HIGHLIGHTS in RADIOTERAPIA | Update degli Studi Practice Changing 2021
Quali novità da Congressi Internazionali 2021

SBRT nelle metastasi ossee: solo palliazione?

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Advanced Radiation Therapy

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OUTLINE

- Conclusions
- Issue's Description
- Palliative SBRT – Spine
- SBRT – Non- Spine
- Non-Palliative (OLIGO) SBRT – Bone
- Focal Issues Overview (Constraints, Retreatments)
- Conclusions

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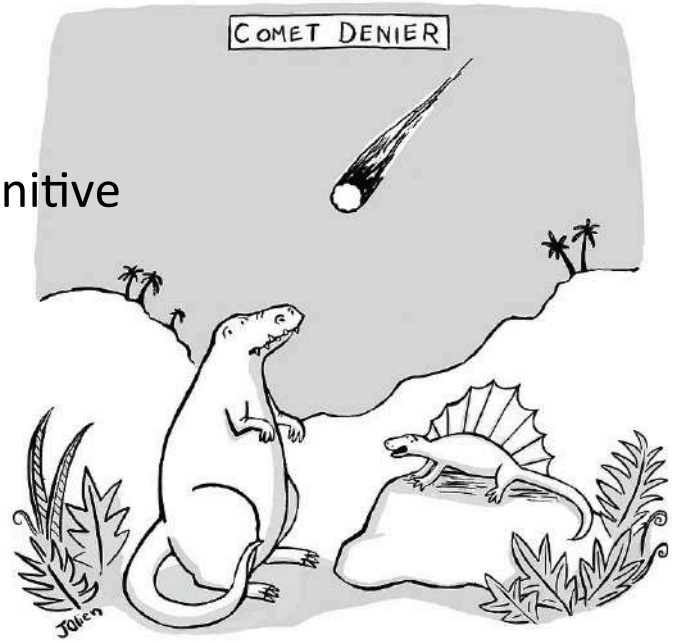
Conclusions

- ✓ Palliative Bone SBRT should not be (still, for a while) widely applied since some controversies have to be deepened
- ✓ Bone SBRT for OligoMts is highly promising but definitive technical details are lacking (still for a while)
- ✓ Bone SBRT includes indications for retreatment
- ✓ Standardization of procedure is promisly growing



"That thing's always been there."

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Issue's Description

Clinical Presentations:

- Oligometastatic Asymptomatic
- Oligometastatic Symptomatic
- Multiple Metastatic (Bone ± Visceral) Symptomatic

Metastasis Presentations (type, stability, compression, "extra-bone",etc):

- Spinal (cervical, C1-C2) 
- Non-Spinal (Sacral, Pelvic, Long bone) 

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Palliative SBRT Spine: Landmark Trial 2021

Articles

Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled phase 2/3 trial

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)
Sex		
Female	54 (47%)	55 (48%)
Male	61 (53%)	59 (52%)
Age, years		
18–59	36 (31%)	47 (41%)
60–69	36 (31%)	25 (22%)
≥70	43 (37%)	42 (37%)
Median age, years	65 (55–73)	63 (56–72)
Primary malignancy		
Breast	27 (23%)	23 (20%)
Genitourinary (excluding renal cell carcinoma)	25 (22%)	21 (18%)
Lung	26 (23%)	35 (31%)
Gastrointestinal	15 (13%)	14 (12%)
Renal cell	7 (6%)	13 (11%)
Head and neck	3 (3%)	5 (4%)
Melanoma	5 (4%)	2 (2%)
Other	7 (6%)	1 (1%)
Primary tumour classification		
Radioresistant	30 (26%)	30 (26%)
Radiosensitive	85 (74%)	84 (74%)

Shagal et al.; Lancet Oncol 2021; 22: 1023–33

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)
(Continued from previous page)		
Mass-type tumour*		
Absent	43 (37%)	41 (36%)
Present	72 (63%)	73 (64%)
ECOG performance status score		
0	14 (12%)	16 (14%)
1	90 (78%)	90 (79%)
2	11 (10%)	8 (7%)
Spinal location of target vertebrae		
Cervical	8 (7%)	11 (10%)
Thoracic	61 (53%)	50 (44%)
Lumbar	42 (37%)	41 (36%)
Sacral	4 (3%)	8 (7%)
Number of consecutive spinal segments in target volume		
1	46 (40%)	63 (55%)
2	37 (32%)	32 (28%)
3	32 (28%)	18 (16%)
>3	0	1 (1%)
Worst pain score		
2–4	43 (37%)	46 (40%)
5–7	45 (39%)	42 (37%)
8–10	27 (23%)	26 (23%)
Median pain score	5 (4–7)	5 (4–7)
SINS score		
0–6	46 (40%)	57 (50%)
7–12	69 (60%)	57 (50%)
Median SINS score†	7 (6–8)	7 (5–8)
Extent of epidural disease‡		
Unknown	0	4 (4%)
None	56 (49%)	61 (54%)
Low grade	53 (46%)	47 (41%)
High grade	6 (5%)	2 (2%)
Mean baseline oral morphine equivalent dose, mg	69·5 (105·4)	184·4 (816·7)
Geographical region		
Canada	103 (90%)	102 (89%)
Australia	12 (10%)	12 (11%)

Spine: Landmark Trial 2021

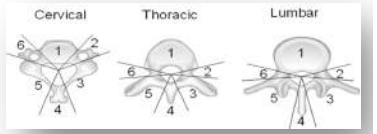
RT Schedule:

3D(mandatory)RT = 20 Gy in 5 fx

SBRT = 24 Gy in 2 fx

Baseline Imaging: MRI mandatory (compression + GVT delineation

Delineation: Cox et al Guidelines (ASTRO, IJROBP 2012)



Primary Endpoint:

Complete Response Rate @3 mth

Endpoint Measure:

International Consensus Criteria ICPRE (Chow 2012)

Secondary Endpoint:

CR Rate @6 mth; Site-PFS, OS, QoL,

Shagal et al.; Lancet Oncol 2021; 22: 1023–33

Landmark Trial 2021

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)	p value
1-month assessment			
Complete response	20 (17%)	30 (26%)	0·10*
Partial response	33 (29%)	34 (30%)	..
Stable pain	38 (33%)	26 (23%)	..
Progressive pain	14 (12%)	9 (8%)	..
Indeterminant	10 (9%)	15 (13%)	..
Mean daily OME consumption, mg	44 (122)	27 (95)	0·26
3-month assessment			
Complete response	16 (14%)	40 (35%)	0·0002*
Partial response	29 (25%)	20 (18%)	..
Stable pain	34 (30%)	27 (24%)	..
Progressive pain	14 (12%)	7 (6%)	..
Indeterminant	22 (19%)	20 (18%)	..
Mean daily OME consumption, mg	43 (106)	37 (97)	0·70
Mean change in SINS from baseline	−0·49 (1·61)	−0·94 (1·69)	0·034
6-month assessment			
Complete response	18 (16%)	37 (32%)	0·0036*
Partial response	18 (16%)	10 (9%)	..
Stable pain	32 (28%)	26 (23%)	..
Progressive pain	8 (7%)	5 (4%)	..
Indeterminant	39 (34%)	36 (32%)	..
Mean daily OME consumption, mg	36 (126)	36 (84)	1·00
Mean change in SINS from baseline	−0·74 (1·99)	−0·73 (1·86)	0·88

	Conventional external beam radiotherapy group (n=115)			Stereotactic body radiotherapy group (n=110)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Dysphagia	0	0	0	1 (1%)	1 (1%)	0
Oesophagitis*	2 (2%)	0	0	2 (2%)	0	0
Nausea	2 (2%)	1 (1%)	0	1 (1%)	0	0
Pain†	4 (3%)	5 (4%)	0	2 (2%)	5 (5%)	0
Fatigue	0	1 (1%)	0	0	0	0
Vertebral compression fracture	0	0	1 (1%)	0	1 (1%)	0

Data are n (%). Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. No grade 5 adverse events were reported. *Oesophagitis events are presented as an aggregate of oesophageal pain, oesophagitis, and pharyngeal mucositis. †Pain events are presented as an aggregate of general disorders pain, neoplasm-related tumour pain, and musculoskeletal and connective tissue disorders.

Table 5: **Incidence of grade 2 or higher treatment-related adverse events in the safety analysis population**

Shagal et al.; Lancet Oncol 2021; 22: 1023–33

Palliative SBRT Spine: Landmark Trial 2021

Spinal stereotactic radiotherapy for painful spinal metastasis

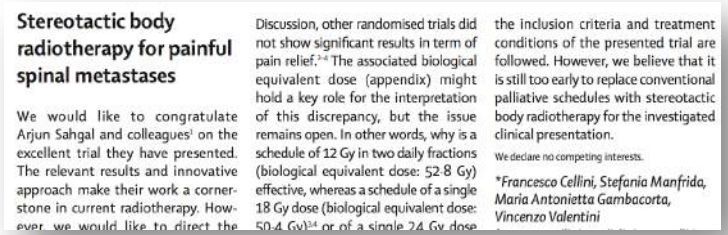
Conventional external beam radiotherapy is the standard of care for patients with cancer who have localised metastatic bone pain. Pain response is reported as a combination of complete (defined as a pain score of 0 on an 11-point scale of 0–10) and partial (defined as a reduction of ≥2 points, without an increase in analgesic consumption) responses, in accordance with the International Consensus Pain Response Endpoints to promote consistent reporting in clinical trials.[1] Pooled data from almost 30 randomised trials show that 65% of patients treated with conventional external beam radiotherapy had an overall response for pain (ie, a partial or complete response) and 25% had a complete response for pain.[1] This review[1] also showed that dose escalation with multiple fractions of conventional external beam radiotherapy did not increase the complete response rate for pain. Therefore, a dose of 8 Gy in a single fraction is considered the gold standard for treating painful bone metastases. With the aim of further improving response rates for pain, stereotactic body radiotherapy, which enables the delivery of high doses of radiation with high precision, has been studied over the past 15 years in patients with bone metastases.

In *The Lancet Oncology*, Arjun Sahgal and colleagues[2] report the findings of an open-label, multicentre, randomised, controlled, phase 2/3 trial comparing pain responses in patients with painful spinal metastases following delivery of conventional external beam radiotherapy at a dose of 20 Gy in five fractions or stereotactic body radiotherapy at a dose of 24 Gy in two fractions. Commendably, the authors completed this randomised controlled trial involving 229 participants in less than 4 years. The results showed that 16 (14%) of 115 patients in the conventional external beam radiotherapy group versus 40 (35%) of 114 patients in the stereotactic body radiotherapy group had a complete response for pain at 3 months (p=0·0002). The authors concluded that their findings support a shift toward the use of stereotactic body radiotherapy for spinal metastases in the palliative setting.

- Pooled data from almost 30 randomised trials show conventional EBRT response for pain
- Multiple fractions of conventional EBRT did not increase complete response rate for pain
- In other available Random Trials overall response rates for pain in the ITT at 3 months did not find a significant difference between conventional EBRT and SBRT
- Shagal et al. did not compare significance for Overall and specifically Partial Response
- Other Random Trials differ in size of study population and location of bone mets.
- Relevant difference among other Random Trials in applied SBRT Schedule

van der Velden, van der Linden Lancet Oncol 2021; 22
Shagal et al.; Lancet Oncol 2021; 22: 1023–33

Palliative SBRT Spine: Landmark Trial 2021



Stereotactic body radiotherapy for painful spinal metastases

We would like to congratulate Arjun Sahgal and colleagues[1] on the excellent trial they have presented. The relevant results and innovative approach make their work a cornerstone in current radiotherapy. However, we would like to direct the

Discussion, other randomised trials did not show significant results in term of pain relief.[2–4] The associated biological equivalent dose (appendix) might hold a key role for the interpretation of this discrepancy, but the issue remains open. In other words, why is a schedule of 12 Gy in two daily fractions (biological equivalent dose: 52·8 Gy) effective, whereas a schedule of a single 18 Gy dose (biological equivalent dose: 50·4 Gy)[3,4] or of a single 24 Gy dose

the inclusion criteria and treatment conditions of the presented trial are followed. However, we believe that it is still too early to replace conventional palliative schedules with stereotactic body radiotherapy for the investigated clinical presentation.

We declare no competing interests.

*Francesco Cellini, Stefania Manfrida, Maria Antonietta Gambacorta, Vincenzo Valentini

- ✓ The workflow to select the best treatment for each presentation needs to be further refined
- ✓ The biological equivalent dose (BED) associated to different schedules applied might hold a key role for the interpretation of this discrepancy
- ✓ Delineation is not yet unanimously agreed on by clinicians and could affect real-word practice
- ✓ We believe that it is still too early to replace conventional palliative schedules with SBRT

Cellini, Manfrida, Gambacorta, Valentini; Lancet Oncol 2021; 22
van der Velden, van der Linden; Lancet Oncol 2021; 22
Shagal et al.; Lancet Oncol 2021; 22: 1023–33

Palliative SBRT Spine: Landmark Trial 2021

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50·4 Gy)[3,4] or of a singl

Author/Protocol	N° of Fractions	Total Dose	Dose per Fraction	BED10	Symptom Relief Statistical Significance
Sprave et al[2]	1	24	24	81,6	Not significant
Ryu et al /RTOG 0631[4]	1	18	18	50,4	Not significant
Pielkenrood et al/VERTICAL[3]	1	18	18	50,4	Not significant
Pielkenrood et al/VERTICAL[3]	3	30	10	60	Not significant
Pielkenrood et al/VERTICAL[3]	5	35	7	59.5	Not significant
Shagal et al[1]	**2**	**24**	**12**	**52,8**	**Significant**
Cellini et al/PREST[5]	3	30/21 (SIB GTV/vertebra)	10/7 (SIB GTV/vertebra)	60 /35,7 (SIB GTV/vertebra)	Ongoing study

(Abbreviations: N°= number; BED_{10}= Biological Equivalent Dose; SIB= Simultaneous Integrated boost

tment for each presentation needs

associated to different schedules

interpretation of this discrepancy

greed on by clinicians and could

replace conventional palliative

Cellini, Manfrida, Gambacorta, Valentini; Lancet Oncol 2021; 22
van der Velden, van der Linden; Lancet Oncol 2021; 22
Shagal et al.; Lancet Oncol 2021; 22: 1023–33

Palliative SBRT Spine: Landmark Trial 2021

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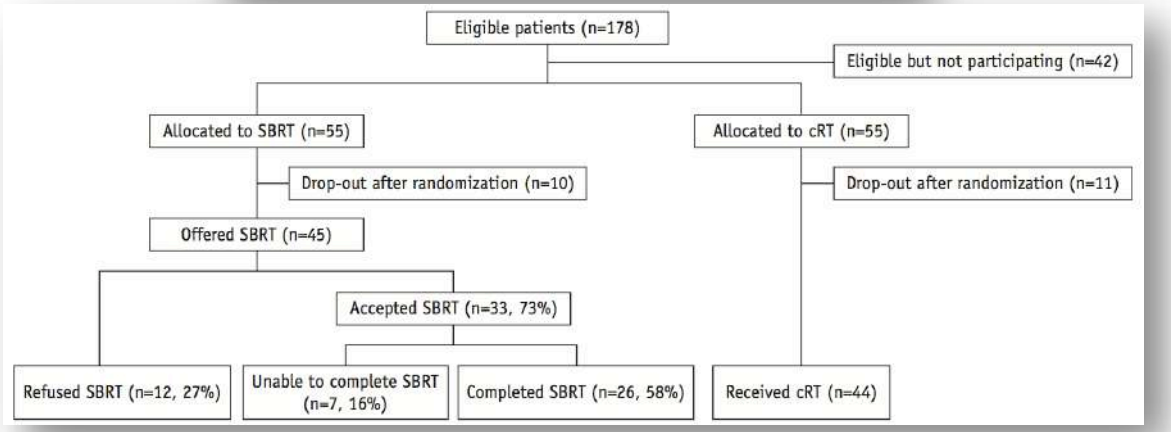
Clinical Investigation

Pain Response After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases—A Phase 2 Randomized Controlled Trial Within a Prospective Cohort



Pielkenrood et al.; IJROBP 2021; Volume 110 Number 2 2021

ve SBRT Spine: Landmark Trial 2021

Table 1 Baseline characteristics of patients with painful bone metastases enrolled in the VERTICAL trial

Characteristics	Conventional radiation therapy group (N = 44)	Stereotactic body radiation therapy group N = 45
Male sex, n (%)*	31 (70)	24 (53)
Median age (IQR), y	63 (57-73)	65 (61-72)
Median Charlson comorbidity index (IQR)†	6 (6-7)	6 (6-7)
Karnofsky performance status, n (%)‡		
0-50	1 (3)	2 (6)
60-7	11 (37)	14 (40)
80-100	18 (60)	19 (42)
Primary tumor site, n (%)		
Lung	9 (21)	14 (31)
Breast	8 (18)	9 (20)
Prostate	9 (21)	11 (24)
Other§	18 (40)	11 (24)
Location bone metastases, n (%)		
Spine	22 (50)	27 (60)
Nonspine	22 (50)	18 (40)
Median pain score at baseline, NRS (IQR)	6.2 (2)	6.6 (1.8)
Pain medication at baseline, n (%)		
None	7 (16)	7 (16)
Nonopioid	15 (34)	15 (33)
Weak opioid	1 (2)	1 (2)
Strong opioid	21 (48)	22 (49)
Median oral morphine equivalent dose in mg (IQR)	60 (40-120)	60 (40-110)

RT Schedule:

3D RT = 8 Gy in 1 fx
20 Gy in 5 fx
30 Gy in 10 fx

SBRT = 18 Gy in 1fx
30 Gy in 3fx
35 Gy in 5fx

Baseline Imaging: MRI mandatory (compression + GVT delineation)

Delineation: SIB (margin expansion for non-spinal)

Primary Endpoint: Pain Response @3 mth (Complete + Partial)

Endpoint Measure: International Consensus Criteria ICPRE (Chow 2012)

Secondary Endpoint: OMED us; QoL, Toxicity

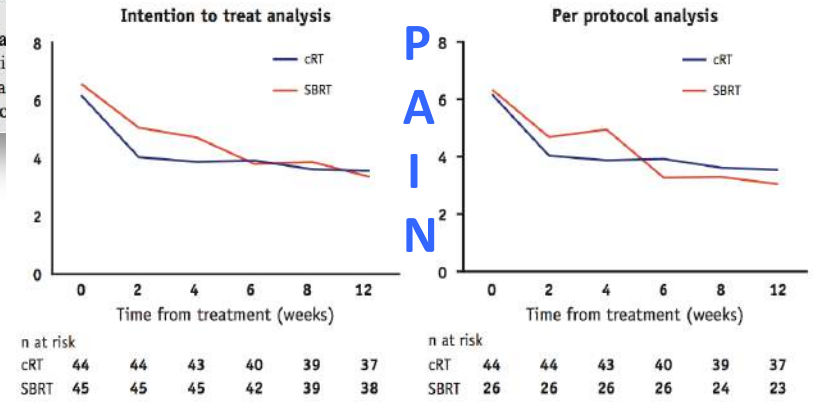
Pielkenrood et al.; IJROBP 2021; Volume 110 Number 2 2021

Palliative SBRT Spine: Landmark Trial 2021

Table 3 Patients who perceive a pain response after radiation therapy (n), according to treatment*

Analyses	At 2 wk	At 4 wk	At 6 wk	At 8 wk	At 3 mo
ITT analysis					
cRT	19/44 (43%)	19/44 (43%)	13/44 (30%)	16/44 (36%)	14/44 (32%)
SBRT	18/45 (40%)	16/45 (36%)	19/45 (42%)	17/45 (44%)	18/45 (40%)
PP analysis (patients undergoing allocated treatment)					
cRT	19/44 (43%)	19/44 (43%)	13/44 (30%)	16/44 (36%)	14/44 (32%)
SBRT	12/26 (46%)	10/26 (39%)	13/26 (50%)	11/26 (42%)	12/26 (46%)
ITT analysis of evaluable patients†					
cRT	19/32 (59%)	19/33 (58%)	13/27 (48%)	16/28 (57%)	14/23 (61%)
SBRT	18/37 (49%)	16/36 (44%)	19/32 (59%)	17/33 (52%)	18/31 (58%)

Abbreviations: cRT = con… …ctic body radiation therapy.
* Presented as n/N (%). Pa… …sensus criteria.[4] In the ITT and PP analysis, pati… …nalysable patients, only patients who returned a…
† Number of patients repo…



PAIN

Table 4 Global quality of life scores of the EORTC-QLQ-C15 questionnaire*

	Baseline	At 4 wk	At 8 wk	At 3 mo
Conventional external beam radiation therapy	67 (50-67)	67 (50-83)	67 (67-83)	67 (67-83)
Stereotactic body radiation therapy	67 (50-67)	50 (50-67)	67 (50-83)	67 (50-83)

* Presented as median (interquartile range).

Pielkenrood et al.; IJROBP 2021; Volume 110 Number 2 2021

Palliative SBRT Spine: Landmark Trial 2021

- It might be argued that a 25% improvement was already an ambitious expectation (unfortunate loss of participants in the SBRT arm, a clinically significant difference of say 10% or more would be easily missed)
- Higher response rates in the SBRT arm; however wide confidence intervals highlights the statistical uncertainty
- Pielkenrood et al suggests that SBRT logistics remain less efficient
- Cost effectiveness is also not addressed in the current literature
- Dose response for metastatic bone pain at greater than a single dose of 8 Gy, not demonstrated: tumor cell kill is not the entire answer to pain relief
- Central issue in this discussion: we must not be transfixed by the lure of new technology but acknowledge that a small subgroup, possibly those with spinal oligometastases

Hoskin et al.; IJROBP 2021; Vol. 110, No. 2, pp. 368-370, 2021
Pielkenrood et al.; IJROBP 2021; Volume 110 Number 2 2021

Palliative SBRT Spine: Summary RANDOMIZED Trial (published)

Author/ Year	Trial Type	N° Pat	Spine/ Non-Spine	Selection	Baseline Pain	Chow Criteria ICPRE	Blisky	Paraspinal	N° Vert Irradiated	MRI	Delineation
Sprave 2018	Ph 2	55	Spine (Thor-Lumbar)	Max 3 Lesion		Yes	Over 3 mm	NS	Max 2	Mandatory	Margin Expansion
RTOG (Ryu) 2019	Ph 2/ Ph 3 (Planned)	339	Spine (Cervical Included)	Max 3 Lesion	>5	No	Over 3 mm	<5 cm	Max 2	Mandatory	Vertebral Body + Pedicles + GTV paraspinal
Shagal 2021	Ph 2/ Ph 3 (Unplanned)	229	Spine (Cervical + Sacral Included)	Any Lesion	≥2	Yes		Included	Max 3 (RT on other M allowed)	Mandatory	Cox 2012 ASTRO
Pielkenrood 2021	Ph 2	110	Spine (apart C1-C2) + Non-Spine	Max 2 Lesion (part of Present Trial)	≥3	Yes				Mandatory	SIB (Margin Expansion)

Palliative SBRT Spine: Summary RANDOMIZED Trial (published)

Author/ Year	Trial Type	Total Dose	Dose Fraction	N° Fractions	BED	Set-Up	IGRT
Sprave 2018	Ph 2	SBRT 24	SBRT 24	SBRT 1	SBRT 81	Mask, VacLoc	2 CBCT
		RT 30	RT 3	RT 10	RT 39		
RTOG (Ryu) 2019	Ph 2/ Ph 3 (Planned)	SBRT 16 (18)	SBRT 16 (18)	SBRT 1	SBRT 41,6 (50,4)	NS	<2 mm error Images (2D-3D)
		RT 8	RT 8	RT 1	RT 14,4		
Shagal 2021	Ph 2/ Ph 3 (Unplanned)	SBRT 24	SBRT 12	SBRT 2	SBRT 52,8	Mask	2 CBCT <1 mm <1 degree
		RT 20	RT 4	RT 5	RT 28		
Pielkenrood 2021	Ph 2	SBRT 8/18 SBRT 15/30 SBRT 20/35	SBRT 8/18 SBRT 5/10 SBRT 4/7	SBRT 1 SBRT 3 SBRT 5	SBRT 14,4/50,4 SBRT 22,5/60 SBRT 28/59,4	Mask, VacLoc	NS
		RT 8 RT 20 RT 30	RT 8 RT 4 RT 3	RT 1 RT 5 RT 10	RT 14,4 RT 28 RT 39		

Palliative SBRT Spine: Summary RANDOMIZED Trial (published)

Author/Year	Primary Endpoint	Median Fup	Compliance	Pain Response 3 mth	QoL	Local Control	OS	Toxicity	% Collapse
Sprave 2018	Pain Response 3 + 6 mth	8,1 mth	100% (both arms)	SBRT 43,5 vs RT 17,4 (p=0,0568) [6 mth SBRT 52,6 vs RT 10 (p=0,0034)]	No Diff	NR	Mean 7,9 mth	No Grade 3	0%
RTOG (Ryu) 2019	Pain Response 3 mth	NR	NS	SBRT 40,3 vs RT 57,9 (p=0,99)	NS	NR	NR	No Diff	NR
Shagal 2021	Complete Response 3 mth	6,7 mth	97% (both arms)	(CR) SBRT 35 vs RT 14 (p=0,0002)	No Diff	6 mth SBRT 97 vs RT 90	6 mth SBRT 77% vs RT 73%	Grade >3 1-5% both	SBRT 11% vs RT 17%
Pielkenrood 2021	Overall CR + PR 3 mth	NR	84% SBRT 100% RT (27% refused SBRT)	(CR+PR ITT) SBRT 40 vs RT 32 (Not sign.)	No Diff	NR	6 mth 85%		NS

ed)

Clinical Trial > Int J Radiat Oncol Biol Phys. 2021 Jun 1;110(2):348-357.
doi: 10.1016/j.ijrobp.2020.12.045. Epub 2021 Jan 4.

Long-Term Results of Dose-Intensified Fractionated Stereotactic Body Radiation Therapy (SBRT) for Painful Spinal Metastases

Matthias Guckenberger [1], Frederick Mantel [2], Reinhart A Sweeney [3], Maria Hawkins [4], José Belderbos [5], Merina Ahmed [6], Nicolaus Andratschke [7], Indira Madani [7], Michael Flentje [2]

Affiliations + expand

PMID: 33412262 DOI: 10.1016/j.ijrobp.2020.12.045

Abstract

Purpose: To report long-term outcome of fractionated stereotactic body radiation therapy (SBRT) for painful spinal metastases.

Methods and materials: This prospective, single-arm, multicenter phase 2 clinical trial enrolled 57 patients with 63 painful, unirradiated spinal metastases between March 2012 and July 2015. Patients were treated with 48.5 Gy in 10 SBRT fractions (long life expectancy [Mizumoto score ≤4]) or 35 Gy in 5 SBRT fractions (intermediate life expectancy [Mizumoto score 5-9]). Pain response was defined as pain improvement of a minimum of 2 points on a visual analog scale, and net pain relief was defined as the sum of time with pain response (complete and partial) divided by the overall follow-up time.

Results: All 57 patients received treatment per protocol; 32 and 25 patients were treated with 10- and 5-fraction SBRT, respectively. The median follow-up of living patients was 60 months (range, 33-74 months). Of evaluable patients, 82% had complete or partial pain response (responders) at 3 months' follow-up (primary endpoint), and pain response remained stable over 5 years. Net pain relief was 74% (95% CI, 65%-80%). Overall survival rates of 1, 3, and 5 years were 59.6% (95% CI, 47%-72%), 33.3% (95% CI, 21%-46%), and 21% (95% CI, 10%-32%), respectively. Freedom from local spinal-metastasis progression was 82% at the last imaging follow-up. Late grade-3 toxicity was limited to pain in 2 patients (nonresponders). There were no cases of myelopathy. SBRT resulted in long-term improvements of all dimensions of the 5-level EuroQol 5-Dimension Questionnaire except anxiety/depression.

Conclusions: Fractionated SBRT achieved durable pain response and improved quality of life at minimum late toxicity.

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Palliative SBRT Spine: Summary Trial (published)

Cellini et al. Trials (2019) 20:609
https://doi.org/10.1186/s13063-019-3676-x

Trials

STUDY PROTOCOL Open Access

Pain REduction with bone metastases STereotactic radiotherapy (PREST): A phase III randomized multicentric trial

Francesco Cellini[1], Stefania Manfrida[1], Francesco Deodato[2], Savino Cilla[3], Ernesto Maranzano[4], Stefano Pergolizzi[5], Fabio Arcidiacono[6], Rossella Di Franco[6], Francesco Pastore[7], Matteo Muto[8], Valentina Borzillo[9], Costanza Maria Donati[9], Giambattista Siepe[9], Salvatore Parisi[10], Antonia Salatino[11], Antonino D'Agostino[12], Giampaolo Montesi[13], Anna Santacaterina[14], Vincenzo Fusco[15], Mario Santarelli[16], Maria Antonietta Gambacorta[1,17], Renzo Corvò[18], Alessio Giuseppe Morganti[9], Valeria Masiello[1], Paolo Muto[6] and Vincenzo Valentini[1,17]

Abstract

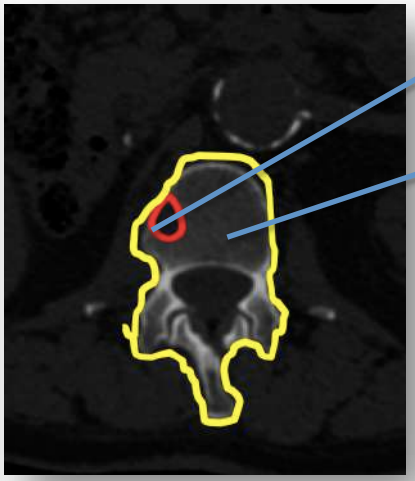
Background: Palliative antalgic treatments represent an issue for clinical management and a challenge for scientific research. Radiotherapy (RT) plays a central role. Techniques such as stereotactic body radiotherapy (SBRT) were largely investigated in several phase 2 studies with good symptom response, becoming widely adopted. However, evidence from randomized, direct comparison of RT and SBRT is still lacking.

Methods/design: The PREST trial was designed as an interventional study without medicinal treatment. It is a phase 3, open-label, multicentric trial randomized 1:1. Inclusion criteria include painful spinal bone metastases presenting with a pain level > 4 (or > 1 if being treated with an analgesic) on the Numeric Rating Scale (NRS); expected intermediate/high prognosis (greater than 6 months) according to the Mizumoto prognostic score; low spine instability neoplastic score (SINS) score (< 7); magnetic resonance imaging (MRI) assessment of the bulky lesion. Patients will be assigned to either standard conventional radiotherapy involving 4 Gy x 5 fractions (fx) to the whole involved vertebra or SBRT by intensity modulated radiotherapy with simultaneous integrated boost (IMRT-SIB) involving 7 Gy x 3 fx to the whole involved vertebra + 10 Gy x 3 fx on the macroscopic lesion (gross tumor volume (GTV)). In the experimental arm, the GTV will be contoured by registration with baseline MR.

Discussion: The primary endpoint is overall pain reduction, defined in terms of variation between baseline and 3-month evaluation; pain will be measured using the NRS. Secondary endpoints include pain control duration; retreatment rates (after a minimum interval of 1 month); local control assessed with RECIST criteria; symptom progression free survival; progression-free survival; overall survival; and quality of life (at 0, 30, and 90 days). Accrual of 330 lesions is planned. The experimental arm is expected to have an improvement in overall pain response rates of 15% with respect to the standard arm (60% according to Chow et al. (Int J Radiat Oncol Biol Phys. 82(5):1730–7, 2012)).

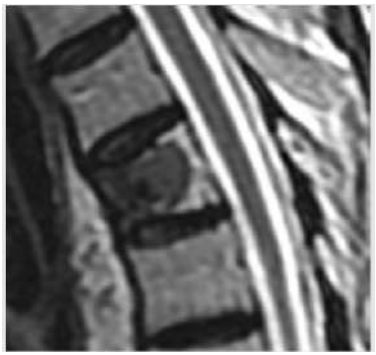
Trial registration: ClinicalTrials.gov, NCT03597984. Registered on July 2018.

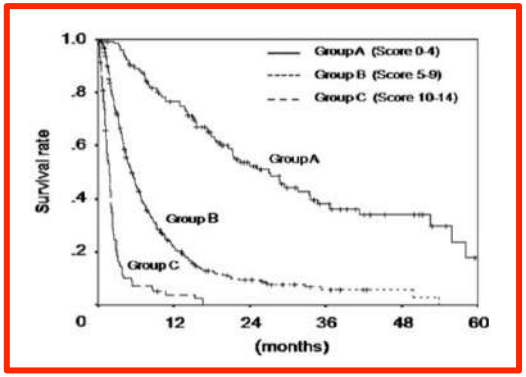
Keywords: Bone metastases, Pain control, Simultaneous integrated boost, Randomised controlled trial



10 Gy x 3

7 Gy x 3





OUTLINE

- Conclusions
- Issue's Description
- Palliative SBRT – Spine
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- Non-Palliative (OLIGO) SBRT – Bone
- Focal Issues Overview (Constraints, Retreatments)
- Conclusions

NON Spine: Landmark Trial 2021

Table 2. Summary of lesion and treatment characteristics

Lesion/treatment characteristics	n=181
Location of lesion	
Pelvis	68 (37.6%)
Rib	62 (34.3%)
Hip/femur	23 (12.7%)
Shoulder/humerus	13 (7.2%)
Sternum	6 (3.3%)
Skull	9 (5.0%)
Type of lesion	
Lytic	37 (22.2%)
Sclerotic	118 (70.7%)
Mixed	12 (7.2%)
GTV, median (range, cc)	5.7 (0.19–552)
PTV, median (range, cc)	23.9 (2.8–686.9)
Prescription regimen (Fractional dose in Gy × fractions)	
9 × 3	42 (23.2%)
10 × 3	34 (18.8%)
6 × 5	27 (14.9%)
15 × 1	12 (6.6%)
5 × 5	11 (6.1%)
8 × 3	9 (5.0%)
7 × 3	8 (4.4%)
8 × 5	8 (4.4%)
11 × 3	4 (2.8%)
Other	21 (11.6%)
BED10, median (range, Gy)	51.3 (28–81.6)

- Retrospective (largest series to date)
- 181 lesions in 116 patients
- Oligometastatic: 100/116 patients (85.5%)
- CTV= expansion margin at the treating radiation oncologist's discretion was applied to the GTV
- Median Dose was 27 Gy (range 15-40) in 3 fractions (range 1-6)
- Local Recurrence: @6 mth=2.8%; @1 yr = 7.2% ; @2 yrs=12.5%
- Fractures: 11/181 lesions (6%)
- Notes: -increasing PTV predicted for Local Recurrence;
  -predictors of fracture risk: lytic lesions and poorer KPS

Cao et al.; JRS Vol. 7, pp. 199-206 - 2021

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Università Cattolica del Sacro Cuore

Palliative SBRT NON Spine: Landmark Trial 2021

International Multi-institutional Patterns of Contouring Practice and Clinical Target Volume Recommendations for Stereotactic Body Radiotherapy for Non-Spine Bone Metastases

Timothy K Nguyen[1] MD, Lee Chin[2] PhD, Arjun Sahgal[2] MD, Roi Dagan[3] MD, MS, Wietse Eppinga[4] MD, Matthias Guckenberger[5] MD, Jin Ho Kim[6] MD, PhD, Simon S Lo[7] MD, Kristin J Redmond[8] MD, MPH, Shankar Siva[9] MBBS, PhD, Bradley J Stish[10] MD, Rachel Chan[11] PhD, Liam Lawrence[12] MASc, Angus Lau[11-12] PhD, Chia-Lin Tseng[2] MD

- Eleven cases of Non SPINE were contoured by nine international radiation oncologists
- GTV was provided on the simulation CT scans with accompanying MR imaging
- Six participants used a single dose level, while 3 used a two-dose level simultaneous integrated boost (SIB) technique. For the SIB cases, the largest volume receiving an SBRT dose was used for contour analysis

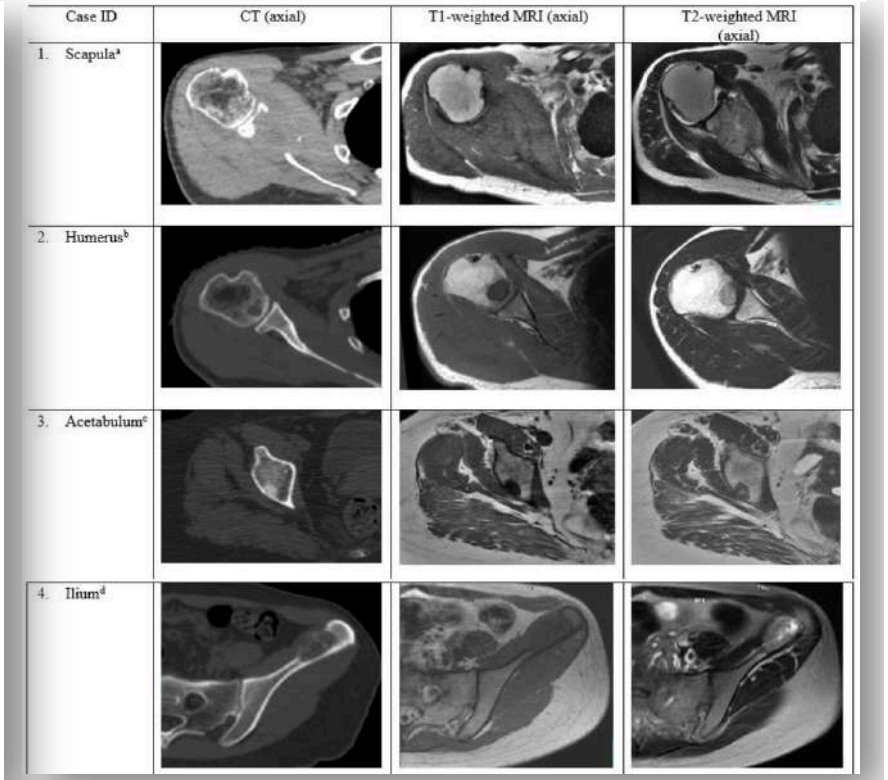
Nguyen et al.; IJROBP; Feb 1;112(2):351-360 -2022

Palliative SBRT NON Spine: Landmark Trial 2021

Table 2: Contour agreement between participants using STAPLE analysis

Case Identification	Mean volume (range) (cm^3)	STAPLE Volume (cm^3)	Mean SPEC ± SD	Mean SENS ± SD	Kappa (κ)	Mean DSC Value
1. Scapula	174.1 (101.4-217.2)	179.9	0.97±0.03	0.91±0.14	0.82	0.86
2. Humerus	12.1 (3.4-23.1)	11.4	0.96±0.07	0.82±0.15	0.61	0.67
3. Acetabulum	19.7 (8.0-43.0)	16.9	0.96±0.07	0.87±0.16	0.65	0.72
4. Ilium	32.6 (15.2-39.0)	33.9	0.97±0.03	0.86±0.16	0.86	0.74
5. Ischium	24 (15.5-36.4)	22.0	0.96±0.04	0.9±0.1	0.73	0.78
6. 5th Rib	61.0 (36.4-76.2)	71.1	0.99±0.01	0.82±0.18	0.79	0.77
7. Ilium	65.6 (43.9-157.3)	60.0	0.99±0.03	0.86±0.11	0.71	0.70
8. Sternum	13.6 (7.4-21.7)	14.5	0.97±0.04	0.80±0.14	0.68	0.82
9. Clavicle	7.9 (4.4-12.1)	10.0	0.99±0.02	0.72±0.19	0.69	0.73
10. Femur	225.7 (142.3-357.0)	210.2	0.94±0.08	0.91±0.1	0.74	0.82
11. Pubic Symphysis	12.0 (6.4-23.8)	9.6	0.95±0.08	0.90±0.12	0.65	0.73

Final Pre-proof



Nguyen et al.; IJROBP; Feb 1;112(2):351-360 -2022

Palliative SBRT NON Spine: Landmark Trial 2021

Table 4: Consensus Recommendations for CTV Delineation of Non-spine Bone Metastases

Recommendation	Level of Participant Agreement
An intraosseous CTV margin of 5-10mm within contiguous bone should be strongly considered.	Strongly agree (n=7) Agree (n=2)
An extraosseous CTV margin of 5-10mm should be strongly considered in cases of associated soft tissue disease and/or significant cortical bone disruption.	Strongly agree (n=8) Agree (n=1)
All CTVs should be manually cropped to respect natural anatomical barriers to spread including: uninvolved joint spaces, uninvolved organs-at-risk, peritoneal cavity, pleura, and intact cortical bone.	Strongly agree (n=9)

Proof

Nguyen et al.; IJROBP; Feb 1;112(2):351-360 -2022

Palliative SBRT Spine: Summary Remarks

METASTASI OSSEE E SALUTE DELL'OSSO — LINEE GUIDA 2021 — AIOM

6.8. Il paziente con metastasi ossee può beneficiare anche delle tecniche di Radiochirurgia e Radioterapia Stereotassica?

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Per pazienti, sintomatici, a buona prognosi con coinvolgimento del rachide, l'impiego di moderne tecnologie radioterapiche dovrebbe essere preso in considerazione preferibilmente all'interno di studi clinici, oppure per casi selezionati, applicando l'approccio riportato da Shagal et al., preferibilmente in Centri ad alto volume per SBRT IGRT.	**Positiva Debole**

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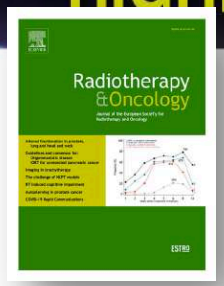


Palliative SBRT OLIGO M+: Landmark Trial 2021

Journal Pre-proofs

Original Article

An international pooled analysis of SBRT outcomes to oligometastatic spine and non-spine bone metastases

Yilin Cao, Hanbo Chen, Arjun Sahgal, Darby Erler, Serena Badellino, Tithi Biswas, Roi Dagan, Matthew C. Foote, Alexander V. Louie, Ian Poon, Umberto Ricardi, Kristin J. Redmond

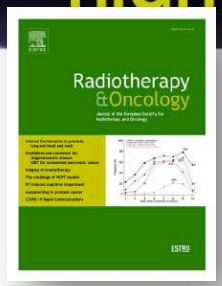
PII: S0167-8140(21)06705-0
DOI: https://doi.org/10.1016/j.radonc.2021.08.011
Reference: RADION 8938

- Retrospective (2007-2016)
- Oligometastatic (<5 cumulative extracranial metastases)
- 356 patients (Bone lesions: Spine; NON Spine; Both)
- 288 spine and 233 NON Spine

- Local Recurrence: @6 mth=6,3%; @1 yr = 12,6% ; @2 yrs=19,3%

- Notes: Univariable analysis suggested inferior LC and OS in spine patients; this did not hold true in multivariable analysis

Cao et al.; Radiother Oncol; 2021 Nov;164:98-103



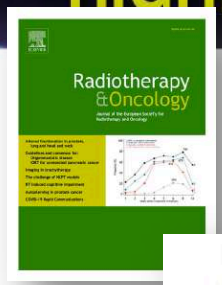
Palliative SBRT OLIGO M+:

Table 2: Summary of lesion and treatment characteristics

Lesion-level characteristics	Non-spine bone lesions n = 233	Spine lesions n = 288	pValue
Non-Spine Bone Location			
Hip/Lower Limb	38 (16.3%)		
Pelvis	82 (35.2%)		
Rib	68 (29.2%)	N/A	
Shoulder/Upper Limb	27 (11.6%)		
Skull	3 (1.3%)		
Sternum	10 (4.3%)		
Other	5 (2.1%)		
Spinal Level Location			
C-Spine		15 (5.2%)	
T-Spine	N/A	147 (51.0%)	
L-Spine		80 (27.8%)	
Sacrum		30 (10.4%)	
Overlapping		16 (5.6%)	
Soft Tissue/Paraspinal Extension	37 (15.9%)	78 (27.1%)	0.002
Epidural Disease	N/A	51 (17.7%)	
Dose/Fractionation (Gy/fx)			
15-18/1	6 (2.6%)	12 (4.2%)	
20-28/1	10 (4.3%)	27 (9.4%)	
24-31/2	27 (11.6%)	28 (9.7%)	
24-28/3-5	10 (4.3%)	116 (40.3%)	
30-35/3-5	87 (37.3%)	76 (26.4%)	
40-45/4-5	10 (4.3%)	--	
50/5	47 (20.2%)	15 (15.2%)	
50/10	36 (15.5%)	14 (4.9%)	
Mean BED10, Gy (SD)	66.5 (18.3)	57.6 (14.8)	<0.001
Mean PTV, cc (SD)	71.7 (123.3)	82.7 (72.3)	0.204
Mean PTV Dmax (BED10), Gy (SD)	81.9 (26.5)	86.1 (22.6)	0.051
Mean PTV Dmin (BED10), Gy (SD)	43.9 (17.3)	22.8 (12.7)	<0.001
Mean PTV Dmean (BED10), Gy (SD)	70.6 (20.9)	63.8 (15.8)	<0.001
Re-irradiation	10 (4.3%)	9 (3.1%)	0.637

Journal Pre-proof

Cao et al.; Radiother Oncol; 2021 Nov;164:98-103



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			0.002
			<0.001
			0.204
			0.051
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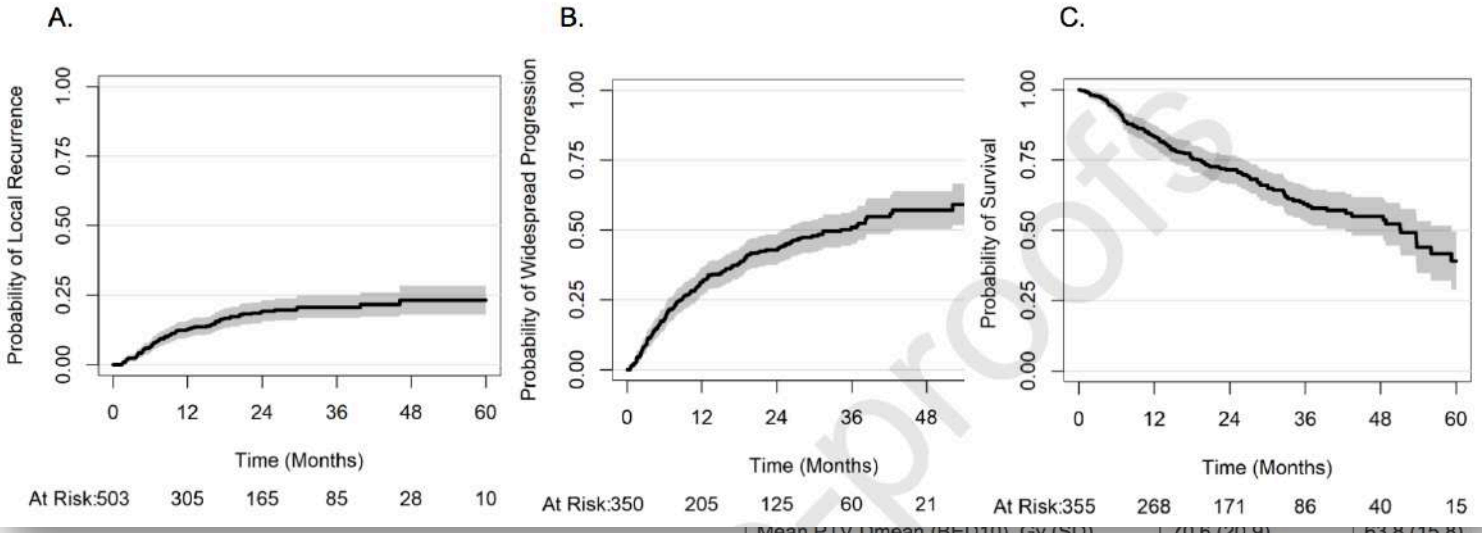
Mean PTV Dmean (BED10), Gy (SD)	70.6 (20.9)	63.8 (15.8)	<0.001
Re-irradiation	10 (4.3%)	9 (3.1%)	0.637

Figure 1: Plots of cumulative incidence of local recurrence, cumulative incidence of widespread progression, and overall survival



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Cao et al.; Radiother Oncol; 2021 Nov;164:98-103

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Review > Int J Radiat Oncol Biol Phys. 2021 May 1;110(1):124-136.
doi: 10.1016/j.ijrobp.2019.09.038. Epub 2019 Oct 10.

Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

Arjun Sahgal [1], Joe H Chang [2], Lijun Ma [3], Lawrence B Marks [4], Michael T Milano [5], Paul Medin [6], Andrzej Niemierko [7], Sc
Ellen Yorke [10], Jimm Grimm [11], Andrev

Abstract

Spinal cord tolerance data for stereotactic body radiation therapy (SBRT) were extracted from published reports, reviewed, and modelled. For de novo SBRT delivered in 1 to 5 fractions, the following spinal cord point maximum doses (D_{max}) are estimated to be associated with a 1% to 5% risk of radiation myelopathy (RM): 12.4 to 14.0 Gy in 1 fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions. For reirradiation SBRT delivered in 1 to 5 fractions, reported factors associated with a lower risk of RM include cumulative thecal sac equivalent dose in 2 Gy fractions with an alpha/beta of 2 ($EQD2_2$) D_{max} ≤70 Gy; SBRT thecal sac $EQD2_2$ D_{max} ≤25 Gy, thecal sac SBRT $EQD2_2$ D_{max} to cumulative $EQD2_2$ D_{max} ratio ≤0.5, and a minimum time interval to reirradiation of ≥5 months. Larger studies containing complete institutional cohorts with dosimetric data of patients treated with spine SBRT, with and without RM, are required to refine RM risk estimates.

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Advanced Radiation Therapy

> Strahlenther Onkol. 2021 May;197(5):369-384. doi: 10.1007/s00066-021-01748-7.
Epub 2021 Feb 26.

Cumulative dose, toxicity, and outcomes of spinal metastases re-irradiation : Systematic review on behalf of the Re-Irradiation Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO)

Antonio Pontoriero [1], Sara Lillo [2], Luciana Caravatta [3], Fabiana Bellafiore [4], Silvia Longo [5], Elisabetta Lattanzi [6], Silvana Parisi [7], Francesco Fiorica [8], Mariangela Massaccesi [9]

> Strahlenther Onkol. 2021 May;197(5):369-384. do
Epub 2021 Feb 26.

Cumulative dose, toxicity, a
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behalf of the Re-Irradiation
Italian Association of Radiot
Oncology (AIRO)

Antonio Pontoriero [1], Sara Lillo [2], Luciana Caravatta
Elisabetta Lattanzi [6], Silvana Parisi [7], Francesco Fic

Abstract

Purpose: The aim of this study was to identify patient-, tumor-, or treatment-related factors which may affect disease-related outcomes of re-irradiation (reRT) in patients with previously irradiated vertebral metastases.

Methods: A computerized search of the literature was performed by searching for terms related to reRT and spinal metastases in MEDLINE, EMBASE, OVID, and the Cochrane database from 1995 to 2019. Studies including at least 10 patients who had received reRT at the same site of initial radiotherapy for vertebral metastases with localized external beam radiotherapy were included. To determine the pooled ≥G3 acute and late toxicity rate, pain relief, local control, and overall survival, a meta-analysis technique of single-arm studies was performed.

Results: Nineteen studies including 1373 patients met the inclusion criteria for this systematic review. The pooled pain relief, neurological improvement, 1-year local control, and 1-year overall survival rates were 74.3%, 73.8%, 78.8%, and 54.6%, respectively, with moderate to high heterogeneity among studies. No difference in heterogeneity was evidenced for pain relief or local control after omitting studies not using stereotactic body radiotherapy (SBRT) or studies delivering biologically effective dose (BED) < 45 Gy_{10}, whereas heterogeneity for 1-year OS was lower after omitting studies not using SBRT and delivering BED < 45 Gy_{10}. The pooled results of grade ≥ 3 acute and late toxicity were 0.4% (95% confidence interval: 0.1-1.2%) and 2.2% (95% confidence interval: 1.2-37%), respectively, with low heterogeneity among studies.

Conclusion: While this systematic review confirmed that reRT is both safe and effective for treating patients with recurrent spinal metastases, it could not identify factors which may affect outcomes of reRT in this patient population.

Keywords: Pain; Radiotherapy; Retreatment; SBRT; Spinal cord.

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Conclusions

- ✓ Palliative Bone SBRT should not be (still, for a while) widely applied since some controversies have to be deepened
- ✓ Bone SBRT for OligoMts is highly promising but definitive technical details are lacking (still for a while)
- ✓ Bone SBRT includes indications for retreatment
- ✓ Standardization of procedure is promisly growing

Thank you for your attention

Thank to AIRO Palliative RT and Supportive Therapy

Thank Dr Stefania Manfrida
for all the support dealing with the collaboration on palliative Radiotherapy