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REVIEW

Single-Fraction Radiotherapy (SFRT) For Bone Metastases: Patient Selection And Perspectives

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Abstract: Bone metastases are a frequent and important source of morbidity in cancer patients. Stereotactic body radiation therapy (SBRT) is an established treatment option for local control and pain relief of bone metastases, and it is increasingly used as upfront treatment, postoperative consolidation or salvage treatment after prior RT. However, heterogeneity of dose schedules described in literature represents a severe limitation in the definition of the role of SBRT as a standard of care. No consensus is available on the use of single versus multiple fraction SBRT for bone metastases. Advantages of single-fraction SBRT include shorter overall duration of treatment, absence of inter-fraction uncertainty, improved compliance, theoretical increased efficacy, and lower costs. However, caution has been advised due to reports of severe late toxicities, in particular, vertebral collapse fracture (VCF). The aim of this paper is to review dose fractionation and indications for the management of bone metastases using SBRT.

Keywords: SBRT, stereotactic radiotherapy, radiosurgery, bone metastases, spine, non-spine

Introduction

Metastatic bone involvement is a frequent occurrence in cancer patients. It is present in approximately 15 to 70% of advanced stage cancer patients according to primary tumor localization, with an estimated incidence of 100,000 cases per year only in the United States.[1,2] Refractory pain is found in 70% of patients with bone metastases.[1] Uncontrolled bone metastases (BM) are an important source of morbidity in cancer patients, resulting in pathologic fractures, hypercalcemia, and neurologic impairment.[3] Bone metastases-related complications, collectively defined as Skeletal-Related Events (SRE), represent a serious threat to well-being and quality of life in cancer patients.[4] Moreover, the socio-economic burden of this condition is also of primary concern, since monthly treatment cost raised from €190 in asymptomatic patients to €4672 in patients with SRE in a prospective multicentric cohort.[5] Conventional radiotherapy (CRT), delivering a range of radiation doses between 8 Gy in 1 fraction to 30 Gy in 10 fractions, is a mainstay of BM management, providing prompt symptom palliation with a benign toxicity profile, and resort to other surgical or medical treatment modalities does not obviate the use of radiotherapy.[6] However, long-term results are often disappointing, showing complete pain response only in 24% of patients, with no particular benefit of one dose schedule over the other.[7] Lack of symptom control may also lead to high retreatment rates, in particular following single fraction radiotherapy, though no benefit was found in over 40% of patients regardless of initial response to treatment or dose schedule.[8] Achievement of durable

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disease and symptom control is of particular interest, due to constant improvement in survival among cancer patients,[9] most notably in specific subsets such as oligometastatic patients who experience extended survival compared to polymetastatic patients.[10] Stereotactic body radiation therapy (SBRT), defined as delivery of high dose per fraction in a short treatment course, allows the administration of potentially ablative radiation doses to the core of target metastases with a steep dose gradient that minimizes radiation exposure of neighboring critical organs. For these reasons, SBRT is an established treatment option for bone metastases as primary treatment, and, particularly in case of spinal involvement, as postoperative consolidation or salvage treatment after prior RT.[6] In comparison with conventional palliative radiotherapy, delivery of highly biologically effective radiation doses with SBRT may result in improved tumor control and fast symptom palliation.[11] Results from the exploratory trial IRON-1 favors 24 Gy single-fraction SBRT over 30 Gy in 10 fractions three-dimensional radiotherapy (3DRT) in terms of pain relief,[11] and randomized phase III studies[12,13] are ongoing to assess superiority of SBRT over CRT in terms of tumor control, palliation of symptoms, and quality of life. Of note, SBRT could be of particular interest in oligometastatic patients, who may draw further benefit in survival and systemic therapy-free survival from reduction of disease burden with the use of locally ablative therapies:[14] pathologic assessment of operated tumor specimen after SBRT proved the absence of residual viable tumor in over 80% of cases, thus confirming the reliability of instrumental assessment and demonstrating that SBRT is an ablative procedure in the majority of cases.[15] However, heterogeneity of dose schedules described in literature represents a severe limitation in the definition of the role of SBRT as a standard of care. Comparable to CRT, no consensus is available on the use of single versus multiple fraction SBRT for bone metastases. Theoretical advantages of single-fraction radiotherapy over multifractionated SBRT include shorter overall duration of treatment, absence of inter-fraction uncertainty, improved compliance, and lower costs.[16] However, while historical series mainly reported promising results following single fraction irradiation, late occurrence of severe toxicities (particularly in spinal treatment) motivated an increasingly widespread use of multi-fractionated schedules in an attempt to dampen toxicity. It is unclear whether fractionation may influence clinical outcome of patients treated with SBRT with regard to time to symptom palliation, duration of pain control, need for a second radiotherapy course, and risk of treatment-induced toxicities. This has important implications in clinical practice, since appropriate choice of treatment schedule should be warranted in function of clinical presentation of patients eligible for SBRT. The aim of this paper is to review dose fractionations and indications for the management of bone metastases using SBRT. A PubMed search was performed on March 7th, 2019 using the terms ‹‹‹(stereotactic OR SBRT OR radiosurgery) AND (bone OR spinal OR spine OR vertebral OR osseous) AND metastases››, resulting in the identification of 767 records. Screening for appropriateness was carried out by 2 independent author teams (ML/ID, DG/LL) in order to identify relevant papers. For the purpose of this study, reviews, dose planning studies or case reports were excluded, and articles focusing on unrelated topics (including re-irradiation following prior conformal/stereotactic radiotherapy, post-surgery consolidation radiotherapy, miscellaneous sites including extraosseous localizations) were, likewise, removed. In case of disagreement, a final decision was formulated with a third author (JJN). Full-text papers assessed for eligibility and included for review are listed in Tables 1 and 2.

Spinal Metastases

General Considerations

Axial skeleton is the most common site of secondary localization, accounting for 40% of metastatic bone sites.[17] Use of SBRT in the management of painful spinal metastases was tested as early as the mid-1990s.[18] SBRT was initially intended as a single 8-Gy boost to the gross tumor volume following conventional palliative radiotherapy, in order to maximize dose to the tumor while respecting dose constraints to the spinal cord: this resulted in promising rates of pain palliation with no additional acute toxicity.[19] Upfront use of SBRT in previously non-irradiated lesions was prospectively validated by Garg et al.[20] Feasibility of dose escalation to 16 Gy was confirmed in the phase II trial RTOG 0631.[13] Interestingly, precise tumor targeting did not result in increased rate of marginal failures: since one of the major arguments against the use of SBRT was the omission of the adjacent vertebral level, this finding justified the treatment of the involved spine only as previously reported by Ryu et al,[21] who reported a relapse rate of <5% in the immediately adjacent vertebrae. This was confirmed by Leeman et al, who showed involvement of the adjacent vertebra in 2% of cases.[22] A subsequent, large prospective cohort study[23] investigated the clinical

Table 1 Selected Studies On The Use Of Stereotactic Radiotherapy For Bone Metastases, Reporting Data On Efficacy Endpoints

Study	Type	Site	N° Patients	N° Metastases	Histology	1-yr LC	1-yr PC	Dose (Gy)	N° Fractions
Yu et al,[68] 2019	Retrospective	Extraspinal	33	38	Miscellaneous	75.7%	N/A	18-60	1 to 5
Nguyen et al,[73] 2019	Prospective, phase II	Extraspinal	81	81	Miscellaneous	100%	13-43%	12-16	1
Kelley et al,[44] 2019	Retrospective	Spine-only	127	287	Miscellaneous	74.7%	N/A	16-40	1 to 5
Mc Gee et al,[78] 2018	Retrospective	Spine-only	96	96	Miscellaneous	85-41%	89-17%	14-18	1
Ito et al,[51] 2018	Retrospective	Spine-only	131	134	Miscellaneous	72.3%	61.7%	24	2
Silva et al,[61] 2018*	Retrospective	Spine-only	61	72	Miscellaneous	83%	N/A	24-40	3 to 5
Loi et al,[74] 2018*	Retrospective	Miscellaneous	48	54	Miscellaneous	N/A	63%	20-45	1 to 5
Mehta et al,[79] 2018	Retrospective	Spine-only	83	98	Miscellaneous	84%	N/A	24^	3^
Zeng et al,[80] 2018	Retrospective	Spine-only	52	93	Miscellaneous	86-94%	N/A	24^	2^
Tseng et al,[40] 2018	Prospective, phase II	Spine-only	145	279	Miscellaneous	73%	N/A	24	2
Erler et al,[69] 2018	Retrospective	Extraspinal	81	106	Miscellaneous	91.7%	N/A	20-50	1-5
Fanetti et al,[81] 2018*	Retrospective	Miscellaneous	55	77	Prostate	83%	N/A	15-30	1 to 5
Guckenberger et al,[82] 2018	Prospective, phase II	Spine-only	54	60	Miscellaneous	85.9%	87%	35-48.5	5 to 10
Yoo et al,[34] 2017	Retrospective	Spine-only	33	42	HCC	68.3%	73%	16-45	1 to 3
Ito et al,[67] 2018	Retrospective	Extraspinal	17	17	Miscellaneous	59%	N/A	30-35	5
Bernard et al,[83] 2017	Retrospective	Spine-only	127	148	Miscellaneous	83%	N/A	18-27	1 to3
Bishop et al,[24] 2017	Retrospective	Spine-only	48	66	Sarcoma	81%	N/A	24-27	1 to 3
Chang et al,[52] 2017*	Retrospective	Spine-only	60	72	Miscellaneous	92%	N/A	16-52.5	1 to 3
Yamada et al,[25] 2017	Retrospective	Spine-only	657	811	Miscellaneous	90%	N/A	16-26	1
Pichon et al,[50] 2016	Prospective, phase I	Spine-only	30	30	Miscellaneous	94%	N/A	27	3
Bernstein et al,[84] 2016	Prospective, phase II	Spine-only	23	27	Thyroid	88%	N/A	18-30	1 to 5
Ho et al,[60] 2016*	Retrospective	Spine-only	38	38	Miscellaneous	85%	N/A	16-30	1 to 5
Leeman et al,[22] 2016	Retrospective	Spine-only	88	120	Sarcoma	86%	N/A	18-36	1 to 6
Jawad et al,[41] 2016	Retrospective	Spine-only	580	594	Miscellaneous	80%	N/A	8-40	1 to 5
Ghia et al,[31] 2016	Prospective, phase II	Spine-only	43	47	RCC	82%	N/A	24-30	1 to 5
Napierska et al,[37] 2016*	Retrospective	Miscellaneous	51	71	Prostate	97%	90%	6-45	1 to 5
Germano et al,[85] 2016	Retrospective	Spine-only	79	143	Miscellaneous	94%	95%	10-18	1
Lee et al,[86] 2015	Retrospective	Spine-only	23	36	HCC	80-61.9%	68%	18-50	1to 10
Amini et al,[87] 2015	Retrospective	Miscellaneous	50	50	RCC	74.1%	74.9%	27^	3^
Bishop et al,[88] 2015	Retrospective	Spine-only	285	332	Miscellaneous	88%	N/A	18-27	1 to 3
Anand et al,[89] 2015	Retrospective	Spine-only	52	76	Miscellaneous	94%	90%	24-27	1to 3
Thibault et al,[42] 2014	Retrospective	Spine-only	37	71	RCC	83%	N/A	18-30	1 to 5
Owen et al,[70] 2014*	Retrospective	Extraspinal	74	85	Miscellaneous	91.8%	N/A	15-50	1 to 5
Folkert et al,[32] 2014	Retrospective	Spine-only	88	120	Sarcoma	87.9%	N/A	24^-28^	1 to 6
Balagamwala et al,[90] 2013	Retrospective	Spine-only	57	88	RCC	71%	67.7%	8-16	1
Heron et al,[30] 2012	Retrospective	Spine-only	228	348	Miscellaneous	70-96%	71%	16^-23.8^	1 to 5

(*Continued*)

Table 1 (Continued).

Study	Type	Site	N° Patients	N° Metastases	Histology	1-yr LC	1-yr PC	Dose (Gy)	N° Fractions
Garg et al,[20] 2012	Prospective, phase II	Spine-only	60	63	Miscellaneous	88%	N/A	16-24	1
Ahmed et al,[91] 2012	Retrospective	Spine-only	66	85	Miscellaneous	83.3%	N/A	10-40	1 to 5
Wang et al,[92] 2012	Prospective, phase II	Spine-only	149	166	Miscellaneous	80.6%	N/A	27-30	3
Martin et al,[93] 2012	Retrospective	Spine-only	53	41	Miscellaneous	91%	N/A	8-30	1 to 3
Muacevic et al,[94] 2011*	Prospective, phase II	Miscellaneous	40	64	Prostate	95.5%	N/A	16-22	1
Nguyen et al,[95] 2009	Retrospective	Spine-only	48	55	RCC	82.1%	52%	24-30	1 to 5
Amdur et al,[96] 2009	Prospective, phase II	Spine-only	25	25	Miscellaneous	95%	43%	15	1
Tsai et al,[97] 2009	Retrospective	Spine-only	69	127	Miscellaneous	96.8%	N/A	16^	1
Ryu et al,[21] 2008	Retrospective	Spine-only	49	61	Miscellaneous	84%	80.1%	16	1
Chang et al,[98] 2007	Prospective, phase II	Spine-only	63	74	Miscellaneous	84%	N/A	27-30	3 to 5
Gibbs et al,[99] 2007	Retrospective	Spine-only	74	102	Miscellaneous	N/A	84%	16-25	1 to 5
Gerszten et al,[23] 2007	Prospective, phase II	Spine-only	500	500	Miscellaneous	88-90%	N/A	12-25	1

Note: *Oligometastatic cohort.
Abbreviations: 1-yr LC, local control at 1 year; 1-yr PC, pain control at 1 year; N/A, not available; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma.

outcome of single-fraction (20–25 Gy) SBRT in 500 spinal metastases from mixed primary tumors, confirming excellent pain control in symptomatic tumors (290/336, 86%) and neurologic impairment relief (27/32, 84%) at a median follow-up of 21 (3–53) months. Modern series of SBRT shows promising rates of 1-year local control between 60 and 95% and 1-year symptom control in 43 to 90% of patients (Table 1 and Figure 1). Irrespective of the use of single or multifractionated SBRT, a dose-response relationship has been highlighted: superior local control was found in sarcoma metastases receiving a BED > 48 Gy,[24] while, in another report on spinal metastases of miscellaneous histology, local failure rate did not exceed 2% in patients receiving a dose of at least 23.56 Gy EQD2 to 95% of the Gross Tumor Volume.[25] Similar considerations also apply to symptom relief: in the study by Jahaveri et al, renal cell carcinoma patients (RCC) treated with a fractionated schedule delivering a BED > 85 Gy achieved faster and more durable pain control[26] than patients receiving inferior cumulative doses.

Single Or Multifractionated Spine SBRT?

While dose escalation might prove beneficial, careful attention has been paid to attain clinically active doses while respecting healthy tissues' tolerance constraints. In particular, use of single fraction SBRT, the historical treatment modality, has been questioned due to reported incidence of vertebral collapse fracture (VCF) in up to 39% of cases after a single dose of 24 Gy or higher,[27] thus advocating for the use of fractionated schedules in an attempt to reduce severe adverse events while maintaining effective cumulative dose. However, optimal fractionation schedule allowing acceptable trade-off between efficacy and safety is a matter of debate. It has been speculated that radiobiological effects of a single radiation dose >15-20Gy may involve additional biological activity compared to lower fractionated dose, including asmase/ceramide pathway-related endothelial damage.[28] Pathologic assessment of resected metastases, preoperatively treated with a single 18 Gy fraction, showed significant onset of tumor necrosis and decrease in vessel density within 24 hrs.[29] This observation supports the hypothesis that more pronounced tumoricidal action, as well as osteoradionecrosis, may occur after single fraction SBRT following microvascular damage: hence, theoretical superior efficacy of single-fraction SBRT and increased risk of local adverse events may represent two sides of the same coin. However, in clinical practice no formal evidence is available.

Table 2 Selected Studies On The Use Of Stereotactic Radiotherapy For Bone Metastases, Reporting Data On VCF Incidence And Predictors

Study	Type	VCF (%)	Dose (Gy)	N° Fractions	Risk Factor
Ozdemir et al,[49] 2019	Retrospective	4	16-18	1	Male gender, no bisphosphonates use, high SINS
Kelley et al,[44] 2019	Retrospective	9.5	16-40	1 to 5	N/A
Ito et al,[51] 2018	Retrospective	11.9	24	2	N/A
Tseng et al,[40] 2018	Prospective, phase II	13.8	24	2	Spinal misalignment, lytic metastasis, dose to 90% of the PTV
Yoo et al,[34] 2017	Retrospective	28.5	16-45	1 to 3	Pre-existing VCF, lytic metastasis
Boyce-Fappiano et al,[38] 2017	Retrospective	11.9	10-60	1 to 5	Pre-existing VCF, lytic metastasis
Chang et al,[52] 2017	Retrospective	6.7	16-52.5	1 to 3	N/A
Sharma et al,[100] 2017	Retrospective	7	14-16	1	N/A
Hashmi et al,[101] 2016	Retrospective	4.5	18-24	1 to 3	N/A
Pichon et al,[50] 2016	Prospective, phase I	2	27	3	NB use of concurrent zoledronate
Bernstein et al,[84] 2016	Prospective, phase II	0	18-30	1 to 5	N/A
Jawad et al,[41] 2016	Retrospective	5.7	8-40	1 to 5	Pre-existing VCF, solitary metastasis, EQD2 prescription dose >38.4 Gy
Germano et al,[85] 2016	Retrospective	21	10-18	1	Colorectal histology, pre-existing VCF, severe pain
Moussazadeh et al,[102] 2015	Retrospective	36.1	24	1	N/A
Thibault et al,[42] 2015	Retrospective	18	16-24	1	Dose per fraction, pre-existing VCF, spinal misalignment
Guckenberger et al,[53] 2014	Retrospective	7.7	8-60	1 to 20	N/A
Balagamwala et al,[90] 2013	Retrospective	14	8-16	1	N/A
Sahgal et al,[27] 2013	Retrospective	14	8-35	1 to 5	Dose per fraction, pre-existing VCF, lytic metastasis, spinal misalignment
Cunha et al,[36] 2013	Retrospective	11	8-35	1 to 5	Spinal misalignment, lytic metastasis, NSCLC and HCC primary, dose per fraction ≥20 Gy
Boehling et al,[43] 2012	Retrospective	20	18-30	1 to 5	Age > 55 years, preexisting fracture, and baseline pain

Abbreviations: VCF, vertebra collapse fracture; N/A, not available; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; EQD2, equivalent dose in 2 Gys; PTV, planning treatment volume; SINS, spinal instability score.

On one hand, several papers comparing different SBRT dose schedules suggest significantly higher pain control rates[30] and local control rates[31,32] for single-fraction SBRT compared to multiple fraction. Nevertheless, fractionated regimens employed in these studies may not be as dose-intensive as single fraction SBRT. For example, in the study by Ghia et al,[31] 24 Gy in a single fraction proved superior to 27 Gy in 3 fractions and 30 Gy in 5 fractions in terms of local control in spinal metastases from RCC: however, using an alpha/beta ratio of 10, this translated into very different corresponding BED of 81.6, 51.3, and 48 Gy, respectively. Hence, use of single fraction was associated with a nearly 1.5–2 fold BED increase as compared to multifractionated schedules, which may possibly explain superior outcome in this group of patients; of note, follow-up at 5 years did not show increased toxicity in patients receiving single-fraction SBRT, and global incidence of VCF was 14%.[33] Interestingly, in the paper by Heron et al,[30] a median single dose of 16 Gy (corresponding to a BED=41.6 Gy), while providing faster pain relief, resulted in inferior local control as compared to a median 23.8–25 Gy in 4–5 fractions (corresponding to BED 37.1–38.4). In a large cohort by Bishop et al, local relapse was correlated to inadequate tumor coverage independently of the fractionation, advising a GTV Dmin above 14 Gy in 1 fraction and 21 Gy in 3 fractions.[24] It should be eventually pointed out that, among the previously cited studies, superior tumor control of single fraction schedule was assessed in subsets of patients affected by radio-resistant primary tumors such as sarcoma and RCC,[31,32] while a single fraction of 14–18 Gy was insufficient to overcome radioresistance in hepatocellular carcinoma compared to other histotypes:[34] therefore, though tantalizing, the hypothesis of superior activity of single-fraction SBRT according to tumor histology cannot be definitely ruled out.

On the other hand, dose per fraction to the vertebral body has been correlated to VCF and, most interestingly, the use of single fraction doses as high as ≥20 Gy have been questioned as a major risk factor. Incidence of VCF (de novo or progression of existing fracture) varies greatly among different authors (Table 2), and may occur within 5 years from the treatment.[35] Following reports by Sahgal et al, showing dose per fraction ≥20 and as ≥24 as an independent risk factor for VCF (HR: 4.9 and 5.2, respectively), caution has been advised concerning the use of single fraction SBRT for spinal metastases.[36] Since SBRT schedules are not dose-equivalent, it is unclear whether VCF risk is strictly dependent on dose per fraction rather than cumulative dose: Jawad et al reported higher VCF incidence for a 2-Gy equivalent dose (EQD2) >38.4 Gy (corresponding approximately to 17, 24, and 29 Gy in 1, 3

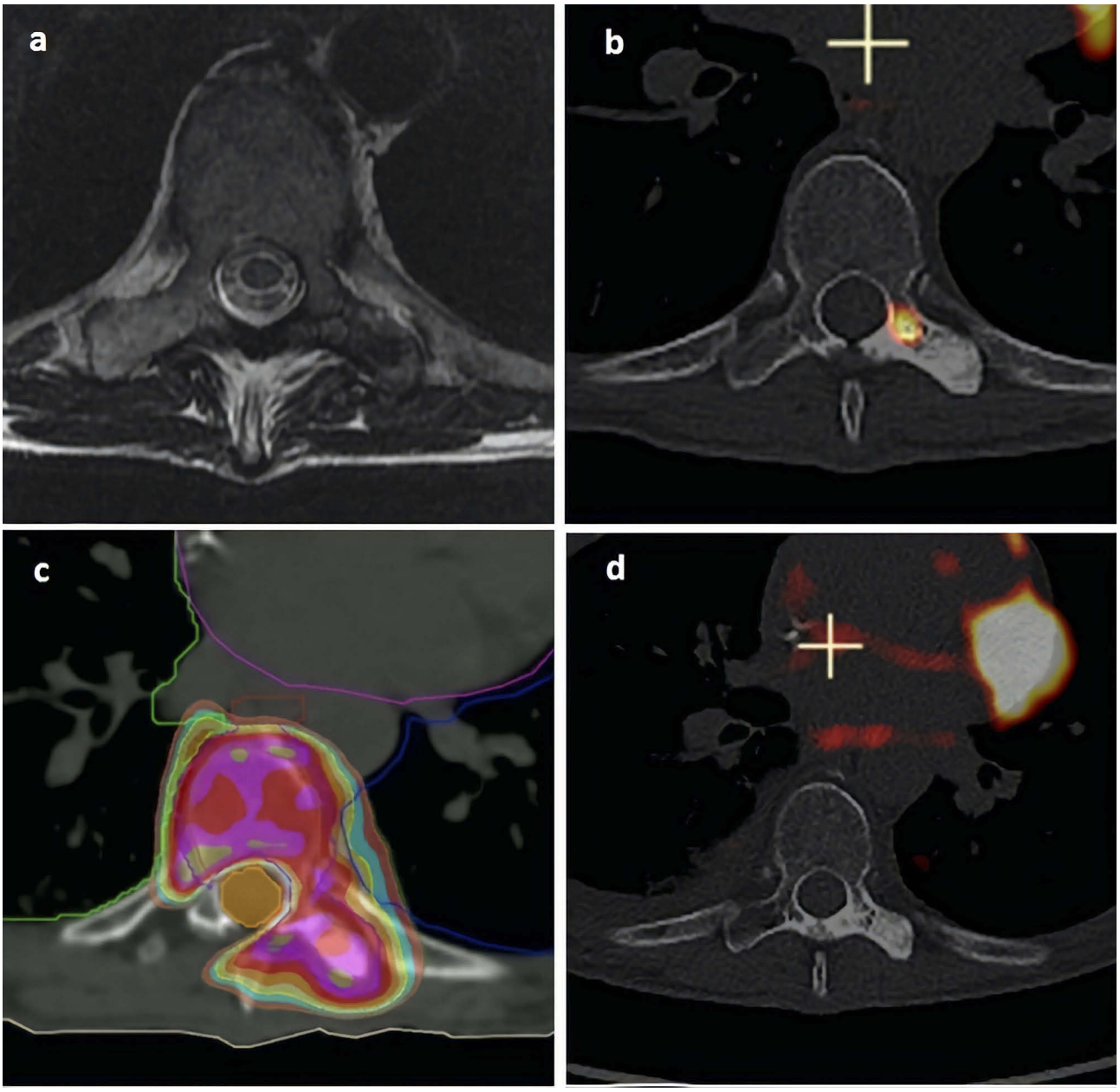

Figure 1 A 68 year old woman affected by metastatic breast cancer was referred for SBRT of a painful metastasis of the left transverse pedicle of the 8th thoracic vertebra.
Notes: (**A**) MRI view prior to SBRT. (**B**) 18FDG-PET view prior to SBRT. (**C**) Dose planning prior to administration of a single fraction of 18 Gy to the 80% isodose line (color wash deep orange, light blue, yellow, gold, purple, red and olive corresponding respectively to 14, 15, 16, 17, 18, 19, 20 and 21 Gy), resulting in conformal dose distribution sparing the spinal canal (light orange). (**D**) 18FDG-PET view 6 months after SBRT, showing stable mineralization of the treated area and metabolic complete response. Acute toxicity consisted of G2 dysphagia due to proximity of the esophagus. No late toxicity was observed at 1 year, while complete pain control was obtained.

and 5 fractions, respectively) independently of the use of a single or multiple fraction.[37] However, to avoid oversimplification, it should be pointed out that VCF is a complex entity, that may result from a certain number of predisposing factors other than dose schedule. Lytic metastases show higher risk of VCF,[27,34,36,38] and automatic calculation of the lytic component volume has been tested to predict the risk of VCF.[39] Spinal misalignment has also been frequently found in patients experiencing VCF,[27,36,40] as well as pre-existing VCF.[27,34,40–43] Put together, all these factors may participate in global mechanical instability of the vertebra, that is of particular concern since it has been correlated both to VCF onset and to local failure: interestingly, Kelley et al reported superior local control after single-fraction SBRT with a median dose of 16 (16–20) Gy as compared to hypofractionated SBRT.[44] Mechanical instability of vertebra should be constantly addressed in patients potentially eligible for SBRT in order to select candidates for this option and predict the risk of complications. Consensus statement led to the development of the Spinal Instability Neoplastic Score (SINS),[45] encompassing both clinical and radiological findings: a subset analysis from a prospective phase II trial confirmed the performance of SINS in predicting the onset of VCF after spine SBRT, showing a 2 year-VCF rate of 31.6% in patients with high (7–12) SINS score compared to 7.1% in patients with low (<7) SINS score.[46] Careful spinal instability assessment may guide the choice to consider prophylactic surgical stabilization or cement augmentation after SBRT, that has been successfully practised in CRT[47] and prospectively evaluated in a phase II trial.[48] Besides mechanical instability, other predictors of VCF have been analyzed. Concurrent or prior biphosphonate administration, in particular for a treatment interval of at least 6 months, may prevent the onset of VCF:[49] use of prophylactic zoledronic acid injection before hypofractionated SBRT has been tested in a phase I trial, reporting a 2% incidence of VCF.[50] A protective effect of obesity[27] and prior irradiation[42] has also been suggested.

Apart from VCF, no other toxicity seems to be influenced by SBRT schedule and few data are available due to low incidence of late complications. In particular, radiation myelopathy is exceedingly rare, presenting in less than 1% of cases in current literature:[35,51–53] interestingly, only a maximum point dose (Dmax) corresponding to a BED> 110 Gy to spinal cord or cauda equina was correlated to neurologic impairment, independently of the dose per fraction.[35] Conversely, esophageal toxicity is a frequent occurrence following chest SBRT and may be life-threatening in a small but significant fraction of patients,[54] leading to fatal outcome in rare cases due to massive bleeding or fistula.[55–57] Interestingly, multiple dose constraints have been proposed, showing significant inconsistencies among authors: for example, suggested Dmax extrapolated from clinical studies for esophagus single-fraction SBRT ranged between 15.4 and 22 Gy.[55,56] It is likely that other variables, including organ motion, individual radiosensitivity, prior chemotherapy and iatrogenic manipulation may influence the incidence of esophageal toxicity.[54]

Spine SBRT In Oligometastatic Disease

Oligometastatic patients represent a subset of metastatic patients with low disease burden (inferior or equal to 3–5 metastases) potentially suitable for focal treatment in order to obtain control of the macroscopic site of disease and theoretically prolong survival.[58] Focusing on metastatic spinal involvement, a recent prospective cohort confirmed a significant survival advantage (+22% at 6 months) in patients with oligometastatic versus polymetastatic (>5 lesions) involvement, regardless of treatment modalities. SBRT has been widely applied in this setting in order to maximize disease control and symptom relief.[59] In all the available experiences (Table 1), the authors report excellent local control rates in oligometastatic patients with spinal involvement treated by SBRT, translating to 62–67% of patients achieving durable systemic-progression free survival at 1-year with modest incidence of severe adverse events.[52,60] Interestingly, superior local control was shown in oligometastatic patients receiving hypofractionated (3 to 5 fractions) SBRT to spinal metastases as compared to polymetastatic patients. This may be explained by elicitation of background immune response toward tumor cells, or by retention of a less aggressive phenotype in oligometastases.[61] Therefore, it could be speculated that dose fractionation may be involved in the modulation of the local effect of SBRT through interaction with tumor-host synergy;[62] however, use of heterogeneous dose schedule in these limited experiences do not allow further analysis. Hence, no data are available concerning the optimal dose schedule in oligometastatic patients, though longer expected survival implies a more stringent trade-off between risk of late toxicity and need for durable local control. In order to guide the choice of the clinician, multiple prognostic tools integrating clinical variables

(PRISM, NOMS) in a decision framework are currently available.[63-65]

Extra-Spinal Bone Metastases

General Considerations

Use of SBRT in non-spinal bone metastases has been inconsistently described. First, there is a scarcity of literature specifically addressing SBRT for extra-spinal disease, since most studies report miscellaneous data from spinal and non-spinal treatment: however, treatment efficacy seems comparable with 1-year LC and pain control rate of 75–100% and 13–100% (Table 1). Secondly, studies addressing extra-spinal bone SBRT frequently include heterogeneous bone location: hence, choice of cumulative dose and schedule fractionation may be influenced to a variable degree by dose tolerance of neighboring critical structures as compared to spinal SBRT, where radiation myelopathy is commonly accepted as the main dose-limiting toxicity.

Consensual definition of target volume is still lacking in extraspinal metastases delineation, as opposed to spinal SBRT where a consensus statement has been reached following reports on pattern of failure and integration of MRI.[66] To our knowledge, only a recent paper by Ito et al[67] examined pattern of failure in 17 coxal metastases treated with a hypofractionated schedule (30–35 Gy in 5 fractions) on an MRI-delineated Gross Treatment Volume (GTV) plus a 5–10 mm expansion to a Clinical Treatment Volume, showing a 41% marginal/out of field relapse incidence occurring at an average 3.4 cm distance (range 1.5–5.5) from the closer edge of the treated tumor: hence, use of a Clinical Target Volume expansion has been questioned.

Finally, heterogeneity in the study end-points (symptom relief or local control) may indirectly reflect use of different criteria for patient selection, in particular with regard to the decision to allocate patients to SBRT rather than conventionally fractionated radiotherapy: for example, SBRT irradiation of oligometastatic or oligoprogressive non-symptomatic metastasis may underlie a positive bias due to inclusion of a population subset characterized by a more favorable outcome. Interestingly, only a recent retrospective cohort by Yu et al[68] identified patients according to the treatment intent: despite evident differences in overall survival, no difference in local control was found between oligometastatic, oligoprogressive, and polymetastatic patients treated at the dominant site of progression, showing a 1-year LC rate of 75.7%. It is noteworthy that local control rate differed according to criteria for response assessment, resulting in a 11.1% discrepancy between MDA and RECIST criteria, and a more specific correlation between local control rate according to MDA and improved survival was found.

Single Or Multifractionated Bone SBRT?

Since most studies on extra-spinal SBRT delivered miscellaneous dose regimens, dose fractionation has not been specifically addressed in current literature either in regard to tumor and pain control or expected toxicity. Interestingly, use of single fraction SBRT (15–24 Gy) varies between 1.8[69] and 52%[70] in retrospective cohorts.

Underutilization of single fraction SBRT in this setting may result from reluctance among praticians to prescribe single-fraction CRT in particular in long-surviving patients, following widespread opinion that single fraction would expose to increased toxicity, inadequate efficacy, and higher retreatment rate. However, it is currently accepted that single fraction radiotherapy yields the same efficacy as multiple fraction CRT even in patients with favorable expected survival.[71] Moreover, delivering higher dose to the target may further improve the therapeutic ratio of single fraction CRT.[72] Most interestingly, a recent phase II trial[73] comparing single-fraction SBRT to multifraction CRT, reported significantly higher rates of pain response both at early (2 weeks) and late (9 months) evaluation. Interestingly, according to a recent study from our group, no specific SBRT dose fractionation was correlated to pain control, that was mostly influenced by patient-related features identified with the use of validated tools such as the ECS-CP.[74] Concerning toxicity, severe adverse events correlated with bone irradiation included fracture and pain flare (defined as acute onset or exacerbation of pain in relation to radiotherapy).[75] Cumulative incidence of pain flare ranging between 10 and 68%[70,75,76] has been reported, with single-fraction dose regimen[76] and lack of steroid pretreatment[77] being the main predictors. In our experience, pain flare occurred following 34% of SBRT treatments[74] but no variable was associated with its onset.

Owen et al described the occurrence of pain flare and fractures in 10% and 2% of 7 cases with a median dose of 24 Gy in one fraction.[70] Erler et al[69] reported an overall fracture incidence of 8.5%, significantly affecting female patients and lytic metastases: however single-fraction SBRT accounted only for 1.8% of treatment.

Regarding the previously cited prospective trial, no differences in toxicity were shown in particular concerning

bone fracture, occurring in 1.2% of patients in the single-fraction SBRT arm.

Conclusion

Stereotactic Body Radiotherapy (SBRT) is established as a safe and effective treatment option for metastatic bone disease, resulting in prompt pain relief and excellent disease control with acceptable toxicity: its applications range from upfront treatment of painful metastases to re-irradiation of previously treated sites in proximity to dose-limiting organs, and to extend disease remission in oligometastatic patients. Despite extensive literature, no definitive conclusion can be drawn on the superiority of one regimen over another: in particular it is unclear whether the use of multi-fractionated versus single fraction SBRT schedule might ensure a better therapeutic ratio between disease control and adverse event risk.

In spinal metastases, while satisfying clinical efficacy is found with doses as low as 12–16 Gy in a single fraction, a dose-response relationship has been highlighted that may favor single-fraction schedules (in particular in radioresistant histotypes), possibly through theoretical exploitation of alternative radiobiological effects involving vascular apoptosis, occurring at >10-15 Gy/fraction. However, the use of doses per fraction ≥ 20 Gy may increase the risk of severe adverse events such as vertebral collapse fracture, in particular in high risk patients (extended lytic component, spinal misalignment, prior fracture): caution is advised in the use of single fractions, that may be of interest in patients with low spinal instability (SINS) score and/or in combination with vertebroplasty. Conversely, myelopathy is an infrequent event that may occur at high total doses (BED> 110 Gy) independently from fractionation scheme. In extra-spinal bone SBRT, scarce data are available: however, a recent prospective trial suggests that, despite relative underutilization, single fraction SBRT may not be burdened by higher toxicity rates and proved prospectively superior to multi-fractionated CRT in terms of pain relief. Multiple randomized trials (NCT02608866; NCT03028337) are currently comparing single versus multifraction SBRT.

Disclosure

The authors report no conflicts of interest in this work.

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