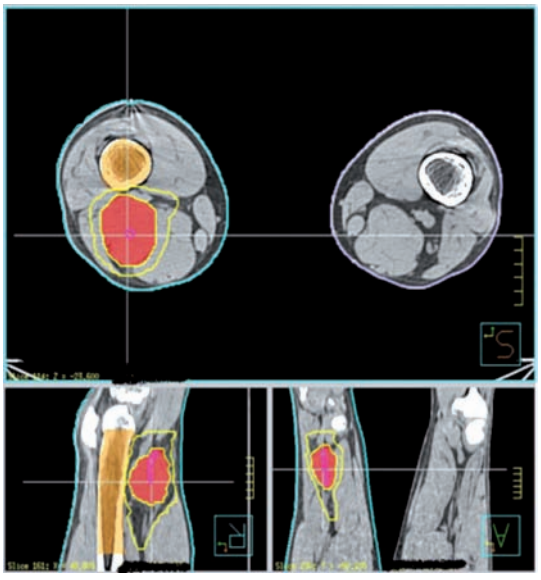

Figure 1. Transverse, sagittal and coronal representation of contours-volumes on CT-scan.

Patients and Methods: A patient with soft tissue sarcoma of the left thigh (cT2bcN0M0) was referred to our

Unit for neoadjuvant radiotherapy. After CT scan image acquisition, we contoured 2 different volumes at 2 different doses: the CTV corresponded to the T2 contrast-enhanced diagnostic magnetic resonance image and received 50 Gy in 25 daily fractions, encompassing the whole anatomical compartment. GTV was the gross tumor defined by T1 contrast enhanced magnetic resonance images and received 55 Gy; a third volume inside the lesion was treated with 60 Gy as a simultaneous integrated boost (SIB) (1-2). The femur and skin were also contoured as organs at risk.

Results: More than 95% of the dose was delivered to the CTV, the femur receiving a maximum dose of 47.35 Gy, a minimum dose of 1.50 Gy and an average dose of 6.90 Gy. The patient experience G1 skin erythema. One month later the patient underwent surgical resection of the lesion. Histology was high grade soft tissue sarcoma with radio-induced necrosis and safe margins (R0). There were no wound-healing complications.

Conclusions: The target volume definition used was appropriate for the patient. Our results show that GTV and CTV MRI-based is feasible during neoadjuvant radiotherapy treatment and can be performed with good isodose curves and good sparing of healthy organs. There would seem to be no wound sequelae after surgery.

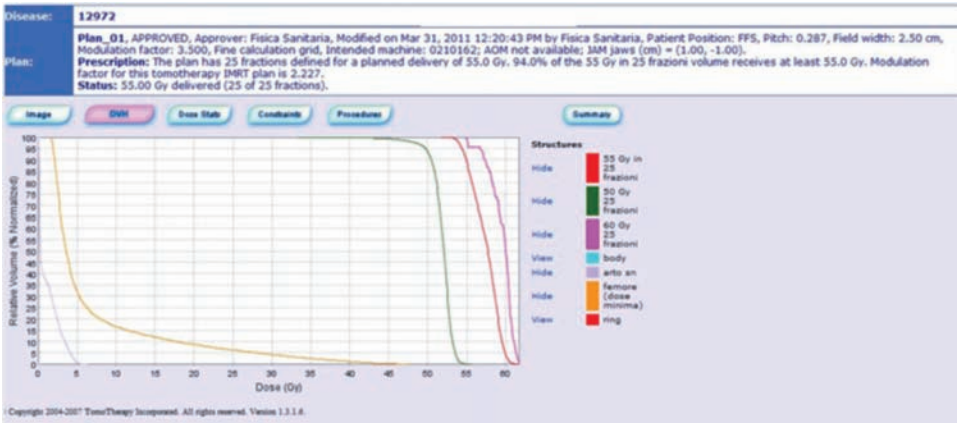

Figure 2. Dose-volume histogram of the treatment plan.

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P240

CONFORMAL RADIOTHERAPY TREATMENT IN PEDIATRIC LOCALIZED RHABDOMYOSARCOMA SOFT TISSUE SARCOMAS

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Introduction: Rhabdomyosarcoma is a typical tumor of childhood, characterized by a high grade of malignancy, local invasiveness and a marked propensity to metastasize, but also a generally good response to chemotherapy and radiotherapy.

Aims: to evaluate outcomes of patients treated at our Institution with radiotherapy for rhabdomyosarcoma.

Materials and Methods: From 1993 to 2011 thirteen patients (7 males and 6 females) affected by rhabdomyosarcoma (8 embryonal and 5 alveolar) were treated at our Institution. Median age at diagnosis was 10 years (age < 10 n=10). The most frequent site of primary tumour was: limbs (n=3), paratesticular (n=1), bladder/prostate (n=2), vagina/uterus (n=3) and parameningeal site (n=2). All patients had previous chemotherapy treatment, the principle schedule used were ESSG RMS 2005 and RMS 96 AIEOP. Only four patients underwent surgery before chemotherapy. 12 patients performed conformal radiotherapy treatment for a total dose ranged from 4400 cGy to 5940 cGy in conventionally fractionated treatment. One patient had external beam radiotherapy (3000 cGy) plus curieterapy (2000 cGy) and one only curieterapy (3000 cGy).

Results: With a median follow-up of 25 months (range 4-179 months) , 9 patients out of the 13 were alive while 4 were dead of disease. Median overall survival were 59 months (range 12-183 months). 7 patients had local progression after chemoradiotherapy treatment and 2 out of them had also lung metastases.

Conclusions: Multimodal therapy is essential to improve the outcome of patients affected by rhabdomyosarcoma.

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POST-OPERATIVE CONFORMAL RADIATON THERAPY IN SOFT TISSUE SARCOMA IN ADULTS: TREATMENT RELATED TOXICITY AND 2 YEAR RESULTS

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Introduction: The Soft Tissue Sarcomas (STS) in adults are rare diseases with poor prognosis. They have a low incidence, high histologic heterogeneity and can occur at any anatomic region (extremities, trunk, retroperitoneum or the head/neck region). Standard treatment is surgery combined with radiotherapy and chemotherapy in selected cases. We reviewed patients with Soft Tissue Sarcoma treated with post-operative RT in our Istitution to evaluate acute and late toxicity post-operative Radiation Therapy.

Patients and Methods: Our experience on Soft Tissue Sarcoma of adults on about six patients treated from April 2008 to June 2012 in our Department affected by STS of the inferior limbs (4 pts) and superficial trunk (2 pts) and surgically treated.

Results: Mean tumor size was 7,5 cm (range 1,6- 12). Histological subtypes were: condrosarcoma (1), leiomyosarcoma (1), liposarcoma (1), synovial sarcoma (1), pleomorphic sarcoma (2). Four patients had G3 histologies. All patients underwent surgical removal of primary tumor and subsequent Radiotherapy. Two patients had a RO resection, two patients a R1, two patients had R0 resection with close margins. Five patients received only post-operative 3D conformal EBRT on tumor bed with 5 cm longitudinal margin and 2 cm radial margin. The total dose received was 60 Gy. Another patient received Interstitial Brachitherapy (total dose 20 Gy) and therefore EBRT (total dose 45 Gy). All patients showed G1 skin toxicity. No other acute toxicity events were recorded. At a median follow-up of 26,5 months (range 9 - 32 months), three patients (50%) developed lung metastases. No patients had local relapse. Two patients are lost at follow-up; the other four patients are alive. Only a patient showed late G2 fibrosis of the limb.

Conclusions: Post-operative Radiation Therapy in Soft Tissue Sarcoma in adults achieves excellent local control and is well tolerated. No late effects with limitation of function or quality of life were seen. However, the incidence of distant metastases is high.

P242

NEOADJUVANT RADIATION THERAPY WITH OR WITHOUT CONCOMITANT CHEMOTHERAPY IN ADULT SOFT TISSUE SARCOMAS OF THE ARMS AND TRUNK: THE EXPERIENCE OF ISTITUTO NAZIONALE TUMORI, MILAN

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Backgrounds: Soft tissue sarcomas are malignant tumors that arise in any of the mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). The goal standard is the surgery approach but the high risk of local recurrence and metastatic potential need a multidisciplinary management. There is a strong evidence that adjuvant radiation therapy improves local control (LC) rate in combination with adequate conservative surgery. A neoadjuvant approach of radiotherapy (ERT) concomitant to medical treatment (epirubicin/ifosfamide based schedule) followed with an adequate conservative surgery, seems to obtain the same results in terms of LC rate. We report on a series of primary STS of the arms and trunk treated with neoadjuvant radiation therapy with or without concomitant chemotherapy (CHT) at our institution.

Materials: We retrospectively reviewed all patients with primary localized adult-type ESTS surgically treated at our institution between 2001 and 2007 focusing on those treated with preoperative radiotherapy with or without concomitant chemotherapy. Among 114 screened patients, all of these pts underwent to ERT, 89 pts underwent to ERT+CHT. RT was started in combination with the onset of the 2nd cycle and administered up to a total dose of 50 Gy in 25 fractions. Surgery was scheduled 4 weeks after the end of RT. We evaluated the feasibility and the wound complications (WC).

Results: Twenty-six pts (24%) had perioperative WC. Five registered hematoma and hemorrhage underwent to surgical revision, two wound infections, twenty flaps-suffering. Only 3 pts didn't undergo to concomitant CHT. Our series provides preliminary evidence that preoperative ERT in high grade soft tissue sarcoma is feasible. WCs are frequent after preoperative RT and occur more commonly in patients with lower extremity tumors. The MWC rate observed in a single-institution setting was comparable to that observed in the literature.

P243

RADIOTHERAPY IN PEDIATRIC LOCALIZED NON RHABDOMYOSARCOMA SOFT TISSUE SARCOMAS: A RETROSPECTIVE SERIES FROM THE UNIVERSITY OF FLORENCE

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Aims: to evaluate outcomes of patients treated at our Institution with radiotherapy for non rhabdomyosarcoma.

Materials and Methods: 9 patients (6 males and 3 females) with non rhabdomyosarcoma soft tissue sarcomas (NRSTS) were treated between 1998 and 2011 with external beam radiotherapy. Median age at diagnosis was 13 (age<10 n=2). All the patients had histologically proven non-rhabdomyosarcoma soft tissue sarcomas. There was only a synovial sarcoma, whereas all the others were adult-type soft tissue sarcoma (fibrosarcoma n=4; malignant peripheral nerve sheath tumor (MPNST) n=3; mesechymal chondrosarcoma n=1).Two patients had Neurofibromatosis-1. The most frequent site of primary tumor was Head and Neck (non parameningeal) location, n=4; there were two cases with primary tumor in the thorax, two cases with intracranial primary and a case of pelvic disease. Four patients were enrolled in the EpSSG NRSTS 2005 protocol, whereas three patients were enrolled in previous protocols (SIOP MMT 95 n=2 and RMS 96 n=1). All patients performed conformal radiotherapy 3DCRT for a median total dose of 54 Gy (range 50.4-64.8 Gy) in conventionally fractionated treatment. Two patients received radiotherapy at relapse, whereas the others had radiotherapy at the diagnosis.

Results: With a median follow-up of 12 months (range 5.6-156.7 months), 3 patients were alive and disease free, while 6 patients were dead of disease. Median overall survival was 2.2 years (range 0.8-19.2 years). Three-year actuarial overall survival was 41.7%. Among patients who progressed, 3 had only local relapse, one had exclusive distant relapse, whereas 2 of them had both local and metastatic progressive disease.

Conclusions: Although the prognosis of NRSTS is still severe, a multimodality treatment combining surgery, radiotherapy and intensive chemotherapy is feasible and in some cases effective in this population.

TRATTAMENTI INTEGRATI NEL CARCINOMA DELLA VULVA

P244

ADJUVANT RADIATION TERAPY IN VULVAR ANCER: OUR EXPERIENCE

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Purpose and Objectives: The objectives of this study was to evaluate our experience on 18 patients with vulvar cancer, treated with adjuvant radiation therapy.

Materials and Methods: Between 2009 and 2011, 18 patients with carcinoma of the vulva diagnosis, were treated with adjuvant radiation therapy. Mean age was 66 years (range: 45 -86). All the patients were treated with radiation therapy after radical vulvectomy or haemivulvectomy. The RT was administered using photon beams with a linear accelerator. The median dose was 45Gy (range 42-46,5 Gy) administered with a conventional fractionation of 1.5-1.8 Gy/die. we have given a boost of 14-16 Gy (2 Gy/die), with electron field to primary site of tumor.

Results: The median follow-up was 16 months. 13 (72%) patients had complete remission, 3 (16%) patients had partial remission, 2 (12%) patients had progressive disease after radiation therapy. There was no treatment break for acute toxicity. Vulvar desquamation was the main acute side effect (80%), 3 patients had skin fibrosis and atrophy (17%), 1 patient had radiation ulcer (6%) and 5 patient had telangectasia (28%).

Conclusions: The adjuvant radiation therapy appears improve clinical response in patients with carcinoma of the vulva and with an acceptable toxicity profile.

P245

THE ROLE OF BRACHYTHERAPY IN THE TREATMENT OF VULVAR CANCER

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Purpose: Our purpose was to evaluate the role of brachytherapy in vulvar cancer management.

Materials and Methods: Between 2002 and 2011, 10 patients with primitive vulvar cancer and 5 with recurrent vulvar cancer were treated with interstitial brachytherapy. 9 of 10 patients after surgery (radical/partial vulvectomy alone or with unilateral/bilateral inguinal lymphadenectomy) were additionally treated using external-beam radiotherapy (EBRT) to the pelvis and regional lymphnodes, in association with chemotherapy in 4 cases. The median external-beam dose was 4560 cGy with five fractions per week, using a 6-18 Mv photon beam with additional 1600 cGy to vulva and positive lymphnodes in only

one case. Chemotherapy consisted of Cis-Carboplatin or FU and Mitomycin administered during EBRT. In 9 cases was utilized interstitial pulsed-dose-rate brachytherapy (PDR) with median total dose of 1942 cGy. In only one case was utilized interstitial high-dose-rate brachytherapy (HDR) with total dose of 1200 cGy in 4 fractions. In 5 patients with recurrent vulvar cancer, the recurrence was local in 4 cases and inguinal in 1 case. The median time between primary treatment and manifestation of recurrence was 28 months. 3 patients were had been treated with surgery and EBRT and 2 with surgery alone at time of diagnosis. The median total PDR dose administered to patient with recurrence was 3796 cGy. 1 patient was additionally treated using EBRT with a dose of 4500 cGy.

Results: The median follow up time (FU) for patients with primitive vulvar cancer was 23 months, we obtained local tumor control in 8 patients (80%); one patient was sent to surgery and she was living at FU and one patient was sent to chemotherapy and lost from FU; 7 patient were alive without disease after 23 months of FU, one patient had a progression of disease and one patient died for other cause. The FU for patients with recurrent vulvar cancer was 29 months, we obtained local tumor control in 3 patients (60%), one patient was sent to surgery for residue of disease and 3 patients had recurrent disease after a median time from brachytherapy of 17 months.

Conclusions: interstitial brachytherapy achieved good local control and its role is important for the treatment of primary vulvar cancer, especially for those sites where is difficult obtained radical of surgery and in recurrent diseases for patients treated yet, no candidated to radiotherapy or surgery.

P246
RADIATION THERAPY FOR VULVAR CARCINOMA: TEN YEARS EXPERIENCE

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Aims: Vulvar carcinoma is an uncommon gynecological malignancy afflicting elderly women with growing incidence over the last decades. Treatment includes surgery, radiotherapy or radiochemotherapy for advanced disease. Due to lack of a multisciplinary dedicated team and few randomised trials, the treatment of locally advanced vulvar cancer (FIGO stage III and IV) remain controversial; advanced vulvar cancer comes often to our observation after an unappropriate surgery. We report a retrospective analysis of our patients (pts) treated for vulvar cancer.

Materials and Methods: Between 2002 to 2011, we evaluated 22 pts affected by vulvar cancer; mean age was 75 years (49-84), IK ≥ 70 (60-100). All patient had a histologically confirmed cancer (21 squamous carcinoma and 1 adenocarcinoma) and were treated with radiotherapy. Patients were classified in two groups according to treatment intent: group A, 5 pts treated with radical radiotherapy; group B, 17 pts treated with postoperative radiotherapy. In the group A, 3 pts had FIGO stage IVa and 2 pts FIGO stage II. In the group B, 13 pts were classified as FIGO stage IIIa-IVa and 4 pts as FIGO stage Ib-II.

Results: In the A group one patient received radiochemotherapy with a 5-FU and cisplatin and hyperfractionated (1.7 Gy twice daily) split course RT; chemotherapy was discontinued after the first cycle due to myelotoxicity. The remaining 4 pts received conventionally fractionationated radiotherapy (1.8-2 Gy/die). One pts stopped radiation at the dose of 34 Gy for progressive worsening of PS. The remaining 3 pts received a dose between 45 and 62 Gy. PTV included small pelvis with perineum and groins in 4 patients; in one stage II pt PTV included the perineum as site of the primary tumor target. In the B group 15 patients underwent to radical vulvectomy and 2 pts to partial vulvectomy; adequate inguinal nodes dissection was recorded in 13/15 pts. Postoperative radiotherapy was delivered to 15/17 pts; 2 stage IIIa-IV pts previously treated with vulvectomy and bilateral lymphadenectomy were excluded because PS and disease worsening after completion of set-up procedures for RT. Post operative radiotherapy for palliation was delivered to 2/15 pts on groins or perineum with a mean total dose of 35 Gy (30-40 Gy). The other 13 pts received a dose of 50 Gy plus a 10 Gy boost for positive surgical margins (R1) in 2 pts. PTV consisted of whole pelvis and groins in 2 pts with pN2 stage; small pelvis and groins in 13 pts. After 6 months follow-up at least, 9/20 pts showed progression for local disease or local lymph node metastases and 3 patients had also para-aortic lymph node and liver metastasis. After local recurrence 1 pt had a savage surgery. Thirteen patients died, 2 due to non-neoplastic cause.

Conclusions: Vulvar cancer has generally poor prognosis. For early stage radiation certainly plays an adjuvant role. For advanced stage radiotherapy alone or in combination with chemotheraoy can be proposed as neoadjuvant, adjuvant, or exclusive treatment. It is necessary to establish common guidelines for practicing rational therapeutic decisions and refer pts to a dedicated multidisciplinary team to avoid unnecessary toxicity and therapeutic problems related to waiting times at our centers.

P247
RADIATION THERAPY IN THE TREATMENT OF VULVAR CANCER: ACUTE TOXICITY AND RESULTS

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Purpose: Vulvar cancer is a relatively rare gynecological malignancy afflicting elderly women. Although radiation therapy plays an important role, due to limited literature, treatment guidelines are less clearly defined. The management of early disease is based on surgery, performing local radical excision and, in case the sentinel node is positive, proceeding to groin dissection. For advanced

disease, surgery combined with radiotherapy or chemoradiation is the most widely used approach.

Materials and Methods: From May 2009 to May 2012, we retrieved the case of 4 patients who were treated at our Center of Barletta. From each case record, we extracted the information regarding clinical details diagnosis, tratment given, survival and complications. Computed tomography (CT)/ magnetic resonance imaging scan (MRI) of the abdominal pelvic region and cysto-sigmoidoscopy were done, if necessary staging was done according to FIGO system. The treatment options contemplated were: wide local excision with or without inguinal node dissection; radical vulvectomy with inguinal node dissection; definitive RT for patients not suitable for surgery. The dose of RT for microscopic disease was 45-50 Gy and for gross disease was 60 Gy with conventional fractionation (1.8-2.0 Gy per fraction, 5 day a week). Two asymmetric AP-PA and two angle fields were used on 6-15 MV linear accelerator. Electrons were used for boosting the inguinal node region. Follow up was done every 3 months till 1 year. At every visit, clinical examination was performed and if necessary CT/MRI scans, to assess the disease status. The overall survival (OS) was calculated by Kaplan Meier survival method. Acute morbidity was assessed as per the Radiation Therapy Oncology Group (RTOG) criteria.

Results: At a median follow up of 27.2 months a total of 4 case records were retrieved for this analysis. Age ranged from 73 to 83 years with a median of 80 years. All patients had advanced disease (stage III-IV). 3 patients underwent surgery and 1 patient received definitive RT. Treatment related grade 3-4 toxicity included fatigue in 1 patients and skin toxicity in 3 patient. Actually 3 patients are NED, while 1 patients is in progression.

Conclusions: Stage of the disease and pathological node positivity were founded to be significant prognostic factors for survival. The toxicity was accettable and all patients have terminated the treatment.

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VULVAR CANCER TREATMENT USING VMAT FOR INTENSITY MODULATED RADIATION THERAPY IN OUR PRELIMINARY EXPERIENCE

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Purpose: Vulvar cancer is a relatively rare gynecological malignancy afflicting elderly women. Surgery is the most common treatment for cancer of the vulva. The goal of surgery is to remove all the cancer without any loss of the woman's sexual function. Although radiation therapy plays an important role, due to limited literature, treatment guidelines are less clearly defined. For early-stage vulvar cancer, radiation therapy continues to play an adjuvant role. For locally advanced vulvar cancer (LAVC), the concurrent chemoradiotherapy CCRT has emerged as a new feasible option both as preoperative and definitive treatment. Future CCRT trials should incorporate newer radiation therapy techniques like intensity-modulated radiation therapy to further reduce the radiation-related morbidity thus enhancing the tolerance of CCRT. We evaluated a regimen of radiationtherapy only as an alternative for those elderly patients in whom the location and extent of advanced vulvar carcinoma make pelvic exenteration the only surgical option.

Methods: Between December 2009 and March 2011, 3 patients with primary squamous carcinoma of the vulva who were not candidates for standard radical vulvectomy were treated with radiation therapy at the V.Fazzi Hospital. The mean age was 80 years. Tumors were stage III in 2 patients and stage IV in 1 patients. For those treatments, we used VMAT® (Volumetric Modulated Arc Therapy), a novel rotational Intensity Modulated RadioTherapy (IMRT). Total radiation doses to CTV 1, defined as tumor location, vulva and positive groings, ranged from 66 Gy (2,2 Gy/die), with doses of 54 Gy (1,8Gy/die) to CTV2, including pelvic and inguinal nodal regions as areas at risk for subclinical disease.

Results: Acute complications included desquamation requiring treatment interruptions in 1 patient, grade 2 cystitis, urinary urgency and acute Grade 2 rectal toxicity during the treatment. There was a clinical complete responses in all patients, with mean survival of 15 months, range 28-14. Surgical excision of the primary site was not performed.

Conclusions: There is a continuing scarcity of prospective and randomized controlled trials due to rarity of vulvar cancer. Most studies in the recent literature are largely retrospective in nature. However, it is evident from the available literature that combined chemoradiotherapy is slowly evolving as a new option in the management of LAVC reducing surgery-related morbidity. Various trials have tested the feasibility of CCRT using different chemotherapeutic agents like cisplatin, 5-fluorouracil, mitomycin-C and have shown encouraging results. In our experience, the radiation with VMAT was found to be effective therapy for locally advanced vulvar carcinoma, with acceptable morbidity even in an elderly population.

P249

THE ROLE OF RADIOTHERAPY IN MYXOID LIPOSARCOMA OF THE VULVA WITH SURGICAL POSITIVE MARGINS. CASE REPORT

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Purpose: Myxoid liposarcoma is a sarcoma arising generally from soft tissues of the limbs or more rarely from the trunk or head and neck, in individuals affected from specific chromosomic translocations t(12;16) or t(12;22). This group of tumors has a good prognosis when surgery has adequate margins, but it is debated when surgical margins are positive, particularly if a round cell component is evident at the histological speciment. The purpose of the case report is to investigate the role of the postope-

rative radiotherapy in the local control of the vulvar mixoid liposarcoma not radically excised.

Methods: We present the rare case of a 38-year-old woman with a large tumor of the vulva, who underwent marginal resection in october 2008. Tumor diameter was 7.5 x 5.4 x 3.0 cm. The histological exam showed a myxoid liposarcoma with a component of round cells, without mithotic figures or necrosis. Neoplastic cells were found in one resection margin. The cytogenetic analysis from periferal blood showed the presence of a robertsonian translocation t(14;22)(q10;q10). The patient was treated postoperatively with conformal radiotherapy on the entire vulva, using four orthogonal fields of 15 MV photon beams, to a total dose of 50 Gy (2 Gy die). Subsequently a boost on the tumor bed with a 12 MeV electron beam to a dose of 16 Gy (2 Gy die) was performed.

Results: During the treatment the woman reported pain in the irradiated area, with an objectiveness of edema, erithema and desquamation (RTOG Grade 2 acute toxicity score). Currently the patient has no evidence of disease, with a follow up of 39 months and no relevant late toxicity. Esthetical results are considered satisfactory by the patient.

Conclusions: Radiotherapy seems to have been effective in reducing the risk of local recurrence in this case of myxoid liposarcoma of the vulva with positive surgical margins.

P250
VULVAR CANCER: OUR EXPERIENCE AND CLINICAL RESULTS

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Purpose: We retrospectively evaluated 18 patients affected by vulvar cancer who underwent RT in our Department from 2005 to 2012.

Materials and Methods: We treated 18 patients (pts): 12 of them underwent adjuvant RT because of positive margins, incomplete resection or nodal spread; 6 pts received definitive RT. Sixteen pts had squamous cell carcinoma, G1 (22.2%), G2 (44.4%) and G3 (22.2%); 2 pts had extramammary Paget's disease. Six pts, median age 78.6 years received definitive RT: 1 cT1N1, 3 cT2N0 and 2 cT2N1. All these pts were evaluated as unfit for radical surgery. Twelve pts, median age 70.16 years received adjuvant RT: 6 pT2N0, 2 pT2N1, 2 pT2N2a, 2 pTisN0. Regarding to surgical treatment, all pts were treated with vulvectomy and pelvic and bilateral lymphadenectomy except one pt who received vulvectomy and local excision of 1 positive lymphnode. Positive margins were reported in 4 cases with *in situ* carcinoma requiring adjuvant RT. The median number of dissected lymphnodes was 18 with only 4 positive lymphonodes in 1 case. In four cases there was extranodal spread requiring adjuvant RT. Regarding to the radiation technique, all the patients were treated in supine position up to 45 Gy, 1.8 Gy/daily, including primary site of tumor and regional lymphnodes; primary site received a boost delivered in the "frog leg position" up to 54-60 Gy in the postoperative setting and 54-66 in the definitive RT.

Results: The median FU was 28.5 months. The group of pts who underwent definitive RT had a one-year overall survival (OS) of 100% but 4 of them (66.6%) had a relapse during the first year of FU and underwent salvage surgery. Only 2 pts reached a two-year OS and died of other causes. The 12 pts who had adjuvant RT had a two-year OS of 66.6%: 4 of them needed salvage surgery. Regarding to toxicities, the most treatment-limiting factor was G3 skin toxicity that in 2 cases caused definitive stop of RT and the need of interstitial brachytherapy boost. Other acute toxicities were: cystitis in 8 patients (44.4%), proctitis in 17 patients (94.4%) and diarrhoea in 6 patients (33.3%). Late toxicities included vaginal stenosis in 7 pts (38.8%), vulvar telangiectasia in 3 pts (16.6%) and 5 cases of leg oedema (27.7%).

Conclusions: In locally advanced vulvar carcinoma cases, or in case of incomplete radical surgery, RT offers a valid alternative of treatment although healing chances remain poor.

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RADIOBIOLOGY: CLINICAL CONSIDERATIONS AND MODELLING FOR EVALUATION OF THE RADIATION-INDUCED TOXICITY AND CANCER RISK USING DIFFERENT TECHNIQUES

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Backgrounds and Purpose: We analyzed the normal tissue sparing possibility of 4 different irradiation techniques for Hodgkin lymphoma (HL) and the technique dependence of second cancer using mathematic model.

Materials and Methods: Planning CT scans from one representative female patient with supra diaphragmatic Hodgkin lymphoma were selected and three different planning target volumes (PTVi) scenarios from small to medium and large volumes were prepared. Four conformal plans were simulated for each PTVi scenario: 2 opposed fields (AP-PA), an inverse intensity modulated plan (IMRT), a forward intensity modulated plan (FIMRT) and a helical tomotherapy plan (TOMO). A total dose of 30 Gy was considered. In order to compare plans, dose-volume histograms (DVHs) of PTVi, lung, whole-heart, heart chambers, breast, and thyroid were calculated. Dose-volume constrains for the organs at risk were assessed according to QUANTEC recommendations. Second cancer risk for breast, thyroid, and lung was estimated using the Organ Equivalent Dose (OED) model. All plans were equally optimized in terms of PTV coverage.

Results: All the scenarios (PTVi) had the same coverage level. In PTV1 and PTV2 scenarios all plans respected the dose-volume constraints, but only TOMO plan was able to reduce whole-heart V25 under 10%. In PTV3 scenario AP-PA, FIMRT, and IMRT plans exceeded whole-heart V25, left atrium V25 and thyroid V30 limits. Only TOMO plan was compliant with all constraints. The risk for breast, thyroid, and lung radiation-induced cancer increased in all scenarios, when using the IMRT and TOMO technique compared with AP-PA and FIMRT technique. The relative risk rate of second breast cancer was the most relevant entity as well as the excess absolute risk.

Conclusions: Considering patient features, co-morbidity and PTV size, advanced radiation techniques can be successfully used in HL patients to better spare organs at risk. Improving the acceptance of treatment and minimizing toxicity should lead to even greater appropriate use in order to improve the outcomes. The estimated increased risk of secondary cancers due to the increased integral dose inherent to TOMO and IMRT techniques should be considered. We found an elevated risk of developing second breast cancer. Further study is warranted in order to establish the clinical relevance of our findings.

RADIOBIOLOGIA CLINICA: IMPOSTAZIONE MECCANICISTICA BIO-MOLECOLARE O MODELLISTA?

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APPLICATION OF A MECHANISTIC MODEL OF RADIATION-INDUCED CANCER FOR HODGKIN'S LYMPHOMA RADIATION TREATMENT TECHNIQUES COMPARISON

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Purpose: To analyze normal tissue sparing capability of different radiotherapy (RT) techniques for Hodgkin's lymphoma (HL), in particular to clarify the trade-offs between radio-induced toxicities and second cancer induction risk.

Materials and Methods: Three different size planning target volume (PTVi) scenarios from a planning CT scan of a representative female patient with supradiaphragmatic HL were generated. Five plans were simulated for each PTVi: a conventional parallel-opposed (AP-PA) plan, a forward intensity modulated plan (FIMRT), an inverse intensity modulated plan (IMRT), a Tomotherapy plan (TOMO), a proton plan (PRO). A radiation dose of 30 Gy or cobalt gray equivalent (CGE) was prescribed. Dose-volume histograms of PTVs and organs at risk (OARs) were calculated and related to available dose-volume constraints (DVCs). Second malignant neoplasm (SMN) risk for breasts, thyroid, and lungs was estimated through the Organ Equivalent Dose (OED) model.

Results: With similar level of PTVi coverage, for PTV1 and PTV2 scenarios the DVCs were respected by all plans except for whole-heart-V25 for which only TOMO and PRO plans were able to reduce it under 10%. In PTV3 scenario AP-PA, only TOMO and PRO plans were compliant with all constraints. In all scenarios, the IMRT and TOMO increased the risk of development of breast, thyroid, and lung SMNs compared with AP-PA technique. Only PRO plans succeeded in reducing the risk of predicted SMN compared with AP-PA technique (Figure 1).

Conclusions: Advanced RT techniques can be successfully used in HL patients to better spare OARs. However, it must be carefully considered the estimated increased SMN risk due to the increased integral dose inherent to TOMO and IMRT techniques.

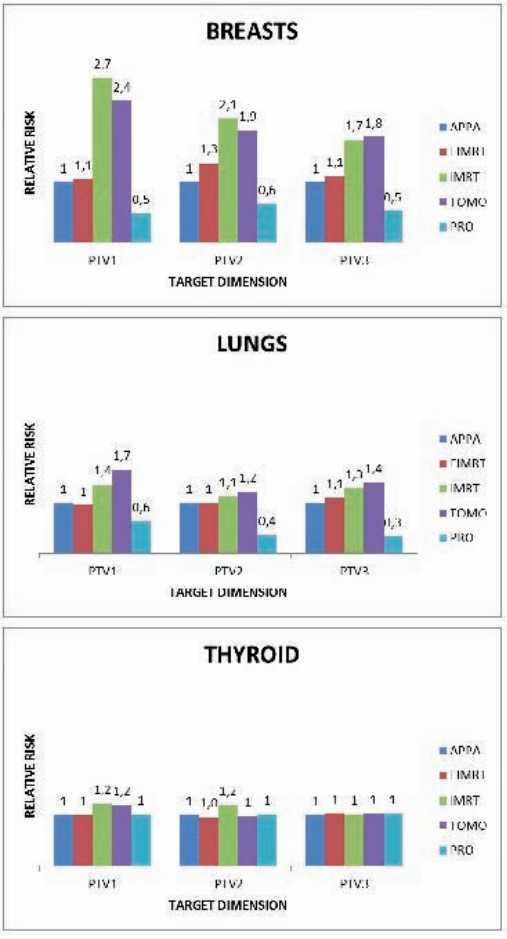

Figure 1.

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CAN DOSE INTENSIFICATION IMPROVE THE OUTCOME IN SBRT?

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Purpose: To demonstrate whether increasing the dose per fraction can improve local control on metastatic liver lesions.

Patients and Methods: We analyzed data on 244 patients with 412 hepatic lesions, treated with stereotactic body radiotherapy. The dose was prescribed to an isodose of 100% at the edge of the PTV with a non-uniform distribution in its interior. The nominal dose was increased from 21 Gy to 56 Gy. The effective biological dose in fractions of 2 Gy (BED2) was calculated using the formula of the linear quadratic model (LQ): BED = D [1 + d (alpha/beta)].

Results: Fourteen patients had disease progression within the PTV, with a median time to local recurrence of three hundred and fifty days and were so considered as local failures. Seven were subjected to a second treatment, one patient has been retreated twice and six patients performed other therapies. Among the fourteen patients who had local progression, the variables considered (histology, BED, previous therapy *vs* only SBRT, diameter of the lesion, dose/fraction, total dose) were not statistically significant in influencing local control of the disease. However, a careful analysis of retrospective data demonstrated that in the seven patients who underwent a second radiation treatment, not one had a second local failure and the median overall survival for these patients was found to be 1033 days. Assuming a ratio alpha/beta for liver metastases in 10/11 Gy, the BED2 in our experience ranged from 28 Gy to 108 Gy.

Conclusions: The improved local control of re-irradiated lesions suggests that there is a dose-effect relationship as shown in several published studies in literature. Hence the need for further studies in radiation biology and molecular biology to determine which cell lines are able to benefit from an increase in dose per fraction possibly in association with chemotherapy to improve local control and ultimately overall survival. Despite the limitations of the linear quadratic model, in fact, the ratio alpha/beta of 10 Gy single doses does not represent the full heterogeneity of cell lines treated.

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RADIOSENSITIZING EFFECT OF ROSIGLITAZONE IN HEAD-NECK CARCINOMA AND PROTECTION IN RADIATION-INDUCED MUCOSITIS

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Aims: Rosiglitazone (RGZ) is a peroxisome proliferator activated receptor (PPAR)gamma agonist with anti-inflammatory, antifibrotic and antineoplastic properties; thus it is an optimal agent to investigate in association with irradiation (IR). The first aim of the study was to evaluate RGZ radioprotective effect in a mouse model of radiation-induced oral mucositis. The second aim was to assess RGZ effect on the irradiated tumour in a xenograft model of head-neck carcinoma in mice.

Materials and Methods: Radiation-induced oral mucositis: C57BL/6J mice oral region was irradiated with a 16.5 Gy single dose. Half of the mice was treated with RGZ (5mg/Kg/day) started 24h before IR. Mucosal reactions were scored every day using the Parkins scoring system (Parkins et al, 1983). Mice were sacrificed 12/23 days after IR and oral mucosal segments collected for histological/molecular analysis. Tumour xenograft: Hep-2 (human pharynx carcinoma) tumour xenograft was obtained by s.c. injection of 6 million cells in CD1-nude mice flank. When tumour diameter reached 7 mm, mice were divided in 4 groups: IR (15 Gy); IR+RGZ (started 24h before IR); RGZ; controls. Tumour response was defined as the relative change in tumour volume *vs*. volume before therapy. Tumour volume was measured for 40 days by the formula (length x width2)/2, then tumours were collected for analysis.

Results: Mucositis: After IR mice showed typical features of oral mucositis, such as oedema and reddening, reaching the peak of damage (exudate, crusting) after 12-15 days. RGZ markedly reduced visible signs of mucositis and significantly reduced the peak, as evaluated by Parkins score. Histology showed the presence of an inflammatory cell infiltrate after IR; RGZ markedly reduced infiltration. RGZ treatment significantly inhibited radiation-induced TNFalpha, IL-6 and IL-1beta gene expression. Tumour xenograft: IR and RGZ significantly reduced tumour volume *vs*. control from the 2nd day after IR. The IR+RGZ-treated mice showed an even higher decrease in tumour volume, reaching the statistical significance *vs*. the two treatments alone after 15 days.

Conclusions: This study shows that RGZ exerts a protective action on normal tissues in radiation-induced mucositis. At the same time we confirmed RGZ antineoplastic properties and demonstrated its radiosensitizing effect in an head-neck carcinoma xenograft model. Thus, RGZ could be further investigated in head-neck cancer both as radioprotective and radiosensitizer agent.

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RADIATION-INDUCED BYSTANDER EFFECT IN PROSTATE ADENOCARCINOMA CELLS

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Radiation-induced bystander effect (RIBE) is the phenomenon in which the non-irradiated cells demonstrate the effects of radiobiological damage as a result of signals received by the irradiated adjacent or distant cells.

Materials and Methods: This is *in vitro* experimental study on two human prostate ADC cell lines of different grade of differentiation: hormone-resistant PC3 line, and hormone-sensitive DU145 line. We proceeded to irradiation of the cells using a linear accelerator in a single fraction with 7 different doses. The radiation "conditioned" medium was collected after 48 hours by the irradiation itself for the formation of the supernatant which was used as a stimulus to induce RIBE in non-irradiated cells. Results were analyzed using spectrophotometer for a quantitative assessment of cell growth. Each "stimulus" conditioned by different dose of radiation has been evaluated for the presence of following 11 cytokines. After irradiation, the cells were monitored daily for the evaluation of the radiobiological damage up to verification of the death of the entire cell population.

Results: Both cell lines were able to induce RIBE and to respond to the same effect (auto/paracrine effect). The RIBE has been anti-proliferative and was obtained with all doses of radiation used in this study for both cell lines. The intensity of this effect is varied according to the dose and the grade of cellular differentiation. While the most effective dose inducing RIBE for the PC-3 was very high, of about 20 Gy, for the DU-145 the strongest proliferative block was obtained after exposure of cells to a ultra-low dose, of 15 cGy. After irradiation of the PC-3, the concentrations of 7 cytokines were significantly increased compared to control (MIP-1-a, TNF-a, VEGF, IL-6, IL-8, Eotaxin and IFN-g ($p < 0.05$)) and for the DU-145, 3 different cytokines reached significant increase in the concentration compared to control: IL-6, IL-8 and TNF-a ($p<0.05$). While the hormone-sensitive DU-145 line was found to be more radio-sensitive and the lethal dose is reached after exposure to 25Gy, for the PC-3 the lethal dose is reached after exposure to 40 Gy.

Conclusions: The effects of the inter-cellular communication in response to radiation may have important clinical implications to improve the effectiveness of radiation treatment especially as it could potentially go to "hit" microscopic, not evident regional disease and therefore not integrable in the field of radiation treatment.