La Radioterapia palliativa con tecniche speciali della malattia metastatica

Colonna: Integrazione radioterapia e terapia con difosfonati

V. Donato

Radioterapia Oncologica

Ospedale San Camillo

Forlanini

Roma

Terni 21 giugno 2013

Finalità della radioterapia sintomatica in medicina palliativa

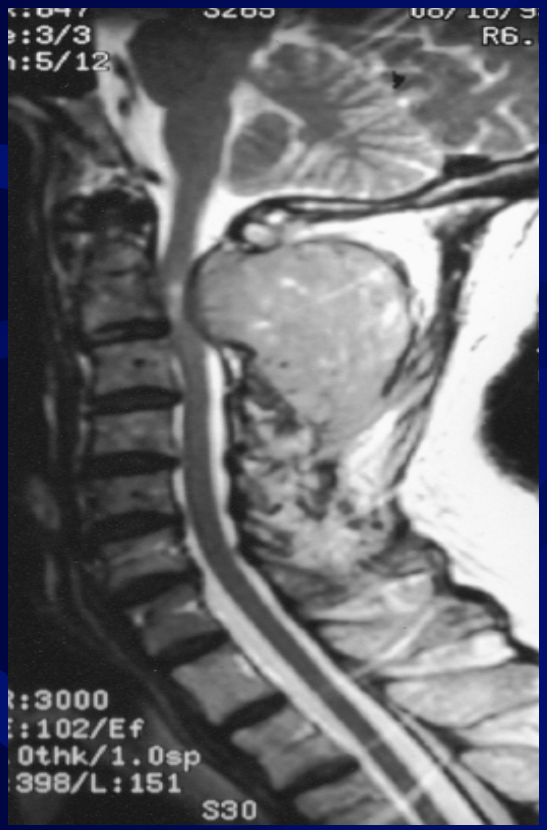
Intervento terapeutico destinato a :

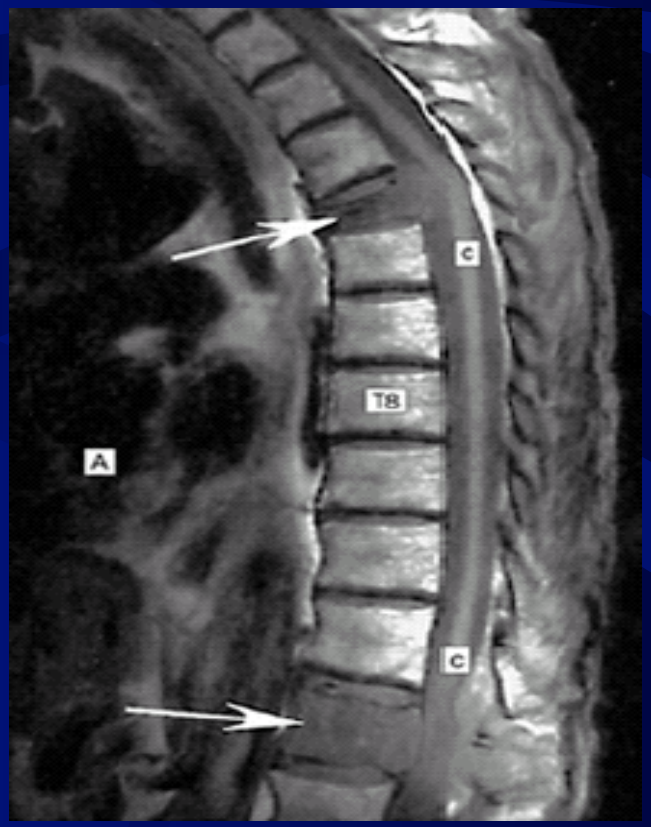
- alleviare i sintomi della malattia
- migliorare la qualità della vita.
- prevenire peggioramento della qualità di vita

Fondamentale è il controllo della sofferenza globale (effetto antalgico sul dolore: *fisico*, psicologico, sociale, esistenziale)

Indicazione principale della radioterapia in medicina palliativa: dolore osseo

Dolore e compressione midollare





Razionale radiobiologico della radioterapia nel trattamento delle metastasi ossee osteolitiche

effetto antalgico:

a) da inibizione della secrezione locale di mediatori chimici algogeni (Garrett IR. Semin Oncol 20:4-9,1993)

b) aumento della risposta intracellulare mediata da enzimi lisosomiali ad azione antiedemigena > *miglioramento della cenestesi*

effetto riparativo:

dovuto alla degenerazione e successiva necrosi delle cellule neoplastiche>

proliferazione collagene e formazione stroma fino alla calcificazione per attivazione osteoblastica > *riparazione ossea*

La radioterapia sintomatica in medicina palliativa

- Il risultato atteso deve essere superiore al costo biologico del trattamento (minimi effetti collaterali)
- La durata del trattamento deve comportare la minore interferenza sulla possibile autonomia e vita di relazione del paziente
- Attualmente indicati tre tipi di frazionamento “short course” 8Gy (1fr), 4Gy x 5 fr, 3Gy x 10 fr o altro… In presenza di malattia controllata e paziente in “buone” condizioni

V. Donato: radioterapia sintomatica

-Radiotherapy in the symptomatic treatment of the oncological patients. Anticancer Research 19: 3375-3382 (1999)

-Radiation therapy for oncological emergencies. Anticancer Research 21: 2219-2224 (2001)

-Short course radiation therapy for elderly cancer patients. Critical Reviews in Oncology/Hematology 45: 305-311 (2003)

-Hypofractionated radiotherapy. Cancer Futures vol:2 202-206 (2003)

“The proposal of treating patients with a single 8 Gy fraction radiotherapy, performing all the procedures in same day, is giving very good results in terms of pain relief, quality of life improvement and patient clinical management”

Rapid Palliative Radiotherapy Unit: multidisciplinary management of bone metastases

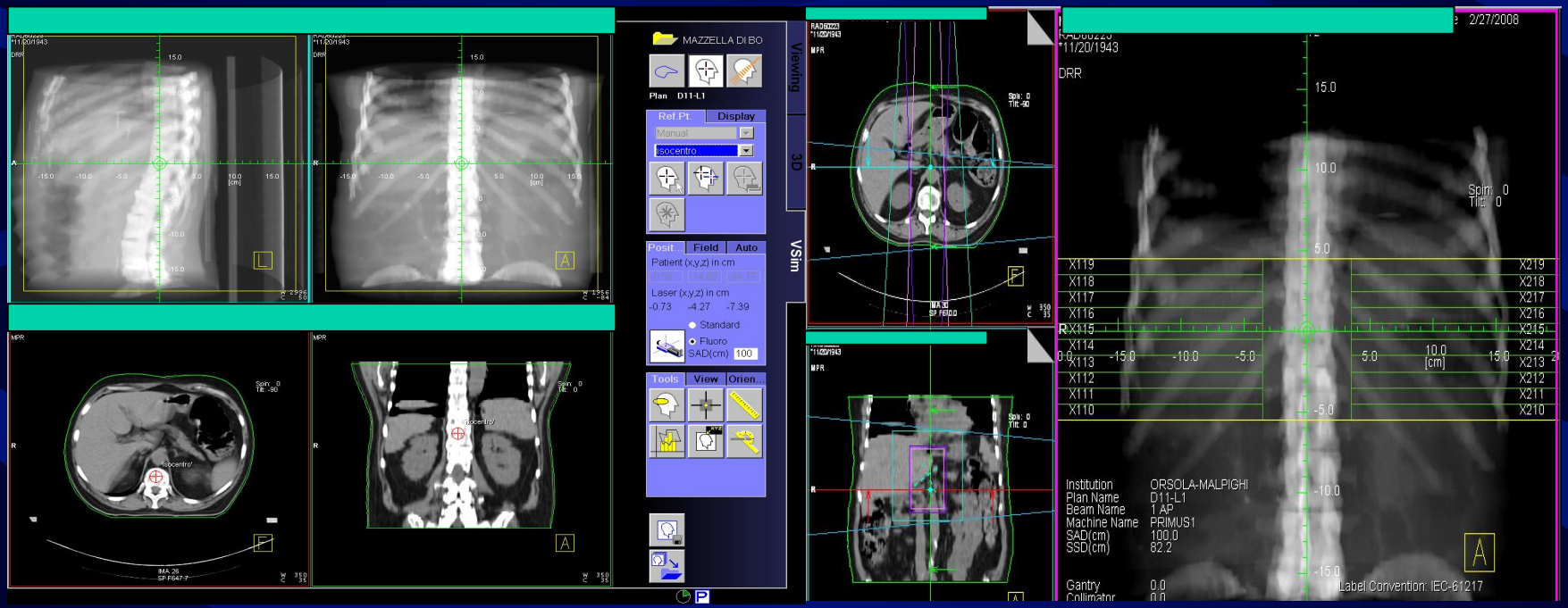
V. Donato, M. Cianciulli, M. Crescenzi, A. Monaco, C. Caruso, A.Morrone

La Radiologia Medica 2012 Vol 117, N.6, pp.1071-1079

Tecnica radioterapica in medicina palliativa

Campi diretti e obliqui con simulazione virtuale esecutiva.

A pari efficacia preferire il trattamento piu' semplice



2719 **Dosimetric Comparison of Two-Dimensional (2D) vs. Three-Dimensional (3D) Planning for Bone Metastases**

A. E. Potter, M. Holwell, D. Fitzpatrick, A. Bezjak, M. McLean, W. Levin, R. Dinniwell, L. Zurawel-Balaura, R. Wong

Department of Radiation Oncology, Princess Margaret Hospital/University Health Network and University of Toronto, Toronto, ON, Canada

Purpose/Objective(s): 2D field based planning remains standard practice in many radiotherapy (RT) centres for treatment of bone metastases. Even if simple plans (non conformal/non IMRT) remain the preferred technique, 3D CT based planning can improve target localization, dose coverage of targets and sparing of normal tissue. We prospectively evaluated the dosimetric impact of 2D field based vs 3D volume based RT planning for bone metastases.

Materials/Methods: Patients undergoing palliative RT for bone metastases suitable for 1-2 beam techniques were enrolled. The study oncologist performed three sequential tasks on each case. First, after reviewing clinical details and diagnostic images, the intended GTV, PTV and RT technique were recorded. Second, using digitally reconstructed radiographs, treatment fields were placed to create a 2D plan for study use only. Third, the full 3D CT dataset was reviewed and the GTV and PTV were defined. Changes to the final GTV and the reasoning were recorded. A 3D plan was created using ≤3 non-IMRT beams to cover the final PTV with 95% while minimizing normal tissue dose. Dosimetric indices were calculated for 2D and 3D plans with 95% as the reference isodose (RI). Two indices assessed target coverage: the proportion of PTV covered by RI (PTV conformity factor: PTVCF), and the ratio of minimum isodose covering PTV to RI (RTOG quality of coverage: QC). Two indices compared dose to normal tissues: the healthy tissue volume covered by RI as a proportion of PTV (healthy tissue overdosage factor: HTOF) and the ratio of PTV to total volume covered by RI (healthy tissue conformity index: CIHT). Two sided *t* tests were used to compare means for each index.

Results: 51 patients receiving RT to 57 bone sites provided data. 29/57 (50.9%) cases received treatment to the spine. 38/57 had diagnostic CT and/or MRI scans available for review. After evaluating the full planning CT dataset, oncologists documented changes in fields and/or PTV in 31/57 (54.4%) cases, due to local disease extent in 22/31 (71.0%) and clinically important distant disease in others. The study 2D plans used single fields in 17/57 and parallel pairs in 40/57, compared to the final 3D plans which used fewer single fields (6/57), more parallel pairs (50/57) and one 3-field technique. PTV coverage in 3D plans was superior to 2D plans as measured by mean QC (88% vs 46%, $p<0.001$) and mean PTVCF (93% vs 77%, $p<0.001$). 3D plans improved healthy tissue sparing compared to 2D plans, with mean HTOF 2.56 vs 4.89 ($p = 0.112$) and mean CIHT 0.34 vs 0.25 ($p<0.01$).

Conclusions: 3D planning for RT to bone metastases resulted in more plans with ≥2 fields compared to 2D field based plans. 3D plans provided superior PTV coverage and improved healthy tissue sparing. The clinical impact of 3D planning in this setting requires further investigation.

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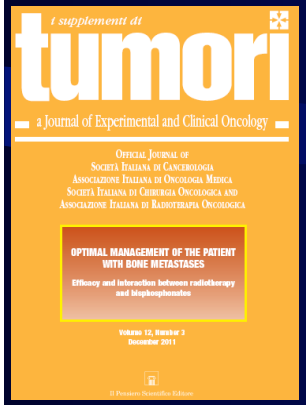


i supplementi di Tumori, vol. 12, No 3: S7-S11, 2011

Integrating radiation therapy and bisphosphonates

Giovanni Mandoliti[1], Sara Ramella[2], Paolo Muto[3], Roberto Orecchia[4], Lucio Trodella[2]

[1]Radioterapia Oncologica, Ospedale Santa Maria della Misericordia, Rovigo; [2]Radioterapia Oncologica, Università Campus Bio-Medico, Roma; [3]Radioterapia Oncologica, Istituto Nazionale Tumori Fondazione Pascale, Napoli; [4]Radioterapia Oncologica, Istituto Europeo di Oncologia, Milano

Abstract. Radiotherapy is a well established treatment for metastatic bone pain and bisphosphonates have been shown to reduce morbidity from bone metastases. Moreover, in preclinical experiences bisphosphonates have been shown to have synergistic effects with radiation. So, a combination therapy of radiotherapy and these drugs might thus be expected to be even more effective than either treatment alone. Several distinct mechanisms for the interaction with radiation have been described. Both prolonged G2/M accumulation and Ras signaling blockade may be associated with the cellular mechanisms of radiosensitization produced by bisphosphonates in tumor cells. In vitro and in vivo studies results are impressive and novel in cancer medicine, because this therapeutic intervention is easily applicable in the clinical setting. Clinical experiences confirm that patients treated with bisphosphonates and radiation therapy had a statistically significant higher objective response, showing evidence of calcification of their osteolytic bone metastases. In conclusion, all these data suggest that it is important for a radiation oncologist to know if a patient is taking or has been treated previously with bisphosphonates because the treatment response might be accelerated. So, a correct multidisciplinary approach should be a fundamental aspect in clinical practice to enhance bone lesion response and, consequentially, to optimize patient outcome.

APPROCCIO INTEGRATO

APPROCIO INTEGRATO
Razionale

Acido zoledronico

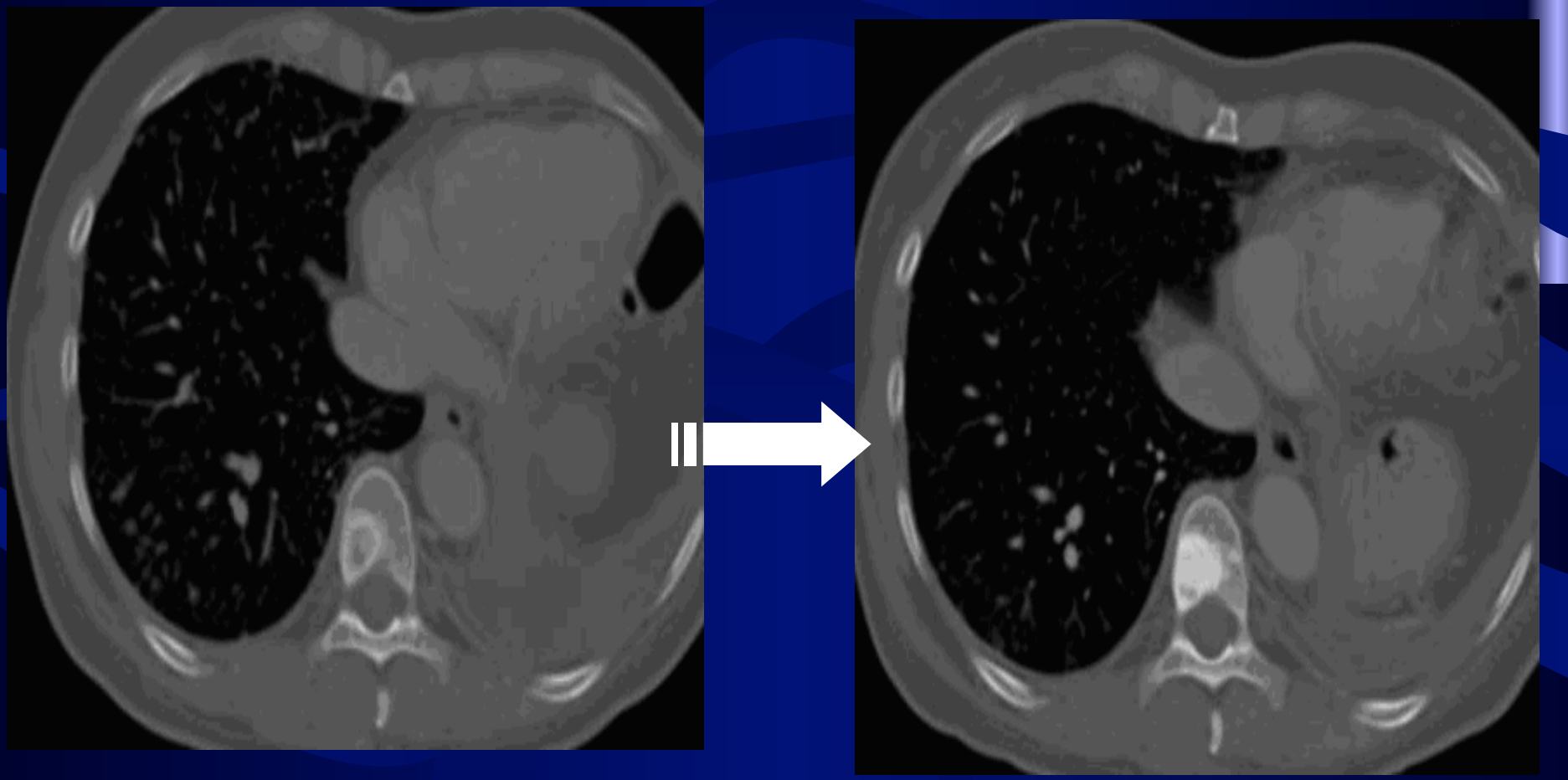
- Inibisce la maturazione degli osteoclasti
- Induce l'apoptosi degli osteoclasti maturi
- Inibisce l'adesione all'osso delle cellule tumorali
- Inibisce la proliferazione delle cellule tumorali
- Mostra effetti inibitori sulle metastasi ossee

Radioterapia

- Effetto citocida sulle cellule neoplastiche
- Apoptosi delle cellule sane radiosensibili con inibizione dei mediatori chimici e riduzione della stimolazione degli osteoclasti

I dati disponibili in letteratura suggeriscono che il trattamento CONCOMITANTE sia più efficace in termini di aumento della densità ossea

RT + BISFOSFONATI



Riflessioni sulla radioterapia sintomatica in sede ossea

- "… Evidence suggests that the reluctance of radiation oncologists to provide single-fraction treatment acts as a barrier to referrals from palliative care professionals."

- "… Shorter courses exemplify common sense end-of- life, especially because most patients who are treated for symptom palliation will not survive to face the increased risk of long-term side effects associated with hypofractionated regimens."

Lutz, et al, Cancer 2007

Concetto di Palliazione e Radioterapia Evoluta

La nozione che la "**palliazione**" vada oltre al controllo dei sintomi , in pazienti selezionati ove la malattia metastatica ossea possa influenzare la sopravvivenza

Dalla radioterapia sintomatica alla radioterapia palliativa

Pazienti in cui il controllo di malattia potrebbe andare oltre la qualità della vita

Utilizzo di sempre più diffuso **di tecniche ad alta conformazione del fascio** (soprattutto la **RT stereotassica)** anche nel paziente metastatico

La maggiore diffusione nella pratica clinica della **re-irradiazione** delle metastasi

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 965–976, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.11.026

ASTRO GUIDELINE

PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE

Stephen Lutz, M.D.,* Lawrence Berk, M.D., Ph.D.,† Eric Chang, M.D.,‡ Edward Chow, M.B.B.S.,§ Carol Hahn, M.D.,¶ Peter Hoskin, M.D.,‖ David Howell, M.D.,# Andre Konski, M.D.,** Lisa Kachnic, M.D.,†† Simon Lo, M.B., Ch.B.,‡‡ Arjun Sahgal, M.D.,§§ Larry Silverman, M.D.,¶¶ Charles von Gunten, M.D., Ph.D., F.A.C.P.,‖‖ Ehud Mendel, M.D., F.A.C.S.,## Andrew Vassil, M.D.,*** Deborah Watkins Bruner, R.N., Ph.D.,††† and William Hartsell, M.D.‡‡‡

*Department of Radiation Oncology, Blanchard Valley Regional Cancer Center, Findlay, OH; †Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL; ‡Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX; §Department of Radiation Oncology, Sunnybrook Odette Cancer Center, University of Toronto, Toronto, ON, Canada; ¶Department of Radiation Oncology, Duke University, Durham, NC; ‖Mount Vernon Centre for Cancer Treatment, Middlesex, United Kingdom; #Department of Radiation Oncology, University of Michigan, Mt. Pleasant, MI; **Department of Radiation Oncology, Wayne State University, Detroit, MI; ††Department of Radiation Oncology, Boston Medical Center, Boston, MA; ‡‡Department of Radiation Oncology, Ohio State University, Columbus, OH; §§Department of Radiation Oncology, Sunnybrook Odette Cancer Center and the Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; ¶¶21st Century Oncology, Sarasota, FL; ‖‖The Institute for Palliative Medicine, San Diego Hospice, San Diego, CA; ##Neurological Surgery, Ohio State University, Columbus, OH; ***Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH; †††University of Pennsylvania School of Nursing, Philadelphia, PA; ‡‡‡Department of Radiation Oncology, Good Samaritan Cancer Center, Downers Grove, IL

Table 2 - ASTRO task force questions and guideline statements regarding palliative radiation therapy for bone metastasis

Questions	Guideline statements
1. Which fractionation schemes have been shown to be effective for the treatment of painful and/or prevention of morbidity from peripheral bone metastases?	Although various fractionation schemes can provide good rates of palliation, numerous prospective randomized trials have shown that 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction can provide excellent pain control and minimal side effects.
2. When is single fraction RT appropriate for the treatment of painful and/or prevention of morbidity from uncomplicated bone metastasis involving the spine or other critical structures?	No evidence from reviewing the data to suggest that a single 8-Gy fraction provided inferior pain relief compared with a more prolonged RT course in painful spinal sites.
3. Are there long-term side effect risks that should limit the use of single fraction therapy?	Numerous prospective, randomized trials have failed to show any significant difference in long-term toxicity between a single 8-Gy fraction and more prolonged RT courses for uncomplicated, painful bone metastases. No additional studies are suggested to confirm this recommendation at this time.
4. When should patients receive repeat treatment with RT for peripheral bone metastases?	The rates of repeat treatment have been 20% with single-fraction palliative RT schedules compared with 8% with lengthier RT courses. The Task Force recommends that, whenever possible, patients should be included in prospective randomized trials.
5. When should patients receive repeat treatment with RT to spinal lesions causing recurrent pain?	Sites of recurrent pain in spinal bones can be successfully palliated with EBRT repeat treatment. Care must be taken when the re-irradiated volume contains the spinal cord, and it might be appropriate to sum the biologically effective doses from the initial and repeat treatment regimens to estimate the risk of radiation myelopathy.
6. What promise does highly conformal RT hold for the primary treatment of painful bone metastasis?	Stereotactic body RT is a technology that delivers high doses to metastatic spinal disease with a steep dose gradient that might allow superior sparing of the adjacent neural structures, including the spinal cord and cauda equina. SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression.
7. When should highly conformal RT be considered for repeat treatment of spinal lesions causing recurrent pain?	Some early data have suggested that repeat treatment to spinal lesions with SBRT might be feasible, effective, and safe, although the Task Force believes that the use of this approach should be limited to the setting of clinical trial participation.
8. Does the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty obviate the need for palliative RT for painful bone metastasis?	The available data have suggested that surgery, systemic radiopharmaceuticals, bisphosphonates, or kyphoplasty/vertebroplasty does not obviate the need for EBRT for patients with bone metastases.

Conclusioni: EBG ASTRO 2011

Kyphoplasty and vertebroplasty have theoretically shown the most promise in patients with metastatic spinal disease causing instability of the vertebral body, although the lack of completed prospective studies should limit their standard use (Table 10). Small series of patients have been treated with kyphoplasty or vertebroplasty plus EBRT, stereotactic radiosurgery, or interstitial samarium-153. However, the results do not allow for definitive statements regarding the use of these combined regimens. Future prospective trials of vertebroplasty and kyphoplasty should address questions such as proper patient selection, efficacy, toxicity, and timing in relation to radiotherapeutic interventions.

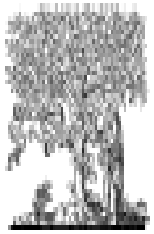
CONCLUSIONS

External beam radiotherapy has been, and continues to be, the mainstay for the treatment of painful, uncomplicated bone metastases. Although various fractionation schemes can provide good rates of palliation, numerous prospective randomized trials have shown that 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction can provide excellent pain control and minimal side effects. The longer course has the advantage of a lower incidence of repeat treatment to the same site, and the single fraction has proved more convenient for patients and caregivers. Repeat irradiation with EBRT might be safe, effective, and less commonly necessary in patients with a short life expectancy. Bisphosphonates do not obviate the need for EBRT for painful sites of metastases and might, indeed, act effectively when combined with EBRT. SBRT might be useful for patients with newly discovered or recurrent tumor in the spinal column or paraspinal areas; however, the Task Force suggests that SBRT be reserved for patients who fit specific inclusion and exclusion criteria, who undergo treatment at centers with sufficient training and experience, and should preferably be treated within the confines of a therapeutic trial.

The use of radionuclides seems most appropriate in circumstances in which patients have several sites of painful osteoblastic metastases in an anatomic distribution greater than that which could conveniently or safely be treated with EBRT. Hemibody RT is an option for these patients who reside in geographic areas where radionuclides are not readily available or when they are medically contraindicated.

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 3, pp. 652–665, 2008

0360-3016/08/$–see front matter



doi:10.1016/j.ijrobp.2008.02.060

CRITICAL REVIEW

STEREOTACTIC BODY RADIOSURGERY FOR SPINAL METASTASES: A CRITICAL REVIEW

ARJUN SAHGAL, M.D.,*† DAVID A. LARSON, M.D. PH.D.,† AND ERIC L. CHANG, M.D.‡

*Department of Radiation Oncology, Sunnybrook Odette Cancer Center, University of Toronto, Toronto, Ontario, Canada; †Department of Radiation Oncology, University of California San Francisco, San Francisco, CA; and ‡Department of Radiation Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston, TX

Table 2. A summary of specified relative inclusion and exclusion criteria for spine SBRS

Inclusion

- Solitary or oligometastatic disease or bone only disease in otherwise high-performance status patients*
- Maximum of two consecutive (28) or noncontiguous (8, 17) spinal segments involved by tumor
- Failure of prior XRT (up to one course and 45 Gy maximum) or surgery (8, 17)
- Nonmyeloma tumor type (8, 17)
- Gross residual disease or deemed high risk for recurrence postsurgery (17)
- Patient refusal or medical comorbidities precluding surgery (17)
- Gross tumor optimally more than 5 mm from the spinal cord (17)†
- Karnofsky performance status >40–50 (17, 50, 51)
- MRI- or CT-documented spinal tumor (17, 20)
- Histologic confirmation of neoplastic disease (17, 20)
- Age >18 (50)

Exclusion

- Pacemaker such that MRI cannot be performed or the treatment cannot be delivered safely (17)
- Scleroderma or connective tissue disease as a contraindication to radiotherapy*
- Unable to lie flat (*i.e.*, tolerate treatment)*
- Treated with ^{89}Sr or systemic chemotherapy within 30 days before SBRT (8, 17)
- External beam radiotherapy to the same area within 3 months before SBRT (8, 17, 28)
- Significant or progressive neurologic deficit (8, 17, 23)
- >25% spinal canal compromise (23)
- Malignant epidural spinal cord compression (8, 19) or cauda equina syndrome (19)‡
- Spine instability (8, 17, 19) or neurologic deficit resulting from bony compression of neural structures (50)

Abbreviations: SBRS = stereotactic body radiosurgery; XRT = X-ray therapy; MRI = magnetic resonance imaging; CT = computed tomography; SBRT = stereotactic body radiotherapy; MDACC = M.D. Anderson Cancer Center.

* These represent unpublished specific criteria and included per the authors' recommendation as general criteria to be considered.

† This criteria, according to the MDACC, is relaxed should the multidisciplinary team judge the case still suitable for spine SBRS.

‡ Malignant epidural spinal cord compression has been allowed by some investigators and treated with radiosurgery alone (11).

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0360-3016/03/$–see front matter

ELSEVIER

PII S0360-3016(02)03864-6

CLINICAL INVESTIGATION **Bone**

CLINICAL RESULTS OF RETREATMENT OF VERTEBRAL BONE METASTASES BY STEREOTACTIC CONFORMAL RADIOTHERAPY AND INTENSITY-MODULATED RADIOTHERAPY

STEFANIE MILKER-ZABEL, M.D.,* ANGELIKA ZABEL, M.D.,† CHRISTOPH THILMANN, M.D.,† WOLFGANG SCHLEGEL, PH.D.,‡ MICHAEL WANNENMACHER, M.D.,* AND JÜRGEN DEBUS, M.D, PH.D.*†

*Department of Clinical Radiology, Radiation Therapy, University of Heidelberg, Heidelberg, Germany; Departments of †Radiotherapy and ‡Medical Physics, German Cancer Research Center, Heidelberg, Germany

Purpose: Reirradiation of spinal tumors is limited by the tolerance of the spinal cord. We evaluated local control, pain relief, neurologic improvement, side effects, and survival rates after fractionated conformal radiotherapy (FCRT) and intensity-modulated RT (IMRT) of recurrent spinal metastases.

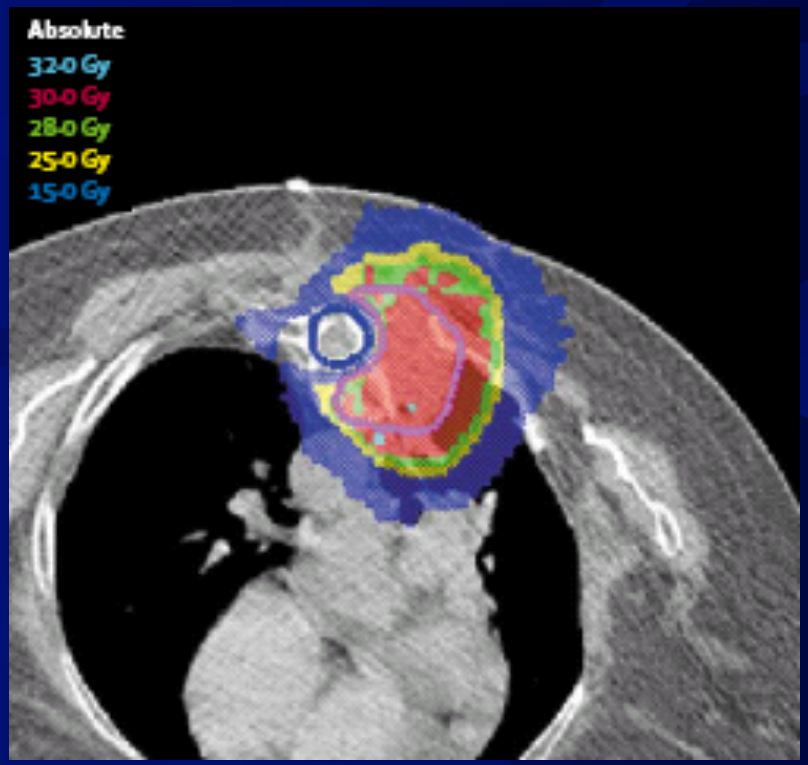
Methods and Materials: Eighteen patients with 19 radiologic manifestations were retreated for recurrent spinal metastases using FCRT (n = 5) or IMRT (n = 14). All patients had previously undergone conventional RT (median dose 38 Gy). The indication for reirradiation was tumor progression associated with pain (n = 16) or neurologic symptoms (n = 12). The median time to recurrence was 17.7 months. The median total dose for reirradiation was 39.6 Gy.

Results: The overall local control rate was 94.7% after a median follow-up of 12.3 months. Of 16 patients with pain, 13 experienced significant relief after reirradiation. Neurologic improvement was obtained in 5 of 12 patients. Tumor size remained unchanged in 84.2%. A partial response was seen in 2 of 19 patients. One patient had local tumor progression 9.5 months after reirradiation. Six patients received chemotherapy after reirradiation because of progressive distant metastases. Twelve patients died 10.5 months median after reirradiation. No clinically significant late toxicity was seen after FCRT or IMRT.

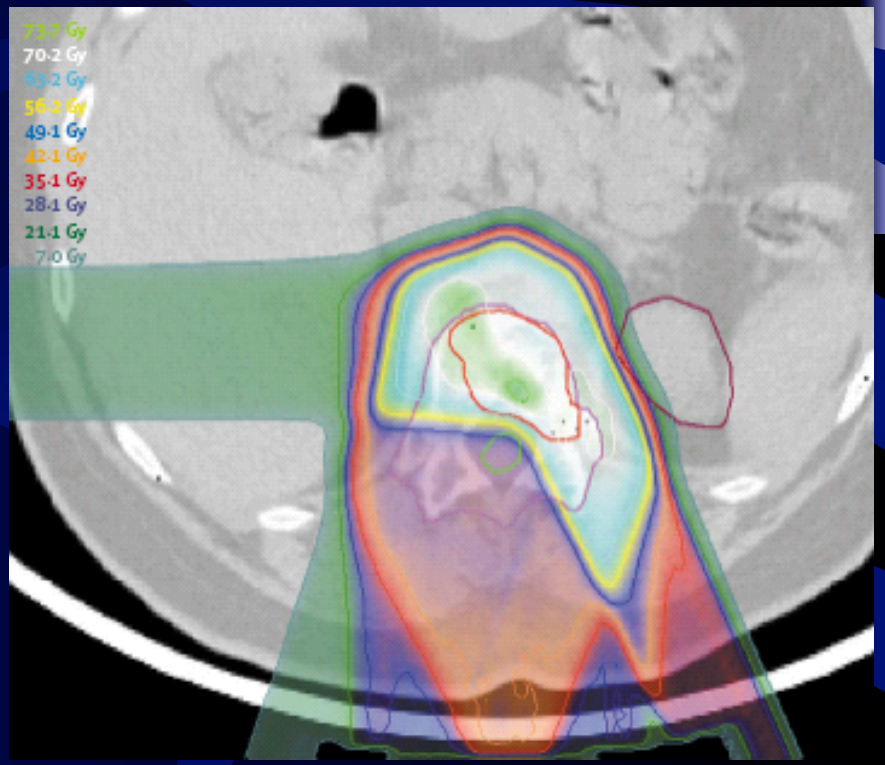
Conclusion: These data demonstrate that FCRT and IMRT are effective and safe in recurrent spinal tumors and can be offered to patients to achieve local control, as well as pain relief. © 2003 Elsevier Science Inc.

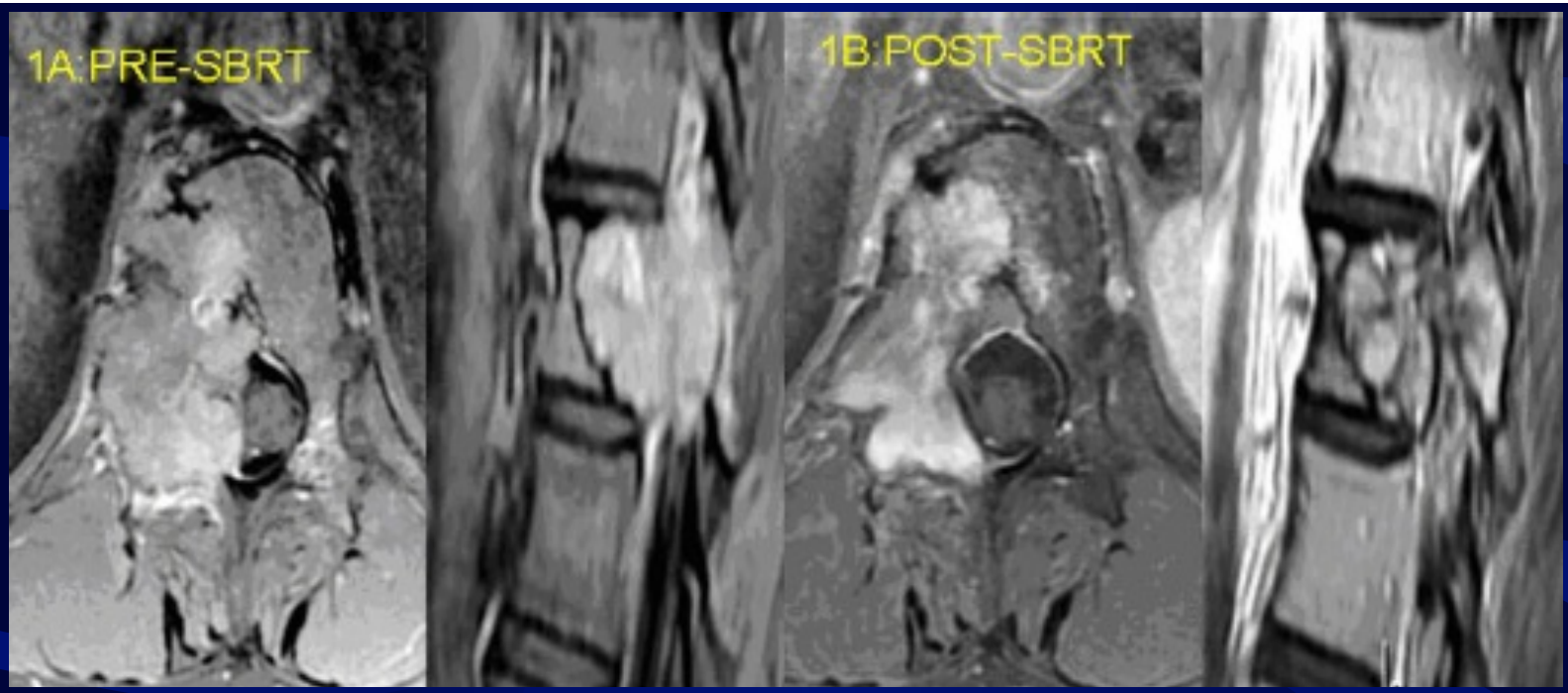
Indicazioni e limiti della radioterapia in medicina palliativa: reirradiazione

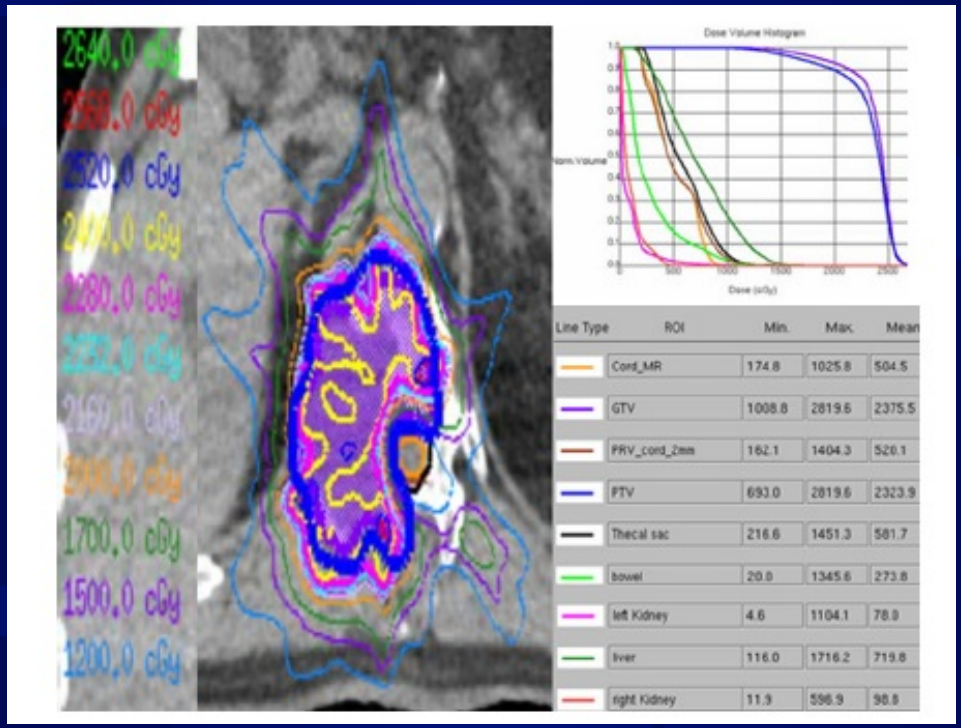
IMRT con tomotherapy



Terapia con protoni




1A:PRE-SBRT
1B:POST-SBRT


2640.0 cGy
2320.0 cGy
1700.0 cGy
1500.0 cGy
1200.0 cGy
Dose Volume Histogram
Line Type ROI Min. Max. Mean
Cord_MR 174.8 1025.8 504.5
GTV 1008.8 2819.6 2375.5
PRV_cord_2mm 162.1 1404.3 520.1
PTV 693.0 2819.6 2323.9
Thecal sac 216.6 1451.3 581.7
bowel 20.0 1345.6 273.8
left Kidney 4.6 1104.1 78.9
liver 116.0 1716.2 719.8
right Kidney 11.3 596.9 98.8

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0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.08.012

CLINICAL INVESTIGATION **Spine**

STEREOTACTIC BODY RADIOTHERAPY REIRRADIATION FOR RECURRENT EPIDURAL SPINAL METASTASES

ANAND MAHADEVAN, M.D.,* SCOTT FLOYD, M.D., PH.D.,* ERIC WONG, M.D.,† SURIYA JEYAPALAN, M.D.,† MICHAEL GROFF, M.D.,‡ AND EKKEHARD KASPER, M.D., PH.D.‡

Departments of *Radiation Oncology, †Neuro-Oncology, and ‡Neurosurgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts and Harvard Medical School

Purpose: When patients show progression after conventional fractionated radiation for spine metastasis, further radiation and surgery may not be options. Stereotactic body radiotherapy (SBRT) has been successfully used in treatment of the spine and may be applicable in these cases. We report the use of SBRT for 60 consecutive patients (81 lesions) who had radiological progressive spine metastasis with epidural involvement after previous radiation for spine metastasis.

Methods and Materials: SBRT was used with fiducial and vertebral anatomy-based targeting. The radiation dose was prescribed based on the extent of spinal canal involvement; the dose was 8 Gy × 3 = 24 Gy when the tumor did not touch the spinal cord and 5 to 6 Gy x 5 = 25 to 30 Gy when the tumor abutted the cord. The cord surface received up to the prescription dose with no hot spots in the cord.

Results: The median overall survival was 11 months, and the median progression-free survival was 9 months. Overall, 93% of patients had stable or improved disease while 7% of patients showed disease progression; 65% of patients had pain relief. There was no significant toxicity other than fatigue.

Conclusions: SBRT is feasible and appears to be an effective treatment modality for reirradiation after conventional palliative radiation fails for spine metastasis patients. © 2011 Elsevier Inc.

Stereotactic body radiotherapy, Stereotactic radiosurgery, Spinal metastases, Reirradiation.

Riferimenti per impostare un corretto trattamento radioterapico palliativo

Caratteristiche del malato

- Performance status
- Età
- Comorbidità

Caratteristiche della malattia

- intervallo libero ,
- pregresse terapie,
- reale estensione delle metastasi,
- concordanza tra la sede della lesione e la sintomatologia,
- aspettativa di vita,
- tossicità del trattamento prescelto

Condivisione della scelta

- Consenso informato del pz.
- Approccio multidisciplinare
- Discussione collegiale del caso

•(courtesy by E. Barbieri)

Dal curare al prendersi cura

Il Dolore totale oncologico

AZIENDA OSPEDALIERA SAN CAMILLO-FORLANINI
SOCIETÀ ITALIANA CURE PALLIATIVE, REGIONE LAZIO

Venerdì 23 Febbraio 2007

Aula Magna Ospedale Forlanini
Piazza Carlo Forlanini, 1 – Roma

DIRETTORE DEL CORSO
Prof. Vittorio Donato
Coordinatore Regionale SICP

Crediti ECM per medici-chirurghi e infermieri
Iscrizione gratuita
Verrà rilasciato un Attestato di Partecipazione

CONVEGNO ANNUALE SICP REGIONE LAZIO

Dal curare al prendersi cura

Il Limite delle cure nel malato oncologico in fase avanzata

AZIENDA OSPEDALIERA SAN CAMILLO-FORLANINI
SOCIETÀ ITALIANA CURE PALLIATIVE, REGIONE LAZIO

Venerdì 22 Febbraio 2008

Ospedale San Camillo - Forlanini
C.ne Gianicolense, 87
Aula A – Struttura Piastra, II piano

DIRETTORE DEL CORSO
Prof. Vittorio Donato

The rapid access palliative radiotherapy program: blueprint for initiation of a one-stop multidisciplinary bone metastases clinic

Fairchild A et al, Support Care Cancer April 2008

Programma RAPR: Unico accesso, 4-6 ore

- Patient oriented to clinic day – RN*
- Screening tools administered – RN, Pharm or RTT
- Medication history – Pharm
- Assessment for suitability of radiotherapy – NP, RO
- X-rays, blood work if necessary
- Multidisciplinary consultations – OT, SW, RD
- Simulation of radiotherapy – RO, RTT
- Meal break for patients while RT is planned - RTT
- Radiotherapy administration - RTT
- Completion of survey by patient – RTT
- Telephone follow-up one and three weeks later - RTT