JOINT MEETING
1ST ADVANCED AIRB COURSE IN RADIOBIOLOGY
BRESCIA MEETINGS IN RADIATION ONCOLOGY - 2015 EDITION

THE POWER OF BIOLOGY
Brescia – October 8th/9th, 2015

Chemotherapy, target therapy, hormonal manipulation and… REIRRADIATION

Filippo Alongi MD,
Head of Radiation Oncology Department

Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

REIRRADIATION:
A RELEVANT ISSUE FOR CLINICIANS

Tumori, 96: 792-795, 2010

LETTERS TO THE EDITOR

Reirradiation: hopes and concerns of the radiation oncologist

Filippo Alongi[1], Nadia Di Muzio[2], and Marta Scorsetti[1]

Radiation retreatment is a problematic issue to resolve in clinical practice: it requires knowledge of the possibility of unforeseen toxicity risks in healthy tissue[2]. The radiation oncologist must consider many parameters before prescribing retreatment with radiation. Key questions to be addressed are: What is the endpoint of retreatment? What is the reirradiation intent? Reirradiation may be useful as a palliative approach for local-regional relapse or may be indicated to obtain or maximize local control of tumor recurrence, especially in the absence of other disease sites. Another case is represented by a second primary tumor in the area of previous radiation treatment

REIRRADIATION:
A RELEVANT ISSUE FOR CLINICIANS

PARAMETERS TO EVALUATE BEFORE RE-RT:

- **Dose** of prior RT and cumulative estimate dose
- **Time** between the two courses of RT(min 6 months)
- **Volumes** of prior irradiation

Obviously…

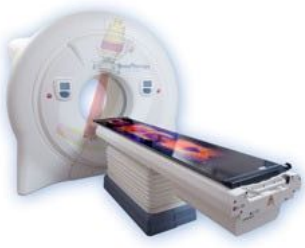
1. **Intent** of the re-treatment
2. **General Condition** of the patient

SUGGESTIONS FOR RE-RT:

- ***TARGET DEFINITION*** using PET/CT and/or MRI to better define recurrence, in order to minimise volume to treat
- ***IMRT/VMAT/PROTONS*** or other advanced techniques for radiation dose sculpting escluding organ at risk(previously involved!)
- (NEW ?)***DRUGS*** to ehnance Effectiveness of Radiation Damage on resistant tumour Tissues, previously irradiated.

REIRRADIATION:
RADIATION DELIVERY ADVANCEMENTS

With new technology devices, now is possible to delivery high (when requested also ablative) doses to the target, especially to small volumes

PRECISION DEVISES TO DELIVERY RADIATION

CHEMOTHERAPY, TARGET THERAPY, AND…
REIRRADIATION: HEAD & NECK


Contents lists available at ScienceDirect
2013 Cancer Treatment Reviews
journal homepage: www.elsevierhealth.com/journals/ctrv

Controversy

The role of re-irradiation of secondary and recurrent head and neck carcinomas. Is it a potentially curative treatment? A practical approach

Jon Cacicedo [a,*], Arturo Navarro [b,1], Filippo Alongi [c,2], Alfonso Gómez de Iturriaga [a,3], Olga del Hoyo [a,3], Elsira Boveda [a,3], Francisco Casquero [a,3], Jose Fernando Perez [d,3], Pedro Bilbao [a,3]

Whenever possible, surgery is proposed as a salvage strategy.

When patients present with unresectable disease or are un-suitable candidates for surgery, three options can be discussed:

- supportive care only,
- palliative chemotherapy
- radiotherapy (alone or combined with systemic therapy).

CHEMOTHERAPY, TARGET THERAPY, AND…
REIRRADIATION: HEAD & NECK

Although the risk of distant metastasis is high, **most of these patients will die as a result of uncontrolled tumor growth at the primary site.**

Nevertheless, *the treatment for these patients is frequently systemic chemotherapy*, which is widely used for palliation.

- The evidence for offering re-irradiation as a curative treatment has come mainly from *retrospective and phase II trials.*
- Currently, there are *no other randomized data that suggest optimal approaches* for patients with recurrent or second primary HNSCC in previously irradiated areas.
- In fact, the RTOG started a similar randomized phase III trial, but it was closed early due to lack of recruitment.

Cacicedo et al, Cancer Treat Review 2013

CHEMOTHERAPY, TARGET THERAPY, AND…
REIRRADIATION: HEAD & NECK

Table 1
Selected chemotherapy (and targeted therapies) trials for locally recurrent and metastatic head and neck cancer.

Author	Type of study	Year	Number of patients		Regimen	Response rate (%)	Median survival (months)
Forastiere et al. [14]	Randomized	1992	277	87	Cisplatin + fluorouracil	32	6.6 NS
				86	Carboplatin + fluorouracil	21	5.0
				88	Methotrexate	10	5.6
Jacobs et al. [16]	Randomized	1992			Cisplatin + fluorouracil	32	5.7 NS
			249		Cisplatin	17	
					Fluorouracil	13	
Schrijvers et al. [17]	Randomized	1998	244	122	Cisplatin + fluorouracil + IFNα-2b	47	6.0 NS
				122	Cisplatin + fluorouracil	38	6.3
Forastiere et al. [13]	Randomized	2001	199	101	Cisplatin + paclitaxel (high dose)	35	7.6 NS
				98	Cisplatin + paclitaxel (low dose)	36	6.8
Soulieres et al. [18]	Phase II	2004	115		Erlotinib	4	6.0
Gibson et al. [15]	Randomized	2005	204	104	Cisplatin + fluorouracil	27	8.7 NS
				100	Cisplatin + paclitaxel	26	8.1
Burtness et al. [12]	Randomized	2005	117	57	Cisplatin + cetuximab	26	9.2*
				60	Cisplatin + placebo	10	8.0
Bourhis et al. [11]	Phase I/II	2006		53	Platinum + fluorouracil + cetuximab	36	9.8
Vermorken et al. [19]	Randomized	2008	442	220	Platin + fluorouracil	20	7.4
				222	Platin + fluorouracil + cetuximab	36	10.1**
Argiris et al. [10]	Randomized	2013	270	136	Docetaxel + placebo	6.2	6.0
				134	Docetaxel + gefitinib	12.5	7.3 NS

Abbreviation: NS, not statistically significant.
* ($p = 0.03$).
** ($p = 0.04$).

In fact, *chemotherapy alone yields a median survival between 5 and 9 months, and long-term survival is unfrequent.*

Cacicedo et al, Cancer Treat Review 2013

CHEMOTHERAPY, TARGET THERAPY, AND…
REIRRADIATION: HEAD & NECK

Summary of studies involving re-irradiation.

Cacicedo et al, Cancer Treat Review 2013

Author (year)	Patients number	Treatment	Surgery before RT (%)	Median follow-up for survivors (months)	Median OS (months) OS (years)	LRC or PFS	Morbidity
Haraf et al. (1996) [20]	45	40 Patients Conv RT 50 Gy (median dose) and 5 patients 1.5 Gy < (b.i.d)/5-FU + HU (±CDDP)	No	41	Median 8.5 2y (22%) 5y (14.6%)	26% (2y-LRC) 20% (5y-LRC)	1/45 Brain necrosis lethal 4/45 (8.8%)
De Crevoisier et al. (1998) [22]	169	Conv RT 65 Gy, 2 Gy Conv RT 60 Gy, 2 Gy/5-FU + HU Hf RT 60 Gy, 1.5 Gy (b.i.d)/5FU + MMC	No	70	Median 10 2y (21%) 5y (9%)	11% (2y-PFS)	Acute: Mucositis G3 :32%, G4:14% Fibrosis G 2–3 41%, osteoradionecrosis 8% Mucosal necrois 21% lethal carotid hemorrhage 5/169 (2.9%)
De Crevoisier et al. (2001) [27]	25	RT 60 Gy (median), 2 Gy daily × 5; alternating weeks × 6/5FU + HU	100	66	Median 16 4y (43%)	35% (2y-PFS)	Acute mucositis G3 40% and G4 12% late: osteoradionecrosis 16%, fibrosis G2-3 40%
Salama et al. (2006) [21]	115	RT 66–74 Gy Conv RT 2 Gy daily or Hf RT 1.5 Gy (b.i.d)/5FU + HU or triple agent	42.6	67	Median 11 22% (3y)	51% (3y-LRC)	G 4-5 21/115 (18.2%) lethal 19/115 (16.5%)
Langendijk et al. (2006) [25]	34	Conv RT 60 Gy, 2 Gy daily continuous course	No	32	Median 13.2 38%(2y)	27% (2y-LRC)	Acute mucositis G 2 (mostly), G3 (30%) late G 3-4 : 22/34 (64.7%)
Janot et al. (2008) [28]	65	Randomized trial. RT 60 Gy (median), 2 Gy daily × 5; alternating weeks × 6/5FU + HU	100	N.R	Median 15 43% (2y)	37% (2y- PFS)	Acute mucositis/ pharyngitis G 3-4 (28%) late (24 months): G 3-4 39% lethal 5/65 (7.7%)
Spencer et al. (2008) [23]	79	Hf RT 60 Gy, 1.5 Gy (b.i.d) × 10, alternating weeks × 4/5FU + HU	No	16.3	Median 8.5 2y (15.2%)5y (3.8%)	–	Acute G 3 (38%) G 4(17.7%) Late G3 (19.4%) G4 (3%) Lethal 6/79 (7.6%)
Langer et al. (2007) [24]	99	Hf RT 60 Gy, 1.5 Gy (b.i.d) × 10, alternating weeks × 4/ CDDP + paclitaxel	No	23.6	Median 12.1 50.2% (1y) 25.9% (2y)	15.8% (2y-PFS)	Acute G4 28 % lethal 8/99 (8%; acute 5, late 3)
Lee el al. (2007) [31]	105	RT 59.4 Gy (median), 1.8–2 daily continuous course/75% chemo → Platin + 5FU or paclitaxel; IMRT 70% patients	34	35	Median 15 2y (37%)	42% (2y-LRPFS)	Acute G3-4 23% late G3-4 (15%)
Sulman et al. (2009) [70]	74	RT 60 Gy (100% IMRT)/48.6% chemotherapy	27	–	Median 27.6 58% (2y)	64% (2y-LCR)	Severe toxicity 15/74 (20%), death 1 (unknown)
Duprez et al. (2009) [6]	84	RT 69 Gy (median) with IMRT/20 % concurrent platinum based chemotherapy	23	19.8	Median 13.4 20% (5y)	48% (2y -LCR)	Acute G3 26/84 (31%) Late G3 11/84 (14%); 2 late deaths (2.83%)
Tortochaux et al. (2010) [26]	57	Randomized trial. 30 patients RT RT 60 Gy (median), 2 Gy daily × 5; alternating weeks × 6/5FU + HU	No	–	Median 6 23% (1y)	Local-regional recurrence 61%	Acute >G3 6.6% late >G3 36.6% lethal 3/30 (10%)

CHEMOTHERAPY AND…
REIRRADIATION: HEAD & NECK

➢The role of *concurrent chemotherapy in re-irradiation* for HNSCC remains uncertain.

➢The results of a recent meta-analysis indicate that the addition of concomitant chemotherapy to primary radiotherapy significantly improves overall survival.

Blanchard P, et al. Radiother Oncol 2011
Pignon, et al. Radiother Oncol 2009

➢However, no study has demonstrated a conclusive benefit of reirradiation with concurrent chemotherapy compared to re-irradiation without chemotherapy.

➢A significant study using a *high radiation dose without chemotherapy* showed a 2-year locoregional control rate of 27%, with an acceptable toxicity profile .

LangendiJk et al, Radiother Oncol 2006

➢***Thus, the role of chemotherapy in reirradiation continues to evolve, and it is presently not optimally defined***.

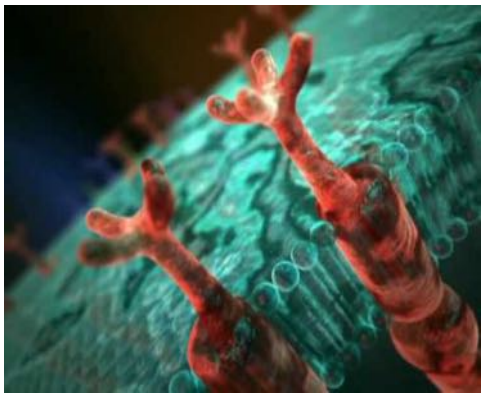
Cacicedo et al, Cancer Treat Review 2013

TARGET THERAPY AND…
REIRRADIATION: HEAD & NECK

➢The **EGFR** is over-expressed in 90–100% of HNSCCs.

➢Indeed, high EGFR copy number has been previously associated with poor prognosis.

➢However, the tumor EGFR status was not found to be predictive for the efficacy of cetuximab plus platinum/5-FU (as first line therapy) administered to patients with recurrent/metastatic HNSCC during the randomized phase III EXTREME trial.



Licitra et al, Annals Oncol 2011

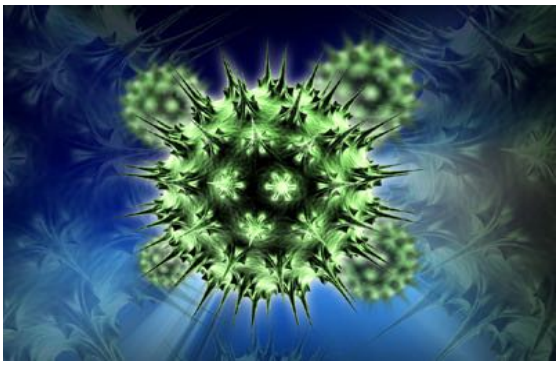
➢***In this context, we cannot derive a definitive conclusion with respect to patients who might be treated with curative intent with re-irradiation plus cetuximab***.

Cacicedo et al, Cancer Treat Review 2013

TARGET THERAPY AND…
REIRRADIATION: HEAD & NECK

➢Moreover, **HPV has recently been established as a risk factor for oropharyngeal cancer**, with emerging data suggesting that *HPV +tumors are more sensitive to chemotherapy and RT than HPV- tumors*.

Therefore, **HPV status and EGFR expression could be included** into future clinical trials (in the context of re-irradiation) to be used for more accurate prognostic patient classification.



LangendiJk et al, Curr Opin Oncol 2007

➢***In this context, we cannot derive a definitive conclusion with respect to patients HPV+ who might be treated with curative intent with re-irradiation plus Chemotherapy or cetuximab***.

Cacicedo et al, Cancer Treat Review 2013

REIRRADIATION:
RADIATION DELIVERY ADVANCEMENTS

Contents lists available at ScienceDirect
2013 Cancer Treatment Reviews
journal homepage: www.elsevierhealth.com/journals/ctrv

Controversy

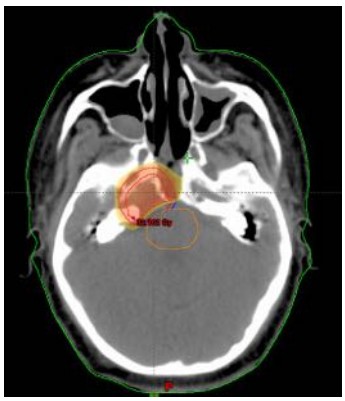
The role of re-irradiation of secondary and recurrent head and neck carcinomas. Is it a potentially curative treatment? A practical approach

Jon Cacicedo [a,*], Arturo Navarro [b,1], Filippo Alongi [c,2], Alfonso Gómez de Iturriaga [a,3], Olga del Hoyo [a,3], Elsira Boveda [a,3], Francisco Casquero [a,3], Jose Fernando Perez [d,3], Pedro Bilbao [a,3]

IMRT, SBRT

High-tech improvements are refining the "ballistic" approach to delivering radiation to target volumes and the surrounding organ tissues by means of IMRT, SBRT and heavy particles [86]. It is critical to understand that many of the published series here reported have used treatment techniques that are currently considered obsolete. Conventional delivery of even small fields, confined to clinically evident disease, can be challenging, particularly when the tumor is close to critical structures. "Dose sculpting" on active tumor with IMRT is a helpful approach to minimize the radiation dose to previously irradiated tissues. Indeed, image-guided radiation therapy (IGRT) reduces repositioning errors and is used to monitor the treatment region and/or to adapt dose distribution to the possibly changing target and organs at risk during radiation [87].

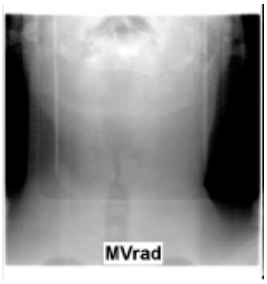
Therefore, in recent years the clinical utilization of IMRT and/or SBRT has improved healthy tissue tolerance [88,89].



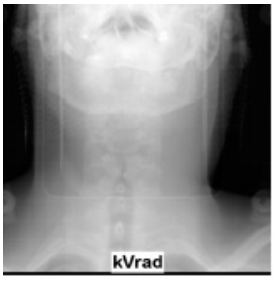
REIRRADIATION:
RADIATION ADVANCEMENTS: IMAGING ON BOARD

Imaging 2-D: → **Imaging 3-D:**

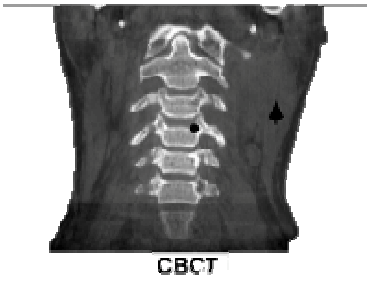
MV imaging



KV imaging



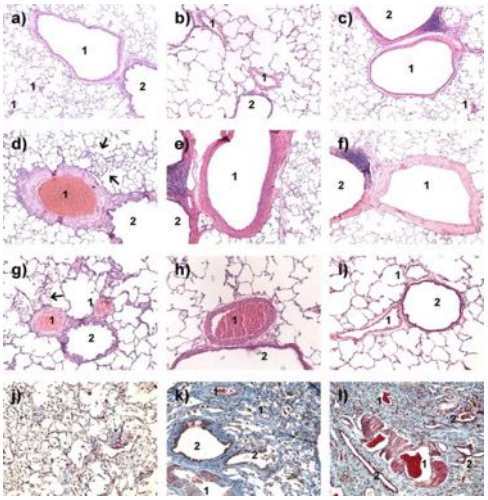
Cone Beam CT imaging



ADVANCED TECHNOLOGIES IN IMAGE-GUIDED RADIATION THERAPY

Balter J et al., Seminars in Radiation Oncology, 2007

SBRT REIRRADIATION:
A NEW BIOLOGICAL RATIONALE ?



- In terms of ***Radiobiology, SBRT*** **/SABRT** may add a novel mechanism of radiation-induced damage.

- At higher doses per fraction (***ablative doses***), emerging data suggest that a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill.
Garcia - Barros M., et al. Science, 2003

Targeting the tumor vasculature for obliteration with high-dose radiation may be beneficial for tumor control.
Fuks and Kolesnick, Cancer Cell 2005 .

TARGET THERAPY AND…
HEAD & NECK SBRT REIRRADIATION?

➢A retrospective matched-pair analysis suggested improved overall survival with the addition of cetuximab therapy to SBRT

Heron, et al:. Am J Clin Oncol 2011

Am J Clin Oncol. 2011 Apr;34(2):165-72. doi: 10.1097/COC.0b013e3181dbb73e.

Concurrent cetuximab with stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: a single institution matched case-control study.

Heron DE[1], Rwigema JC, Gibson MK, Burton SA, Quinn AE, Ferris RL.

⊕ Author information

Abstract

PURPOSE: Locally recurrent head and neck squamous cell carcinoma can be treated with curative intent by surgical salvage or reirradiation with or without chemotherapy. We have previously demonstrated the feasibility and safety of stereotactic body reirradiation at our institution; however, efficacy has been unsatisfactory. Based on the successful combination of cetuximab with radiotherapy in locally-advanced squamous cell carcinoma of the head and neck, we compared stereotactic body radiotherapy alone with combination therapy, using concomitant cetuximab with stereotactic body radiotherapy, to enhance clinical efficacy while minimizing toxicity.

METHODS: In a retrospective-matched cohort study, we compared 2 groups of patients treated over a 6-year period with stereotactic body radiation therapy alone (n=35) or with weekly cetuximab infusion during stereotactic body radiotherapy (n=35), and evaluated clinical response, local control, overall survival, and toxicity. Cox proportional hazard models were used to assess independent prognostic factors.

RESULTS: The median follow-ups for patients alive at last contact were 21.3 months and 24.8 months for stereotactic body radiotherapy only (n=13) and stereotactic body radiotherapy plus cetuximab (n=22), respectively. Our results indicate that cetuximab conferred an overall survival advantage (24.5 vs. 14.8 months) when compared with the stereotactic body radiotherapy alone arm, without a significant increase in grade 3/4 toxicities. This survival advantage was also observed in the subgroup that had received cetuximab therapy during their prior therapeutic regimen.

CONCLUSIONS: Our results suggest an overall survival benefit of concomitant cetuximab with stereotactic body radiotherapy in locally recurrent head and neck squamous cell carcinoma, and suggest a role in this setting. Concomitant cetuximab with stereotactic body radiotherapy is a reasonable approach for unresectable recurrent squamous cell carcinoma of the head and neck, and should be tested in prospective randomized trials to validate its clinical efficacy.

TARGET THERAPY AND…
HEAD & NECK SBRT REIRRADIATION?

Study (ref)	Conventional reirradiation plus chemotherapy	PFS (mo)	OS (mo)	% of cases of toxicity grade 3+
RTOG 9610 (9)	60-Gy hyperfractionated plus 4 cycles of 5FU and hydroxyurea	NR	8.5	85%
RTOG 9911 (10)	60-Gy hyperfractionated plus 4 cycles of cisplatin plus paclitaxel	7.8	12.1	85% †
Chemotherapy with or without Cetuximab				
EXTREME (14) *	Platinum plus 5FU × 6 cycles	3.3	7.4	76%
EXTREME (14) *	Platinum plus 5FU plus cetuximab × 6 cycles	5.6	10.1	82%
SBRT plus cetuximab				
UPCI 06-093	SBRT plus 3 cycles of cetuximab	6.7	10.0	12%
Lartigue et al (21)	SBRT plus 5 cycles of cetuximab	7.1	11.8	30%

Abbreviations: 5FU = 5 fluorouracil; OS = overall survival; PFS = progression-free survival; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiation therapy.

∗ Both recurrent and metastatic patients were included in this trial.

† Estimated in the first 2 years, the crude rates of acute grade 3+ toxicity were 78% and 37% grade 3+ late toxicity.

Vargo et al, Red J 2015

TARGET THERAPY AND…
HEAD & NECK SBRT REIRRADIATION?

➢The combination of *cetuximab and SBRT appears safe in the reirradiation of rSCCHN, and may improve outcomes*.

➢ No significant differences observed in outcome, toxicity, or feasibility between the examined SBRT modalities (Cyberknife, Trilogy, or TrueBeam) in association with Cetuximab.

Heron, et al:. Am J Clin Oncol 2011
Vermorken et, N Engl J Med 2008
Vargo et al, Red J 2015

➢ SCCHN (NCT02057107) : ONGOING prospective randomized phase 2 protocol that combines SBRT (40-50 Gy)+concurrent cetuximab with or without concurrent radiation sensitizing docetaxel in unresectable locally recurrence pts.

➢***Thus, Integration of effective local control modalities (such as SBRT) and more effective novel systemic agents should continue to be investigated.***

Vargo et al, Red J 2015

FUTURE OF REIRRADIATION: PARTICLES?
"IN SILICO" EXPERIENCE: VMAT VS PROTONS

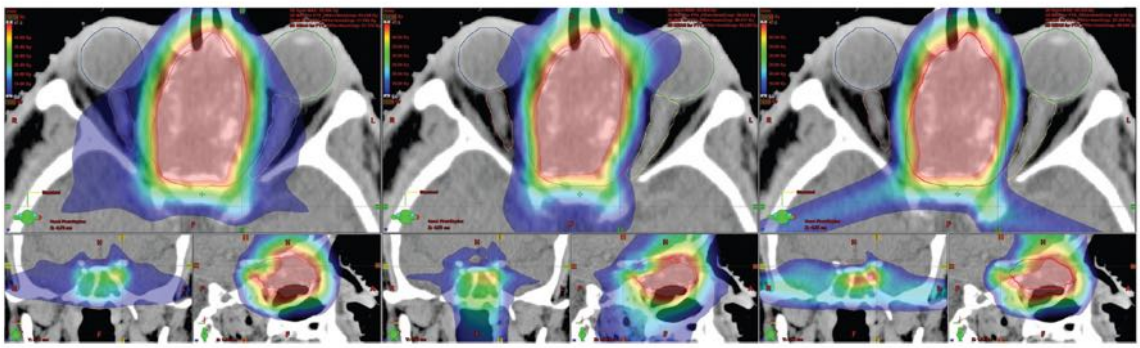
Nasal cavity reirradiation: a challenging case for comparison between proton therapy and volumetric modulated arc therapy

TJ
ISSN 0300-8916
Tumori 2015; 00(00): 000-000
DOI: 10.5301/tj.5000375
CASE REPORT

Ruggero Ruggieri[1], Francesco Dionisi[2], Rosario Mazzola[1,3], Francesco Fellin[2], Alba Fiorentino[1], Marco Schwarz[2], Francesco Ricchetti[1], Maurizio Amichetti[2], Filippo Alongi[1]

[1] Department of Radiation Oncology, Sacro Cuore Don Calabria Hospital, Negrar-Verona - Italy
[2] Proton Therapy Unit, Department of Oncology, Azienda Provinciale per i Servizi Sanitari (APSS), Trento - Italy
[3] Radiation Oncology School, Palermo - Italy

2015



Conclusions: In this challenging scenario, although a clear preference would be given to the MFO proton plan, the RA plan was revealed to be adequate for the clinical goal of target coverage and sparing of organs at risk.

HORMONE THERAPY AND… REIRRADIATION: PROSTATE

Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: A review

Filippo Alongi [a], Berardino De Bari [b,*], Franco Campostrini [c], Stefano Arcangeli [d], Deliu Victor Matei [e], Egesta Lopci [f], Giuseppe Petralia [g], Massimo Bellomi [g], Arturo Chiti [f], Stefano Maria Magrini [b], Marta Scorsetti [a], Roberto Orecchia [h], Barbara Alicja Jereczek-Fossa [h]

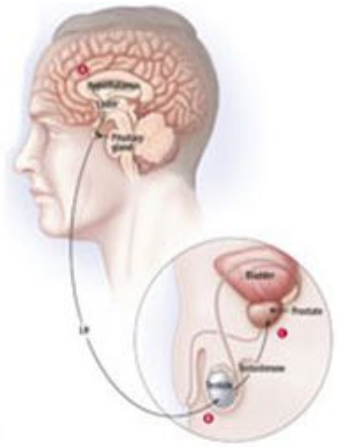
Whenever possible, prostatectomy is proposed as a salvage strategy. In case of local recurrence only

In case of unresectable disease or are un-suitable candidates for surgery, different options can be discussed:

- HIFU, Cryotherapy, Brachytherapy, etc (no robust evidences)
- External radiotherapy (alone or combined with systemic therapy).
- palliative Hormone therapy/Hormone Manipulation

HORMONE THERAPY AND… REIRRADIATION: PROSTATE

- To date, **ADT is the most common management option in the salvage setting** after curative RT, but its deleterious side effects, especially for long-term schedules, should be carefully considered.
- The optimal management and prescription of ADT in patients with localized PC developing BF after a radical course of RT still remains controversial.



- "Small field" RT to limited volume relapsing PC could reduce the tumor clonogen number and, as a consequence, prolong the progression-free interval.
- ***The concept of spatial cooperation between radiation and systemic therapy might also be attractive in this kind of clinical scenario***

Alongi et et al, Criitical review 2013

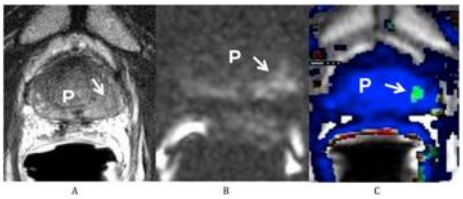
HORMONE THERAPY AND… REIRRADIATION: PROSTATE

➢SBRT is particularly interesting, as it allows *the reduction of the safety margins around the target (thus minimizing the exposure of the previously irradiated surrounding normal tissues*) .

➢Even if this option should be considered only in very selected cases, effective local therapy might reduce the burden of the systemic therapies usually given to patients with recurrent PC

Jereczek-Fossa et al , Red J 2012

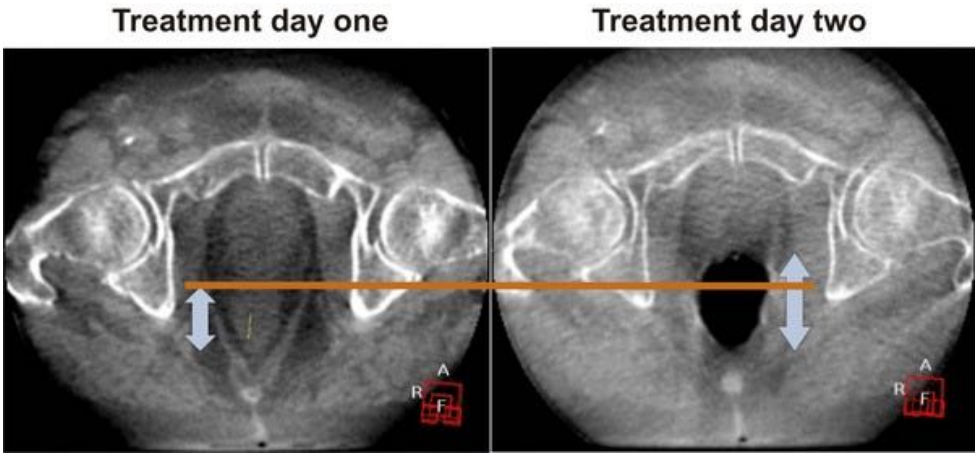
➢Partial re-irradiation has also been proposed with the advance in molecular imaging and radiation treatment planning and delivery.



Wang et al , Radioth Oncol 2009

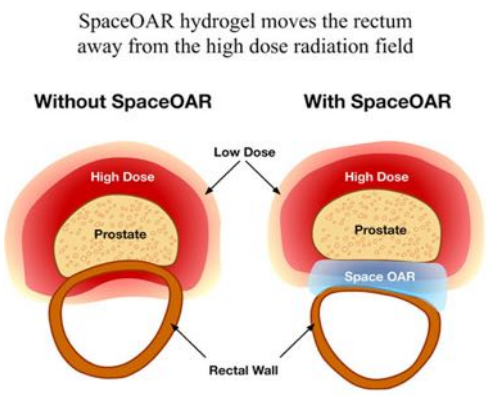
REIRRADIATION:
RADIATION ADVANCEMENTS: IMAGING ON BOARD

CBCT COMPARISON:
geometrical checking (SET UP) ..and anatomic information

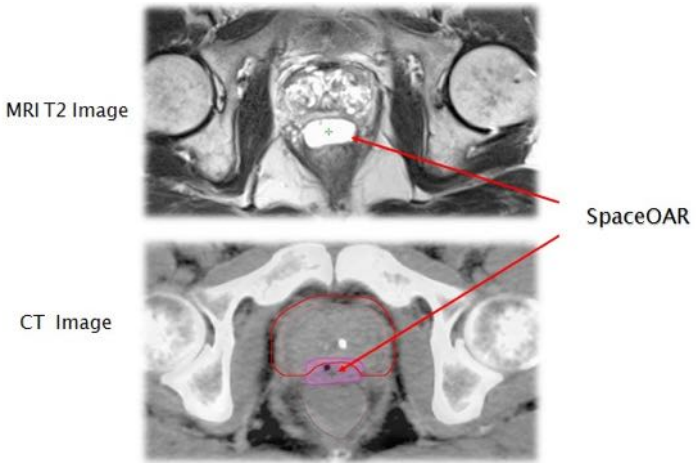


SBRT and (Extreme) Hypofractionation For Prostate

SPACEOAR: A SOLUTION ALSO FOR REIRRADIATION?

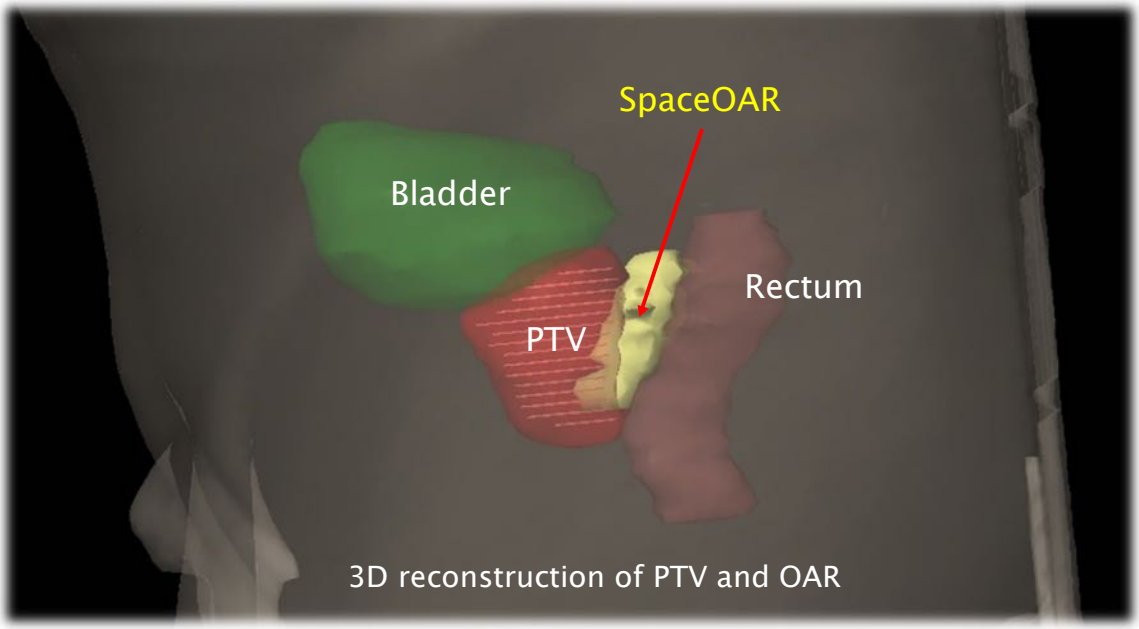


*Self-absorbable



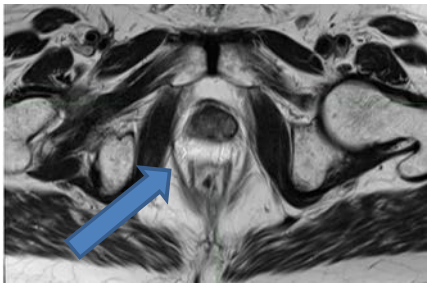
SBRT and (Extreme) Hypofractionation For Prostate

SPACEOAR IN SBRT

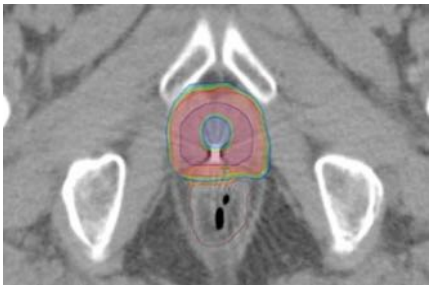


SBRT PROSTATE REIRRADIATION:
CLINICAL EXPERIENCE

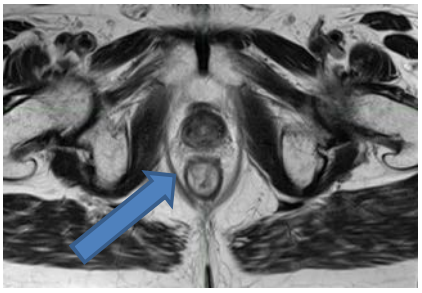
SBRT and hydrogel temporary spacer between prostate and rectum: a salvage re-irradiation strategy for prostate cancer recurrence.



Pre treatment MRI
Pre-RT PSA: 6.2ng/ml



Re-SBRT : 30Gy in 5 fractions
With VMAT FFF



Post treatment MRI
Post-RT PSA: 2.68ng/ml

Ospedale Sacro Cuore - Don Calabria

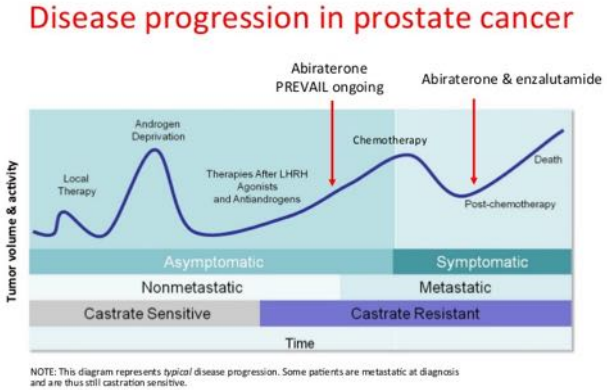
Ospedale Sacro Cuore - Don Calabria

HORMONE THERAPY AND… REIRRADIATION:
PROSTATE

➢No data exist on the best schedule and timing for associating a systemic therapy with the local treatments.

➢No standard doses or protocols are available, and only some patients receive combined therapies(e.g. local treatment and ADT). At present no firm recommendations can therefore be made.

Alongi et et al, Criitical review 2013



➢Abiraterone, Enzalutamide, …a new world to explore in castation resistence patients suitable to local therapy, including reirradiation for Lymph node relapses. .

SBRT REIRRADIATION:
CLINICAL RESULTS?

Contents lists available at ScienceDirect
2015 Cancer Treatment Reviews
journal homepage: www.elsevierhealth.com/journals/ctrv
ELSEVIER

Anti-Tumour Treatment

Available evidence on re-irradiation with stereotactic ablative radiotherapy following high-dose previous thoracic radiotherapy for lung malignancies

Berardino De Bari [a], Andrea Riccardo Filippi [b,*], Rosario Mazzola [c], Pierluigi Bonomo [d], Marco Trovò [e], Lorenzo Livi [d], Filippo Alongi [f]

❑LUNG

Patients affected with intra-thoracic recurrences or secondary lung malignancies after a first course of definitive RT have limited therapeutic options, and they are often treated with a palliative intent.

Re-irradiation with stereotactic ablative radiotherapy (SABR) represents an appealing approach.

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

Table 1
Patients' characteristics of selected studies.

Author publication year [references]	Years of enrollment	Number of patients	Tumor types (no. of patients)	Infield/outfield relapses (no. of patients)	Median target volume (cc, range)	Median RT dose of the primary treatment	Interval between primary and salvage treatment	Salvage SBRT schedule
Coon et al. (2008) [23]	2005–2007	12	Locally recurrent or progressive lung cancer (NA)	NA	14 (3.4–128)	NA	NA	60 Gy/3 fx
Kelly et al. (2010) [24]	2004–2008	36	Primary lung cancer (36)	11/25*	NA	61.5 Gy (range, 30–79)	22 months	50 Gy/4fx 40 Gy/5 fx
Seung et al. (2011) [25]	2009–2010	8	Primary lung cancer (8)	NA	NA	50–68 Gy (1.8–2.5 Gy/fractions)	36 months	40 Gy/5 fx 48 Gy/4fx 50 Gy/5 fx 60 Gy/3 fx
Peulen et al. (2011) [26]	1994–2004	29	Primary (6) and lung metastases (23)	NA	(76, 16–355)	30–45 Gy/2–3 fx 40 Gy/4 fx	14 months	30–45 Gy/2–3fx 40 Gy/fx
Trakul et al. (2012) [27]	2004–2010	15	Primary (12) and lung metastases (5)**	17/0**	(31.6, 7.4–119.7)	Not specified	16 months	20 Gy/1fx 40 Gy/5 fx
Liu et al. (2012) [28]	2004–2010	72	Primary (10) and lung metastases (62)	19/53	NA	63 Gy (range, 30–79)	21 months	50 Gy/4fx
Valakh et al. (2013) [29]	2006–2011	9	Primary (8) and lung metastases (1)	3/6	(22.2 +/− 24.5)	60 Gy (range, 30–60) in 3–5 fx	NR	60 Gy (30–60)/3–5 fx
Meijneke et al. (2013) [30]	2005–2012	20	Primary (17) and Lung metastases (3)	0/20	NA	60 Gy/3fx 60–50 Gy/20–25 fx	11 months	60 Gy/5 fx 50 Gy/5 fx
Reyngold et al. (2013) [31]	2004–2011	39	Primary (17) and lung metastases (22)	22/17	(67, 17–473)	61 Gy (range, 30–79)	37 months	48 Gy/4 fx
Trovò et al. (2014) [32]	Not specified	17	Primary lung cancer (17)	17/0	NA	50–60 Gy/20–30 fx	18 months	30 Gy/5–6 fx
Hearn et al. (2014) [33]	2004–2012	10	Primary lung cancer (10)	NA	NA	50 Gy/5 fx 30 or 34 Gy/1 fx	15 months	50 Gy/5 fx 60 Gy/3 fx
Kilburn et al. (2014) [34]	2001–2012	33	Primary (29) and lung metastases (4)***	NA	NA	66 Gy (range, 45–80)	18 months	50 Gy/5 fx 20 Gy/1 fx

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

1year LC=52-95%
2 years LC=43-92%

Table 2
Clinical outcomes reported by selected studies.

Author publication year [references]	Follow-up (after salvage treatment, months)	Local control	Overall survival	Severe acute and late toxicity rates
Coon et al. (2008) [23]	12	1-Year: 92%	1-Year: 81%	NA
Kelly et al. (2010) [24]	15	2-Years: 92%	2-Years: 59%	G3 pneumonitis: 28% G3 Esophagitis: 4% Chest wall pain: 31%:
Seung et al. (2011) [25]	18	At 18 months: 86%	At 18 months: 87.5%	None
Peulen et al. (2011) [26]	12	1-Year: 52% 2-Years: 43%	1-Year: 59%	G3 pneumonitis: 30% G4–5: 13% (central lesion)
Trakul et al. (2012) [27]	15	1-Year: 65%	1-Year: 80%	None
Liu et al. (2012) [28]	16	1-Year: 95%	2-Years: 74%	G3 pneumonitis: 19% 1 pt: G5 pneumonitis
Valakh et al. (2013) [29]	22	2-Years: 75%	2-Years: 69%	Late G3 pneumonitis: 22% Late G3 chest wall pain: 11%
Meijneke et al. (2013) [30]	12	1-Years: 75% 2-Years: 50%	1-Years: 67% 2-Years: 33%	None
Reyngold et al. (2013) [31]	12	1-Year: 77% 2-Years: 64%	22 months (median)	G3 pneumonitis: 5% G4 skin:25%
Trovò et al. (2014) [32]	18	1-Year: 86%	1-Year: 59% 2-Years: 29%	G3 pneumonitis: 17% −1 pt: G5 pneumonitis −1 pt: G5 bleeding
Hearn et al. (2014) [33]	14	Not specified*	Four patients presented a local failure at a median of 9.9 months.	No G3–5 toxicity
Kilburn et al. (2014) [34]	11	2-Years: 67%	21 months (median)	Late G3 pneumonitis: 3% 1 pt: G5 aorto-esophageal fistula

Abbreviations: fx = fractions; NA = Not Available.
* In this study, authors report a description of the outcomes of the patients. Since salvage SBRT, 3 patients are alive and without evidence of disease, with follow-up of 11.7, 13.0, and 43.5 months. A fourth patient had no evidence of disease and died of medical comorbidities 13.0 months after salvage SBRT. Two patients developed distant disease despite local control at 5.1 and 15.6 months.

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

1year OS=59-87.5%
2 years OS=29-74%

Table 2
Clinical outcomes reported by selected studies.

Author publication year [references]	Follow-up (after salvage treatment, months)	Local control	Overall survival	Severe acute and late toxicity rates
Coon et al. (2008) [23]	12	1-Year: 92%	1-Year: 81%	NA
Kelly et al. (2010) [24]	15	2-Years: 92%	2-Years: 59%	G3 pneumonitis: 28% G3 Esophagitis: 4% Chest wall pain: 31%:
Seung et al. (2011) [25]	18	At 18 months: 86%	At 18 months: 87.5%	None
Peulen et al. (2011) [26]	12	1-Year: 52% 2-Years: 43%	1-Year: 59%	G3 pneumonitis: 30% G4–5: 13% (central lesion)
Trakul et al. (2012) [27]	15	1-Year: 65%	1-Year: 80%	None
Liu et al. (2012) [28]	16	1-Year: 95%	2-Years: 74%	G3 pneumonitis: 19% 1 pt: G5 pneumonitis
Valakh et al. (2013) [29]	22	2-Years: 75%	2-Years: 69%	Late G3 pneumonitis: 22% Late G3 chest wall pain: 11%
Meijneke et al. (2013) [30]	12	1-Years: 75% 2-Years: 50%	1-Years: 67% 2-Years: 33%	None
Reyngold et al. (2013) [31]	12	1-Year: 77% 2-Years: 64%	22 months (median)	G3 pneumonitis: 5% G4 skin:25%
Trovò et al. (2014) [32]	18	1-Year: 86%	1-Year: 59% 2-Years: 29%	G3 pneumonitis: 17% −1 pt: G5 pneumonitis −1 pt: G5 bleeding
Hearn et al. (2014) [33]	14	Not specified*	Four patients presented a local failure at a median of 9.9 months.	No G3–5 toxicity
Kilburn et al. (2014) [34]	11	2-Years: 67%	21 months (median)	Late G3 pneumonitis: 3% 1 pt: G5 aorto-esophageal fistula

Abbreviations: fx = fractions; NA = Not Available.
* In this study, authors report a description of the outcomes of the patients. Since salvage SBRT, 3 patients are alive and without evidence of disease, with follow-up of 11.7, 13.0, and 43.5 months. A fourth patient had no evidence of disease and died of medical comorbidities 13.0 months after salvage SBRT. Two patients developed distant disease despite local control at 5.1 and 15.6 months.

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

Table 2
Clinical outcomes reported by selected studies.

Author publication year [references]	Follow-up (after salvage treatment, months)	Local control	Overall survival	Severe acute and late toxicity rates
Coon et al. (2008) [23]	12	1-Year: 92%	1-Year: 81%	NA
Kelly et al. (2010) [24]	15	2-Years: 92%	2-Years: 59%	G3 pneumonitis: 28% G3 Esophagitis: 4%
Seun				Chest wall pain: 31%:
Peul				None
				G3 pneumonitis: 30%
Trak				G4–5: 13% (central lesion)
Liu e				None
				G3 pneumonitis: 19%
Valal				1 pt: G5 pneumonitis
				Late G3 pneumonitis: 22%
Meij				Late G3 chest wall pain: 11%
				None
Reyngold et al. (2015) [31]	12	1-Year: 77% 2-Years: 64%	22 months (median)	G3 pneumonitis: 5% G4 skin:25%
Trovò et al. (2014) [32]	18	1-Year: 86%	1-Year: 59% 2-Years: 29%	G3 pneumonitis: 17% −1 pt: G5 pneumonitis −1 pt: G5 bleeding
Hearn et al. (2014) [33]	14	Not specified*	Four patients presented a local failure at a median of 9.9 months.	No G3–5 toxicity
Kilburn et al. (2014) [34]	11	2-Years: 67%	21 months (median)	Late G3 pneumonitis: 3% 1 pt: G5 aorto-esophageal fistula

- G3 PNEUMONITIS: 3-30%
- G3 CHEST WALL PAIN: 11-31%
- G4-G5 PNEUMONITIS: 13 %(Centrally)
- G4 SKIN:25%
- G5 OTHER (FISTULA; BLEEDING: ISOLATED CASES)

Abbreviations: fx = fractions; NA = Not Available.
* In this study, authors report a description of the outcomes of the patients. Since salvage SBRT, 3 patients are alive and without evidence of disease, with follow-up of 11.7, 13.0, and 43.5 months. A fourth patient had no evidence of disease and died of medical comorbidities 13.0 months after salvage SBRT. Two patients developed distant disease despite local control at 5.1 and 15.6 months.

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

Table 3
Predictive scoring for grade 3–5 radiation pneumonitis (from Liu et al. [28]).

Score*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
⩾1	100.0	11.5	24.2	100.0
⩾2	93.3	54.4	35.0	96.9
⩾3	93.3	91.2	73.7	98.1
⩾4	26.7	98.2	80.0	83.6

* Assigned scores:
ECOG performance status 2–3 before SBRT = 1 point.
FEV1 ⩽ 65% before SBRT = 1 point.
V20 ⩾ 30% (composite plan) = 1 point.
Previous bilateral mediastinal PTV = 1 point.

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

Table 5
Dosimetric constraints.

Structure	Dose constraints	Refs.
PTV	Dose prescribed at about the 67% isodose at the periphery of the PTV	[26]
	Dose prescribed at about the 70–85% isodose, covering at least 95% of the PTV	[30]
	Dose prescribed to the isodose line covering the PTV (generally 100% isodose line).	[31]
	95% of the prescribed dose covers 95% of the PTV	[32]
	90% of the PTV had to be covered by 99% of the prescribed dose	[25]
Spinal cord	D max (1 cc) < 20 Gy, D max (10 cc) < 15 Gy.	[24,28]
Brachial plexus	D max (any point) < 40 Gy, D max (1 cc) < 35 Gy, D max (10 cc) < 30 Gy.	[24,28]
Trachea	D max (1 cc) < 35 Gy, D max (10 cc) < 30 Gy.	[24,28]
Main bronchus and bronchial tree	D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]
Heart	D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]
Esophagus	D max 35 Gy (≤1 cc), Dose to <10 cc should be max 30 Gy.	[24,28]
Whole lung (−GTV)	V 20 < 20%, V10 < 30%, V 5 < 40%	[24,28]
Major vessels	D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]
Skin	To 5 mm: D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

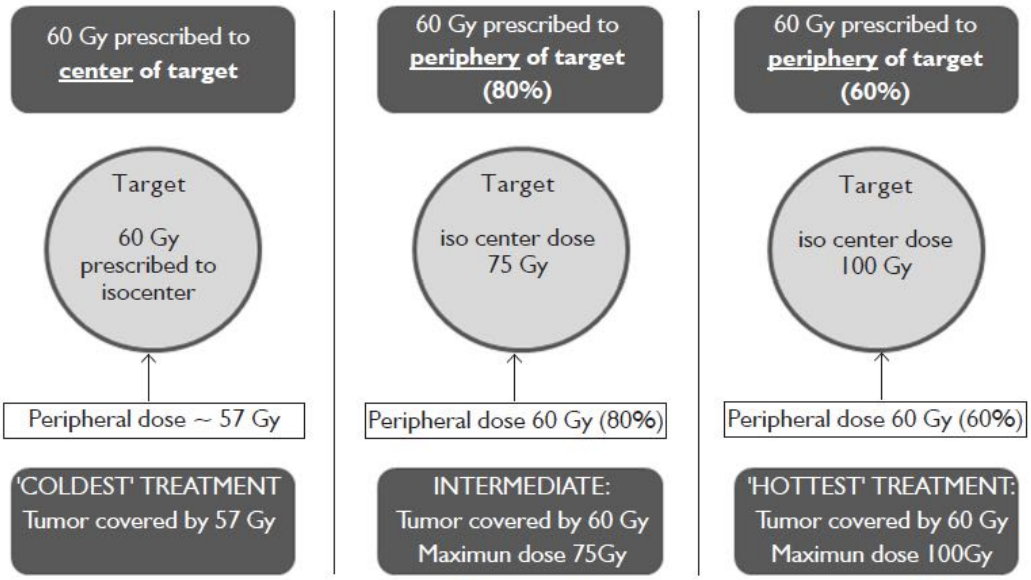
Table 5
Dosimetric constraints.

Structure	Dose constraints	Refs.
PTV	Dose prescribed at about the 67% isodose at the periphery of the PTV	[26]
	Dose prescribed at about the 70–85% isodose, covering at least 95% of the PTV	[30]
	Dose prescribed to the isodose line covering the PTV (generally 100% isodose line).	[31]
	95% of the prescribed dose covers 95% of the PTV	[32]
	90% of the PTV had to be covered by 99% of the prescribed dose	[25]
Spinal cord	D max (1 cc) < 20 Gy, D max (10 cc) < 15 Gy.	[24,28]
Brachial plexus	D max (any point) < 40 Gy, D max (1 cc) < 35 Gy, D max (10 cc) < 30 Gy.	[24,28]
Trachea	D max (1 cc) < 35 Gy, D max (10 cc) < 30 Gy.	[24,28]
Main bronchus and bronchial tree	D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]
Heart	D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]
Esophagus	D max 35 Gy (≤1 cc), Dose to <10 cc should be max 30 Gy.	[24,28]
Whole lung (−GTV)	V 20 < 20%, V10 < 30%, V 5 < 40%	[24,28]
Major vessels	D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]
Skin	To 5 mm: D max (1 cc) < 40 Gy, D max (10 cc) < 35 Gy.	[24,28]

De Bari et al, Cancer Treat Review 2015

SBRT REIRRADIATION:
CLINICAL RESULTS?

The issue of Dose Prescription in SABR



Senan S, J Thorac Dis 2011; 3:189-196

SBRT REIRRADIATION:
CLINICAL RESULTS?

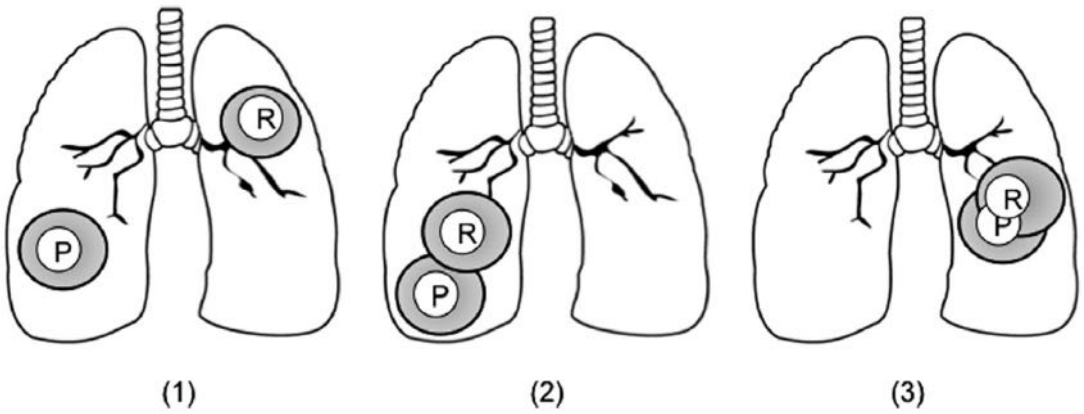
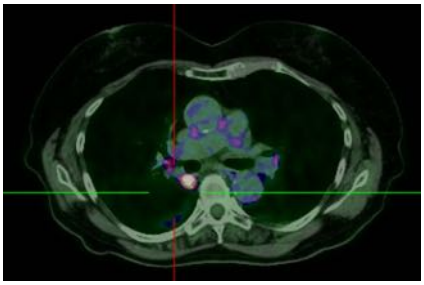
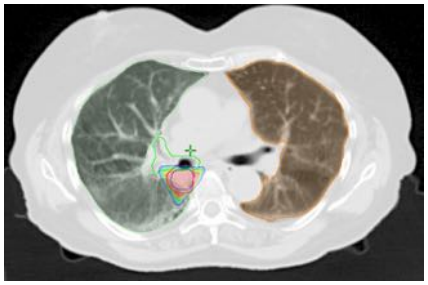
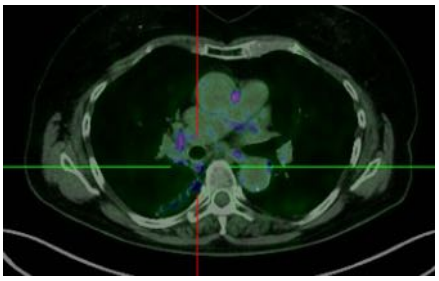


Fig. 1. This figure summarizes the 3 more frequent clinical situations in thoracic reirradiation. In the situation (1), primary tumor (P) and relapse (R) do not overlap (out-field relapse, second primary tumor) and the dose distributions (in light gray) do not overlap too. Situation (2) mimics a border-field relapse: P and R volumes do not overlap, but the doses of the 2 treatment plans do. Situation (3) simulates an in-field relapse: both treatment volumes (P and R) and dose distributions overlap.

DIFFERENT SITUATIONS WITH DIFFERENT DIFFICULTIES RATES

De Bari et al, Cancer Treat Review 2015

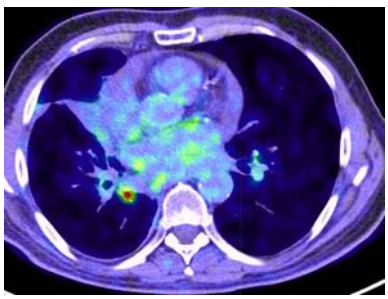
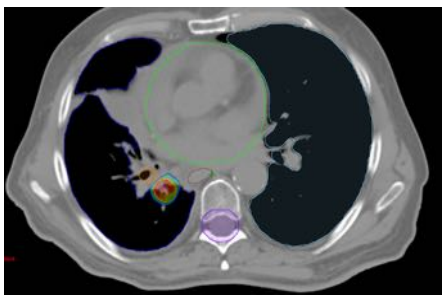
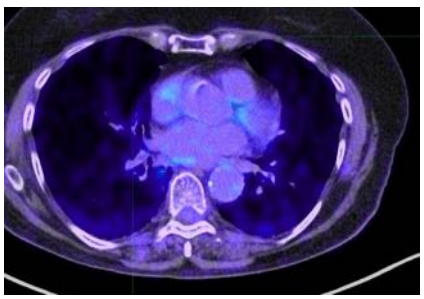
SBRT REIRRADIATION:
CLINICAL EXPERIENCE: VMAT & FFF

PET-CT before SABR | Planning CT | PET-CT at 6 months

- COMPLETE RESPONSE after **re-SBRT** (30 Gy/5) with VMAT and FFF beams.
- Toxicity : G0

SBRT REIRRADIATION:
CLINICAL EXPERIENCE: VMAT & FFF

PET-CT before SABR | Planning CT | PET-CT a 2 months

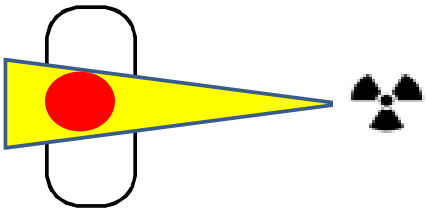
- COMPLETE RESPONSE after **re-SBRT** (30 Gy/5) with VMAT and FFF beams.
- Toxicity : G0

REIRRADIATION:

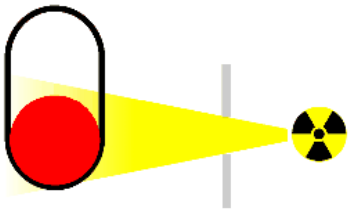
RADIATION ADVANCEMENTS: MOTION MANAGEMENT

MANAGEMENT BY TRACKING OR GATING

TRACKING



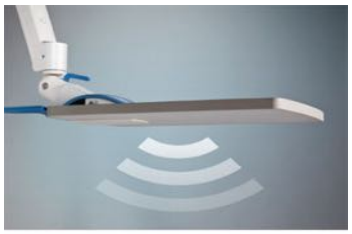
GATING



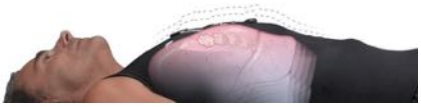
REIRRADIATION:

RADIATION ADVANCEMENTS: MOTION MANAGEMENT

MANAGEMENT BY REAL TIME TUMOR TRACKING



LINAC INTEGRATED DEVICES



DEDICATED ROBOTIC LINAC WITH INTEGRATED TRECKING SYSTEMS

SBRT REIRRADIATION:
CLINICAL RESULTS?

•In conclusion, results suggest that SABR reirradiation may provide durable in-field control for patients with recurrent primary or metastatic lung cancer.

•These outcome results appear superior to those achievable with **conventional RT and/or chemotherapy**, **often used as palliation**. However, a particular caution should be paid in patients at higher risk for radiation pneumonitis and, as central re-irradiation carries substantial risks of high-grade toxicity,

•SABR should be probably limited to favorable disease presentations (peripheral lesions, small tumor diameters, good dosimetric profile).

•No data on concomitant new durgs (**Target therapies &Targeted Re-RT?)….Even if…**

De Bari et al, Cancer Treat Review 2015

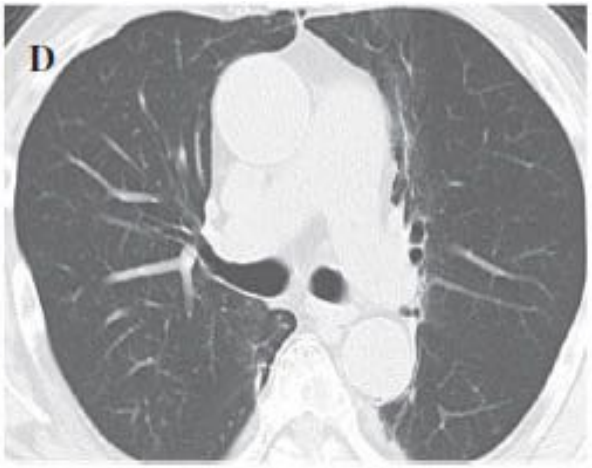
RT and new drugs

CASE REPORT Open Access

Early onset recall pneumonitis during targeted therapy with sunitinib

Takeshi Yuasa[1*], Shinichi Kitsukawa[1], Gen Sukegawa[1], Shinya Yamamoto[1], Keita Kudo[2], Kazunari Miyazawa[3], Takuyo Kozuka[3], Sohei Harada[4] and Junji Yonese[1]

Yuasa *et al. BMC Cancer* 2013, **13**:3



After the steroid pulse therapy, the symptom gradually improved over 7 days

During the treatment, serial sputum specimen and blood culture examinations did not reveal any significant bacteria or fungus.

RT and immunology

ELSEVIER

Seminars in RADIATION ONCOLOGY

The Immunology of Ablative Radiation

Byron Burnette, PhD, and Ralph R. Weichselbaum, MD

Semin Radiat Oncol 25:40-45 © 2015

Effects of Ablative Radiation Within the Target Volume

Direct Sensitization of Tumor Cells to T-cell–Mediated Killing

antigen-negative clones (antigen-loss variants).[24] Given the importance of stromal antigen presentation, Zhang et al[26] demonstrated that a single dose of 10 Gy of local radiation was sufficient to sensitize antigenic tumors to T-cell–mediated rejection through "loading" of the tumor stroma with tumor antigens. Studies from our group demonstrated a similar phenomenon, wherein local radiation of established B16 melanoma tumors with a single ablative dose of 20 Gy facilitated cross-presentation of tumor antigens by dendritic cells in the tumor stroma.[27]

Effects of Ablative Radiation Outside the Target Volume

Clinical Observations of Abscopal Responses

The term "abscopal effect" was originally coined by Mole[40] to describe the still poorly understood capacity of radiation to mediate effects on tumors outside the treatment field. A heavily favored theory suggests that the abscopal effect of radiation is mediated by augmented immune function, either cellular or cytokine mediated.[41] Abscopal regression has been reported in

Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

FUTURE OR….COMING SOON IN PRACTICE:

PROTON THERAPY?HEAVY IONS?

BIOLOGICAL PROFILING BEFORE RE-RT?

WHICH INTERACTIONS WITH NEW DRUGS??

Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

SEE YOU .. IN VERONA?