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Review Article

Stereotactic body radiotherapy for non-spine bone metastases: A *meta*-analysis and international stereotactic radiosurgery society (ISRS) clinical practice guidelines

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A B S T R A C T

Background: While SBRT to NSBM has become common, particularly in the oligometastatic population, the approach to treating non-spine bone metastases (NSBM) with stereotactic body radiotherapy (SBRT) varies widely across institutions and clinical trial protocols. We present a comprehensive systematic review of the literatures to inform practice recommendations on behalf of the International Stereotactic Radiosurgery Society (ISRS).
Methods: A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies with at least 10 patients receiving SBRT for NSBM were identified and *meta*-analyses were completed to estimate pooled local control and overall survival rates. Published guidelines on NSBM SBRT were reviewed and consolidated.
Results: There were 25 studies included for qualitative analysis and 18 studies for quantitative analysis consisting of 13 retrospective studies, 2 non-randomized prospective studies, 1 randomized phase 2/3 trial, and a subgroup analysis of a phase I trial. The pooled local control rates at 1 and 2 years were 95 % (95 % CI: 89 %-98 %) and 94 % (95 % CI: 86 %-98 %), respectively. Pooled overall survival rates at 1 year and 2 years were 84 % (95 % CI: 73 %-91 %) and 81 % (95 % CI: 45 %-95 %), respectively. Consensus was reached on recommendations to inform treatment simulation, target delineation, dose fractionation, and anatomic site-specific recommendations.
Conclusion: We present ISRS-endorsed consensus recommendations to inform best practice of SBRT to NSBM, which we found to be efficacious and associated with low rates of adverse events.

Introduction

Bone metastases are common in patients with metastatic solid tumor malignancies and can cause significant morbidity including disabling pain, fracture and hypercalcemia. In the United States, the age-adjusted incidence of de novo bone metastases in cancer patients has been reported as 18.8 cases per 100,000 [1] and it is estimated that over 350,000 cancer patients die with bone metastases each year [2]. Palliative conventional external beam radiotherapy (CRT) is an established and effective symptom-directed treatment for patients with overall short-term pain relief rates of 70–80 % and decreased narcotic use [3]. However, complete response rates remain poor and long-term durability

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remains modest.

[4,5] Despite the uncertain clinical benefit regarding pain relief, there is increasing adoption and use of SBRT for NSBM driven by the treatment of oligometastatic patients both on and off clinical trials. At the time of preparation of this manuscript, Clinicaltrials.gov lists nearly 50 active trials evaluating SBRT for oligometastatic disease, and multiple oligometastatic randomized trials have demonstrated overall survival (OS) or progression-free survival (PFS) benefits with metastases-directed therapy primarily consisting of SBRT [6,7]. As bone metastases represent a significant proportion of the targets treated in this context, many institutions have developed protocols for delivering spine and NSBM SBRT. Looking to clinical trial protocols for treatment planning guidance for NSBM is challenging as there are often limited radiotherapy specific details provided, and there is considerable variability between trials in terms of dose fractionation and approach to target volume delineation. In fact, a recent systematic review of 20 phase II and III SBRT trials, several including NSBM targets, found that the technical and dosimetric information provided in the published reports was insufficient to allow reproducibility [8].

While spine SBRT practitioners have benefited from comprehensive international guidelines to inform their clinical practice [9–16], the literature supporting NSBM SBRT has been deficient until recently. For example, an international group of radiation oncologists completed a practice pattern survey that provided guidance with respect to dose selection and image-guidance for NSBM SBRT [17]. The same group also contributed a clinical target volume (CTV) contouring guideline based on consensus contours [18]. Subsequently, a consensus treatment planning guideline was published through the Spanish Society of Radiation Oncology (SEOR) [19], which endorsed many of the recommendations from the previous practice pattern survey and CTV contouring guideline. The French Genito-Urinary Group (GETUG) published an extensive guideline for spine and NSBM SBRT, with an emphasis on the former [20]. Finally, a multicentre Delphi consensus study from Memorial Sloan Kettering Cancer Center (New York, USA) provided a multidisciplinary perspective on the management of NSBM [21]. While these publications add value to the literature, each has its own area of focus and even when considered collectively, there are still gaps in the treatment planning guidance provided. One important missing piece is an attempt to comprehensively address the wide variability in anatomical sites with NSBM – a unique challenge for a SBRT disease site that has implications on treatment simulation, dose fractionation and pertinent organs at risk.

We recognized the need for a comprehensive systematic review to inform best practices. Therefore, on behalf of the International Stereotactic Radiosurgery Society (ISRS), we present a comprehensive systematic review and an additional *meta*-analysis to summarize the evidence and inform practice recommendations.

Methods

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Supplementary File 1). Both Medline and EMBASE electronic databases were queried from inception until August 4th 2022 for studies relating to the use of SBRT for NSBM. See Supplementary File 2 for the complete search strategy.

The reports yielded from the search were combined and duplicates were excluded. The resulting list of reports were then screened based on title and abstracts by two investigators (TKN & AT) for appropriateness for inclusion based on the criteria below. Selected studies were then reviewed based on the same inclusion and exclusion criteria. The reference lists for the included studies were individually reviewed to identify additional relevant studies. Studies were included if they met all of the following criteria: published in English language journals, treatment of adult patients (≥18 years of age), reporting on at least 10 patients with NSBM treated with SBRT (defined as 1–5 fractions with ≥ 5 Gy per fraction), mixed population studies including spine and NSBM were included if outcomes for the NSBM patients could be segregated or if the NSBM cohort represented > 50 % of the total study population. Case reports, letters, editorials, and review papers were excluded. Where there were multiple reports originating from the same patient cohort (e.g. from the same institution), only the most recent study was included.

In addition, any existing guidelines or reports that provided expert recommendations on NSBM SBRT identified during the literature search were also included. It was anticipated that these studies would not contribute towards the quantitative analyses but would still be important to review and incorporate into the present guidelines.

Data abstraction

Data pertaining to study methodology, clinical details, treatment, and outcomes were abstracted from each included study. Clinical variables included patient age, gender, the number of patients, the number of lesions treated, performance status, primary histology, and treatment intent. Treatment details included location of bone metastases, dose and fractionation, simulation imaging, gross tumor volume (GTV) and planning target volume (PTV), CTV margin and image-guidance strategies. Outcomes of interest were pain response, local control, OS, PFS and adverse events.

Data analysis

Statistical analyses were completed using RStudio (version 1.1.423, Boston, Massachusetts). R package “metafor” and “meta” were used for *meta*-analyses. Study variances for overall estimates were calculated using the DerSimonian-Laird method. Given the types of studies included in this *meta*-analysis, spanning numerous years in several different populations and varied geographic locations, the random effects model was considered superior to the fixed effects model when calculating pooled estimates. I^2 statistic was used for identifying heterogeneity between studies and $I^2 \geq 50$ % was considered as high heterogeneity, which means in this *meta*-analysis, these studies could not be considered from the same population, in other words, random-effects model will be applied.

We compared the 1-year or 2-year local control and OS rates between studies without missing data to assess for potential statistically significant differences in the pooled estimates.

Finally, we performed *meta*-regression analyses to understand the influence of age, gender, primary histology, bone metastasis location, biologically equivalent dose in Gy using an α/β of 10 (BED10), median BED10, mean BED10, and CTV margin on the effect size separately, and used a p-value of < 0.05 to indicate the significance of the variables in the model. Meta-regression was conducted using the “meta” package.

Development of recommendations

The recommendations presented herein were developed by the study authors in collaboration with the ISRS guidelines committee. These discussions were informed by the included studies, published guidelines from other institutions and societies, and the clinical experience from the authors and ISRS guidelines committee.

Results

In total, 25 studies were included for analysis. Eighteen were suitable for quantitative analysis (Table 1) of which 14 were retrospective studies [22–34], 2 were non-randomized prospective studies [35,36], 1 was a randomized phase 2/3 trial [5], and lastly a subgroup analysis of a phase I trial [37]. The additional studies for qualitative analysis included five consensus guidelines pertaining to the clinical management and/or treatment planning for NSBM SBRT [18–21], two prospective contouring studies [38,39], one retrospective contouring study,

Table 1
Summary of included retrospective and prospective studies.

Author & Year	Study Design	Number of Total Patients /NSBM Patients	Number of NSBM targets	Most Common Dose Fractionations	Imaging used to define GTV	CTV margin	Fracture Rate	Local Control
Cao 2021 [22]	Retrospective	125/125	233	30–35 Gy/3–5 50 Gy/5	NR	NR	N = 6 (4.8 %) Spine&NSBM	NR
Correia 2022 [23]	Retrospective	35/NR	21	24–42 Gy/2–7	CT and fused MRI	3–5 mm	NR	1y: 80 %
David 2020 [35]	Prospective	15/NR	10	20 Gy/1	CT ± NaF PET, MRI	0	NR	Crude: 100 % 2y: 100 %
Deodato 2022[37]	Subgroup Analysis of Phase 1 trial	37/37	49	24 Gy/1	CT ± choline-PET/CT, PSMA-PET/CT, MRI	0	0	2y: 97 %
Erler 2018 [49]	Retrospective	81/81	106	35 Gy/5	CT ± fused MRI	5 mm	N = 9 (8.5 %)	Crude: 93 % 1y: 92 %
Habl 2017 [24]	Retrospective	15/NR	12	25–40 Gy/5	NR	10–20 mm	0	2y: 100 %
Ishigaki 2019 [25]	Retrospective	13/13	32	NR	CT and fused PET/CT	NR	NR	
Ito 2022[26]	Retrospective	17/17	19	35 Gy/5	CT with reference to diagnostic PET/CT and MRI	5–10 mm 20–30 mm craniocaudal for long bones	N = 2 (10.5 %)	Crude: 97 % 1y: 100 %
Ito 2021[36]	Phase 3 single arm trial	38/38	41	35 Gy/5	CT with reference to diagnostic PET/CT and MRI	30 mm within bone 5 mm outside bone	N = 7 (17 %)	1y: 92 %
Madani 2022 [27]	Retrospective	111/111	114	30–50 Gy/5	NR	2–5 mm	N = 8 (7.0 %)	Crude: 92 % 1y: 94 % 2y: 93 %
Mathis 2022 [28]	Retrospective	727/727	727	NR	NR	NR	NR	NR
McDonald 2015[29]	Retrospective	33/33	42	35 Gy/5	CT ± MRI	NR	NR	Crude: 86 % 1y: 80 %
Nguyen 2019 [5]	Phase 2/3 randomized trial	160/160	100	12 Gy/1 or 16 Gy/1	CT	0	N = 1 (1.2 %)	1y: 100 %
Owen 2014 [30]	Retrospective	74/74	85	15–24 Gy/1 24–30 Gy/3 30–50 Gy/5	CT ± MRI or PET-CT	10 mm	N = 2 (2.7 %)	1y: 92 %
Patel 2019 [31]	Retrospective	51/NR	35	30 Gy/3	CT and MR and/or PET/CT fusion	NR	0	Crude: 94 % 1y: 98 % 2y: 95 %
Ursino 2016 [34]	Retrospective	40/28	28	24 Gy/1	NR	2 mm	N = 1 (2.5 %)	Crude: 88 % 1y: 90 % 2y: 80 %
Van de Ven 2020[32]	Retrospective	150/NR	39	18 Gy/1 30 Gy/3	CT and fused MRI	Bony compartment	NR	Crude: 95 %
Yu 2019[33]	Retrospective	33/33	38	18 Gy/1	CT ± MRI	10–20 mm	0	Crude: 95 % 1y: 94 % 2y: 94 %

NR = not reported.

and one patterns-of-practice survey [17].

Regarding location, included publications represented experience across 10 different countries spanning Europe, North America, Asia, and Australia. Across all studies, a total of 1590 NSBM were treated with SBRT in 1499 patients. Most included studies (n = 13, 72 %) reported on an exclusively NSBM patient population. Five studies (28 %) included a mixed cohort of both spine and NSBM [23,24,31,34,35], however, met our inclusion criteria.

The most common anatomical sites involved were the pelvis (n = 728 metastases treated), ribs (n = 250), lower extremities and hips (n = 250), and upper extremities and shoulders (n = 151). The remaining treated sites were sternum (n = 36), skull (n = 28), and other (n = 144). All studies except one, included patients who received SBRT to weight-bearing bones.

Local control

The pooled local control (LC) rate at 1 year was 95 % (CI: 89 %-98 %) with a range of 80 % to 100 % and low heterogeneity (I^2 = 30 %, p-value = 0.16) as summarized in Fig. 1. At 2 years, pooled LC rates were 94 % (95 % CI: 86 %-98 %) with a range of 80 % to 100 % and low heterogeneity (I^2 = 40 %, p-value = 0.11) as summarized in Fig. 2, Table 2.

Predictors of local failure based on univariable analysis were certain histologies (lung, renal cell carcinoma, melanoma) and mixed patient cohorts that included patients who received spine SBRT (Supplementary File 3). Noteworthy variables that were not significant predictors of LC on univariable analysis were median BED10 (1-year LC, p = 0.941; 2-year LC, p = 0.852), mean BED10 (1-year LC, p = 0.709; 2-year LC, p = 0.743), and extent of CTV margin (1-year LC, p = 0.506; 2-year LC, p

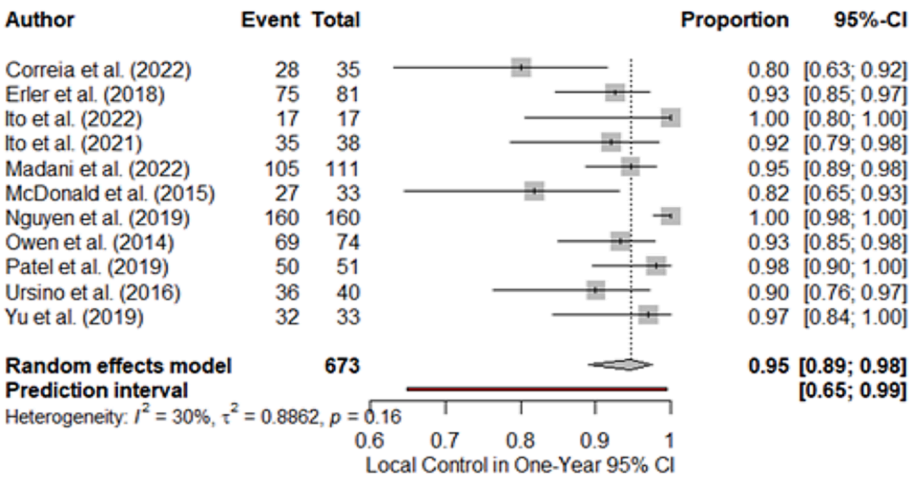

Fig. 1. Forest plot for one-year local control rates.

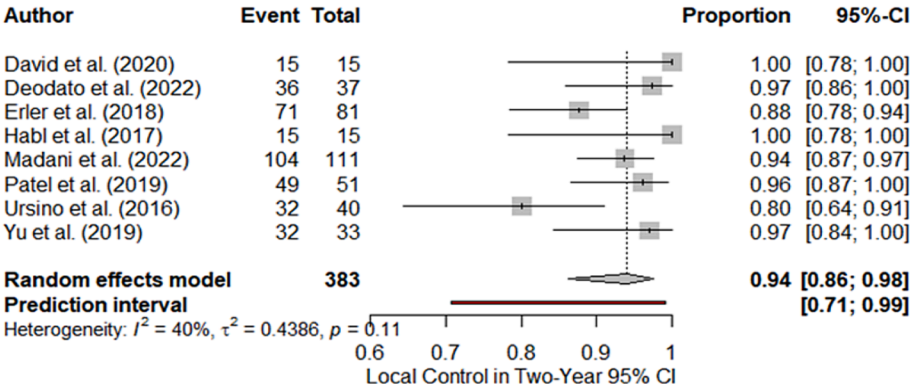

Fig. 2. Forest plot for two-year local control rates.

Table 2
Pooled Local Control and Overall Survival.

	1-year pooled rate (95 % CI)	1-year range across studies	2-year pooled rate (95 % CI)	2-year range across studies
Local Control	95 % (89 %-98 %)	80–100 %	94 % (86 %-98 %)	80–100 %
Overall Survival	84 % (73 %-91 %)	67 %-98 %	81 % (45 %-95 %)	45 %-98 %

CI = Confidence Interval.

= 0.255) (Supplementary File 4).

Multivariable analysis was not conducted given the limited number of studies and the inconsistency of each variable across studies.

Overall survival

The pooled OS at 1 year was 84 % (95 % CI: 73 %-91 %), with a range of 67 % to 98 % and high heterogeneity (I^2 = 73 %, p-value < 0.01) as summarized in Fig. 3. At 2 years, the OS was 81 % (95 % CI: 45 %-95 %), with a range of 45 % to 98 % and high heterogeneity (I^2 = 81 %, p-value < 0.01) as summarized in Fig. 4, Table 2.

On univariable analysis, metastatic prostate cancer patients had

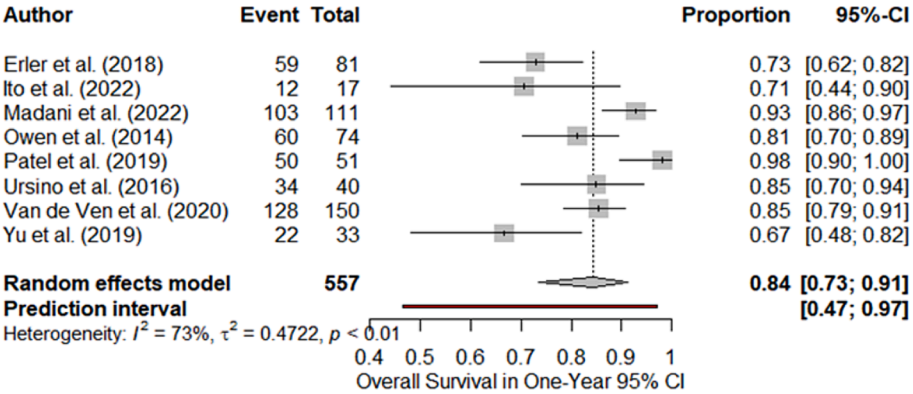

Fig. 3. Forest plot for pooled one-year overall survival rates.

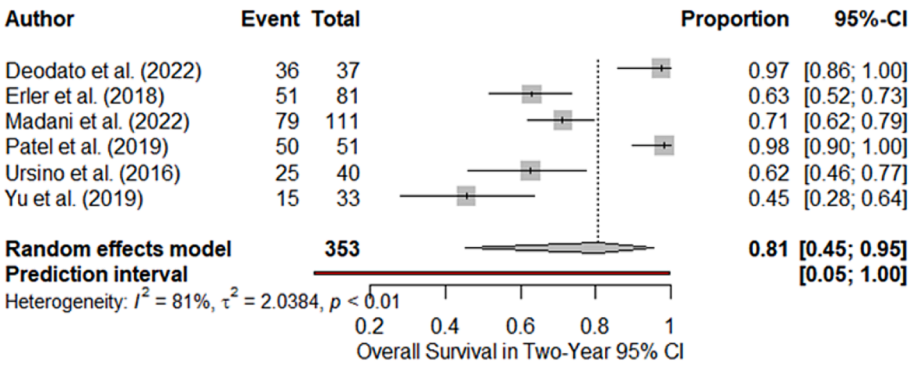

Fig. 4. Forest plot for pooled two-year overall survival rates.

better OS at 1 year, whereas worse 1-year OS was observed for patients with lung cancer, pelvic bone metastases, and rib metastases (Supplementary File 3). Median BED10 (p = 0.557), mean BED10 (p = 0.724), and extent of CTV margin (p = 0.981) were not significant predictors of OS at 1 year (Supplementary File 4). Multivariable analysis was not conducted given the limited number of studies and inconsistency in variables across studies.

Target volumes

Thirteen (72 %) studies (10 retrospective, 2 non-randomized prospective, and 1 randomized prospective) provided specifications as to how target volumes were delineated (Table 1). Of these, 3 did not use a CTV margin (GTV = CTV). Notably there was variability in how the GTV was defined across studies, with some relying solely on CT imaging while others fusing or referencing diagnostic MRI and/or PET/CT. In the studies that applied a CTV margin, 1 study extended the CTV to encompass the bony compartment, 4 studies applied a CTV margin ranging from 2-5 mm, 3 studies between 10–20 mm, and 2 studies between 20–30 mm. The latter 2 studies included a small Japanese retrospective series of 17 patients treated exclusively to long bone metastases with single fraction SBRT. They described a uniform CTV expansion of 5–10 mm, with an additional 20–30 mm cranio-caudal expansion within bone [26]. The second Japanese study was a single-arm phase 2 trial of 38 patients where a 30 mm intraosseous CTV margin and a 5 mm extraosseous CTV margin were applied [36]. The one included randomized trial did not use a CTV margin beyond the GTV.

All reviewed guidelines that commented on target delineation, recommended a CTV margin for NSBM SBRT ranging from 2-10 mm [18–21] (Table 3). Three of the 4 reports recommended intraosseous CTV margins between 2–5 mm plus an extraosseous margin of 5 mm in cases where there was extraosseous extension breaching cortical bone. The CTV contouring paper from Nguyen et al. recommended an intraosseous margin of 5–10 mm. Within this range, most experts in the study favored an intraosseous and extraosseous margin of 5 mm. It was noteworthy that in the absence of an MRI fused to the CT simulation scan, most of the experts increased the size of their intraosseous and extraosseous CTV margins to 7–10 mm. It is also acknowledged that some included studies did not apply a CTV margin, including the only randomized prospective trial [5]. Taken together, a CTV margin of 0 to 10 mm would be reasonable. The extent of the margin used within this range can be guided by the confidence the treating physician has in their GTV delineation based on the available imaging at the time of contouring. A CTV margin of 0–5 mm may be a reasonable consideration in cases where additional imaging (i.e. MRI +/- PET-CT) are co-registered to the treatment planning CT scan for target volume delineation. Conversely, margins between 5–10 mm may be more appropriate for contouring based on CT-simulation imaging alone. The PTV should be determined based on local institutional immobilization and image-guidance practices.

Table 3
Summary of Recommendations from Published Guidelines.

Study/First Author	Year	Indications for NSBM SBRT	Simulation Imaging	CTV	Dose Fractionation
Lopez-Campos et al SEOR Consensus Guideline[19]	2021	1)Oligometastatic (≤5 lesions) 2)Polymetastatic & symptomatic & >3 mo estimated survival	Fused MRI for planning when available. Fused PET for planning when available	GTV + 2–5 mm intraosseous margin. GTV + 2–5 mm extraosseous margin if soft tissue component or cortical bone disruption.	20–24 Gy/1 30 Gy/3 35–50 Gy/5 Favor single fraction to reduce visits.
Vilotte et al GETUG Delphi Consensus Guideline [20]	2022	1)Oligometastatic (≤5 metachronous lesions)	MRI and PET optional. Diagnostic MRI can be used if < 3 weeks old	GTV + 3–5 mm intraosseous margin. GTV + 3–5 mm extraosseous margin if tumor extends into surrounding soft tissue.	27–30 Gy/3 30–35 Gy/5
Gillespie et al MSK Delphi Consensus Guideline [21]	2022	1)Oligometastatic 2)Reirradiation 3)Symptomatic patients & KPS 70+ & radioresistant histology	Recommend fusion of secondary imaging (MRI and/or PET). May omit if targets well visualized on CT and not close to organs at risk.	N/A	5 fractions or fewer
Nguyen et al CTV Consensus Contouring Guideline [18]	2022	N/A	N/A	GTV + 5–10 mm intraosseous GTV + 5–10 mm extraosseous if associated soft tissue component or cortical bone disruption.	N/A

N/A = not available.

Dose fractionations

There was significant heterogeneity in the delivered dose fractionations between and within studies. Two studies had included a minority of patients treated with 40–50 Gy in 10 fractions (representing 5 % [27] and 15 % [22] of targets treated in each study), otherwise, dose fractionations ranged from single fraction to multi-fraction schedules that did not exceed 5 fractions (Table 1). Common schedules included 18–24 Gy in 1 fraction, 27–30 Gy in 3 fractions, and 30–35 Gy in 5 fractions.

Three included guidelines and 1 patterns of practice survey provided suggestions for selecting dose fractionation schedules (Table 3). According to the SEOR guidelines, although single fraction schedules (total dose 20–24 Gy) were preferred, other acceptable dose fractionation schedules included 30 Gy in 3 fractions or 35–50 Gy in 5 fractions [19]. On the other hand, a Delphi consensus study from the GETUG indicated a preference for fractionated schedules with agreement to consider the following in priority order: 30 Gy in 3 fractions, 27 Gy in 3 fractions, 35 Gy in 5 fractions, and 30 Gy in 5 fractions [20].

Toxicities

NSBM SBRT was overall well-tolerated with a low adverse event profile as described in 12 reports providing these data. The most common grade 1–2 acute toxicities were fatigue, pain flare, and nausea/vomiting. Fracture was the most common late toxicity ranging from 0 to 17 %. In the only randomized trial, Nguyen et al. reported grade 1–2 toxicities in 17 % of patients, with grade 2 nausea and vomiting being the most common. Six percent (n = 9) of patients developed grade 3 toxicities, the vast majority of which were fatigue (n = 8) and only one reported incidence of fracture. As an outlier, a phase 2 single arm trial of 38 patients and 41 treated lesions reported the highest fracture rate of 17 % (n = 7) [36]. The treated lesions were mostly in the bony pelvis (n = 23), but there were also 9 extremity metastases and 7 rib metastases. The dose delivered was 30 or 35 Gy in 5 fractions. Of note, Madani et al. conducted a multi-institutional retrospective analysis of exclusively long bone SBRT and reported a pooled fracture rate of 7 % (n = 8) [27].

Discussion

In this systematic review of NSBM SBRT, excellent clinical outcomes were observed, with LC rates of 95 % at 1 year and 94 % at 2 years, and pooled OS rates of 84 % at 1 year and 81 % at 2 years. While there was significant heterogeneity in how NSBM SBRT is planned and delivered, generally treatment-related toxicities were low. The present guideline builds on other recently published guidelines from other radiation oncology societies, through consensus-based recommendations (Table 4).

Members of the expert panel agreed that CT simulation should be obtained with ≤ 3 mm thick slices with the consideration of 1 mm thick slices for small targets or those near critical organs at risk. Ideally, a simulation MR would be obtained to guide target delineation (Fig. 5). There are published data demonstrating that bone metastases are often underrepresented by CT imaging alone and the addition of a fused MR scan increases the size of the contoured target volume [38,39]. When a dedicated simulation MR of the target site is not available, a recent diagnostic MR can be fused instead. At institutions where diagnostic and simulation MR imaging is constrained, the use of MR should be prioritized for cases with associated soft tissue extension and/or cases where the gross tumor volume is not well visualized on CT imaging alone (Fig. 5).

Most of the included retrospective and prospective studies in this report used a CTV margin (n = 13; 72 %), its use is also supported by multiple consensus guidelines [18–21]. Using a CTV margin would also maintain consistency with the practice for spine and sacral SBRT, where expert consensus guidelines recommend a CTV be generated by expanding the GTV to include uninvolved adjacent spinal/sacral

Table 4
ISRS Consensus Recommendation Statements.

Treatment Simulation	Quality of Evidence	ISRS Committee Consensus Level
A CT simulation scan with ≤ 3 mm slice thickness should be obtained	5	Strongly Agree: 89 % (n = 8) Agree: 0 Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
If targets are small or near critical OARs recommend 1 mm slice thickness	5	Strongly Agree: 67 % (n = 6) Agree: 33 % (n = 3) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
Ideally, a dedicated MR simulation scan should be fused to the CT simulation scan to aid target delineation. In the absence of a dedicated MR simulation scan, fusion of a recent diagnostic MRI scan (< 3 weeks between scan and treatment start; T1-weighted and T2-weighted) may be helpful, although the utility can be compromised by differences in slice thickness and/or anatomical orientation. If MR access is limited, consider prioritizing for cases with associated soft tissue disease, poorly visualized target lesion on CT or not visualized on CT (e.g. bone scan/PET uptake without clear CT correlate).	4	% (n = 7) Agree: 11 % (n = 1) Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
If a diagnostic PET-CT (e.g. FDG or PSMA) has been completed and is considered a valid imaging modality for the underlying tumor histology, then this should be fused with the simulation CT scan as well to guide delineation.	5	Strongly Agree: 33 % (n = 3) Agree: 44 % (n = 4) Uncertain: 22 % (n = 2) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 78 % of the ISRS committee members responding with strongly agree or agree.
Motion management (e.g. 4DCT, active breathing control) should be considered for metastases located in ribs and sternum (exception: posteromedial ribs and upper sternum are unlikely to be influenced by respiratory motion).	5	Strongly Agree: 67 % (n = 6) Agree: 33 % (n = 3) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
Consider the use of a mask/shell for immobilization for bony targets T4 and above (e.g. upper ribs, sternum, clavicle).	5	Strongly Agree: 89 % (n = 8) Agree: 0 Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
Gross Target Volume Delineation		

(*continued on next page*)

Table 4 (*continued*)

Treatment Simulation	Quality of Evidence	ISRS Committee Consensus Level
Use a combination of CT-sim and available fused imaging (MRI, PET-CT) to delineate. The GTV should be assessed on both bone and soft tissue windows on CT imaging.	4	Strongly Agree: 89 % (n = 8) Agree: 11 % (n = 1) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
PET scan can help with localization but should not be relied on for target delineation over CT and MRI especially in cases of discordance	5	Strongly Agree: 44 % (n = 4) Agree: 44 % (n = 4) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
Clinical Target Volume Delineation		
When the GTV is delineated based on MRI+/- PET/CT fusion, a CTV margin is recommended as a 0–5 mm expansion of the GTV within contiguous bone.	**5**	Strongly Agree: 33 % (n = 3) Agree: 67 % (n = 6) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
When the GTV is delineated based on CT alone, a CTV margin is recommended as a 5–10 mm expansion of the GTV within contiguous bone.	**5**	Strongly Agree: 33 % (n = 3) Agree: 56 % (n = 5) Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
Where there is extraosseous tumour extension or cortical bone disruption, a minimum of 5 mm extraosseous margin can be considered.	**5**	Strongly Agree: 44 % (n = 4) Agree: 44 % (n = 4) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
When the tumor is confined to the bone and the cortical bone is intact, the CTV should be restricted to bone only. The CTV should be adjusted where necessary to respect natural barriers to spread including the peritoneum, pleura	**5**	Strongly Agree: 78 % (n = 7) Agree: 22 % (n = 2) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
A 2–5 mm PTV should be generated and is dependent on the specific immobilization used and local institutional policies.	**5**	Strongly Agree: 67 % (n = 6) Agree: 33 % (n = 3) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
Dose Fractionation		
Suggested dose fractionation schedules include: 18–24 Gy/1, 27–30 Gy/3, and 30–35 Gy/5.	**5**	Strongly Agree: 44 % (n = 4) Agree: 44 % (n = 4) Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
Consider dose de-escalation (increase in fractionation and/ or reduction in total dose) in cases of: previous radiotherapy, inability to meet OAR constraints, or moderate to severe cortical erosion especially in the presence of extraosseous disease extension.	**5**	Strongly Agree: 22 % (n = 2) Agree: 67 % (n = 6) Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
In cases where dose escalation may be desired, such as radioresistant disease or oligometastatic disease where the intent is cure, consider dose fractionations at the upper limit of the recommended range above for 1 and 3 fractions. For 5 fraction schedules, dose escalation beyond 35 Gy is reasonable to a maximum of 50 Gy. The optimal dose fractionation within this range is unclear.	**5**	Strongly Agree: 33 % (n = 3) Agree: 56 % (n = 5) Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
For long extremity bones consider fractionated over single fraction courses. Caution in escalating dose beyond 27–30 Gy/3 or 30–35 Gy/5.	**5**	Strongly Agree: 33 % (n = 3) Agree: 56 % (n = 5) Uncertain: 0 Disagree: 11 % (n = 1) Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
Special Considerations – Shoulder Girdle		
humerus, ulna, or radius, consider: Positioning the ipsilateral arm away from torso to limit dose to lungs and chest wall.	**5**	Strongly Agree: 33 % (n = 3) Agree: 56 % (n = 5) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
For targets in the **humerus, ulna, or radius,** consider:Using custom immobilization (e.g. VacLoc bag) to minimize rotation		Strongly Agree: 33 % (n = 3) Agree: 56 % (n = 5) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
For targets in the **humerus, ulna, or radius,** consider: A fractionated course to reduce risk of fracture		Strongly Agree: 11 % (n = 1) Agree: 78 % (n = 7) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with

(*continued on next page*)

Table 4 (*continued*)

Treatment Simulation	Quality of Evidence	ISRS Committee Consensus Level
		strongly agree or agree.
scapula or clavicle, consider maintaining consistent arm position as diagnostic imaging, if possible, to help with localization	5	Strongly Agree: 33 % (n = 3) Agree: 67 % (n = 6) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
Special Considerations – Thoracic Targets		
:Respiratory motion should be assessed by 4D-CT and accounted for using institutional protocols (e.g. gating, abdominal compression, active breathing control, etc.) May not be required for proximal rib lesions adjacent to spine	5	Strongly Agree: 67 % (n = 6) Agree: 33 % (n = 3) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
For rib targets consider: Consider fractionated course over single fraction as it may mitigate the risk of fracture		Strongly Agree: 56 % (n = 5) Agree: 33 % (n = 3) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
For rib targets consider: For metastases with intact bony cortex, the CTV should extend along the bone and trimmed at the cortex. For metastases with an extraosseous component or cortical disruption, the CTV should extend into surrounding soft tissue.		Strongly Agree: 67 % (n = 6) Agree: 22 % (n = 2) Uncertain: 11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
For rib targets consider:The CTV should be trimmed at the pleura (i.e. exclude overlap of CTV with lung)		Strongly Agree: 44 % (n = 4) Agree: 56 % (n = 5) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
For sternal targets consider: Respiratory motion should be assessed by 4D-CT and accounted for using institutional protocols (e.g. gating, abdominal compression, active breathing control, etc.) May not be required for superior sternal targets (e.g. manubrium)	5	% (n = 3) Agree: 67 % (n = 6) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
For sternal targets consider: Attention to skin dose		Strongly Agree: 44 % (n = 4) Agree: 44 % (n = 4) Uncertain:11 % (n = 1) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 89 % of the ISRS committee members responding with strongly agree or agree.
Special Considerations – Lower Extremity Targets		
acetabulum, consider: A fractionated course as it may reduce the risk of fracture	5	% (n = 2) Agree: 78 % (n = 7) Uncertain:0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
For targets in the **acetabulum**, consider:A dose de-escalation if PTV overlaps with joint space (e.g. reducing 35 Gy/5 to 30 Gy/5)		Strongly Agree: 11 % (n = 1) Agree: 67 % (n = 6) Uncertain: 22 % (n = 2) Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 78 % of the ISRS committee members responding with strongly agree or agree.
For targets in the **femur, tibia or fibula**, consider: A fractionated course as it may reduce the risk of fracture	5	% (n = 3) Agree: 67 % (n = 6) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.
For targets in the **femur, tibia or fibula**, consider:Consider custom immobilization of ipsilateral leg for distal targets below the knee (e.g. vac-loc bag for limb)		Strongly Agree: 22 % (n = 2) Agree: 78 % (n = 7) Uncertain: 0 Disagree: 0 Strongly Disagree: 0 Strong consensus reached with 100 % of the ISRS committee members responding with strongly agree or agree.

*Levels of evidence based on Oxford Centre for Evidence-based Medicine 2009.

segments at risk of harboring microscopic disease [9,10]. This principle is challenging to apply to the NSBM SBRT population as there may not be a clearly defined bony compartment for non-spine bone targets, or the bony compartment may be too large to reasonably include in its entirety (e.g. femur). Whilst the spine/sacral SBRT guidelines are based on expert opinion, there are data to suggest that deviations from guideline-based contouring can result in compromised local tumor control, which supports the use of a CTV margin [40].

The optimal CTV expansion is unclear as there is a paucity of histopathological data regarding extent of microscopic spread within bone. There was striking variability in the CTV margin used across the included non-guideline studies, ranging from 0 mm to 30 mm. Within individual studies there was also inconsistency, with several reporting ranges such as 2–5 mm, 5–10 mm, and 10–20 mm [23,24,26,27,33]. The included published guidelines, however, had less variance and nearly all recommended margins within the 2–5 mm range for an intraosseous and extraosseous margin [19–21]. An exception was the CTV contouring guideline, which recommended a larger range of 5–10 mm; however, when the participants on that study (all radiation oncologists) were asked for a specific margin they would recommend within that range, the majority reported 5 mm if an MRI of the target site was available to confirm target delineation (n = 8; 89 %). In the absence of an MRI and with CT simulation alone, 3 experts indicated they would increase the CTV expansion to 7 mm and 2 preferred increasing the expansion to 10 mm [18].

There is agreement across guidelines that all cases should have an intraosseous margin and extraosseous margins should be considered in cases where there is associated soft tissue extension or cortical breach which would put the adjacent extraosseous region at risk for microscopic

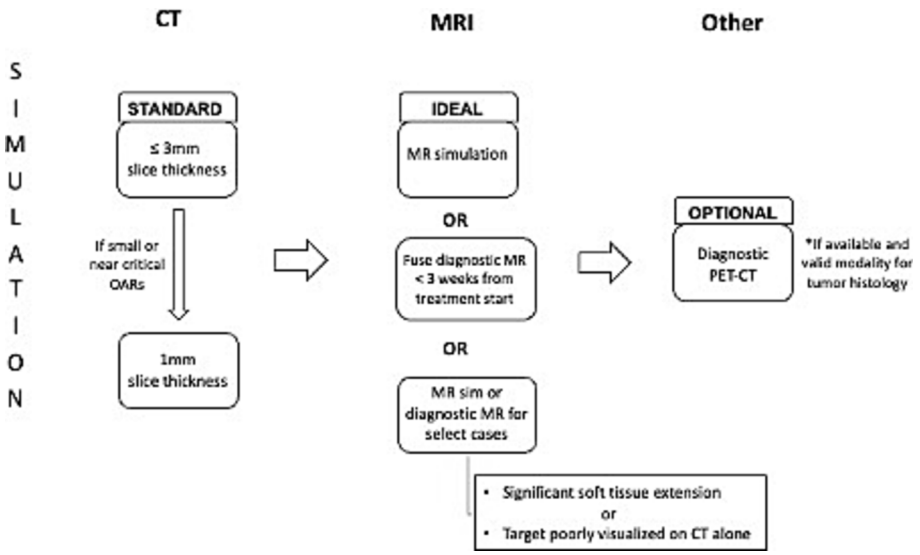

Fig. 5. Algorithm for Simulation Imaging for NSBM SBRT.

extension. These recommendations are under the assumption that the intact cortical bone serves as a natural barrier to tumor spread [17].

[17]With conventional palliative radiotherapy, there are robust data demonstrating that 8 Gy in 1 fraction is equivalent to fractionated schedules with respect to initial pain response rates [41–43]. This has informed the publication of multiple guidelines, the majority of which favour single fraction radiotherapy over fractionated courses for uncomplicated bone metastases [3]. The evidence guiding dose selection for NSBM SBRT, however, is more limited. Recently, a phase 3 multicenter trial randomized patients to receive 24 Gy in 1 fraction versus 27 Gy in 3 fractions in patients with oligometastatic bony or nodal disease (<= 5 metastases) [44]. Local control rates were superior in the 24 Gy in 1 fraction arm, with a cumulative 3-year local recurrence rate of 5.8 % compared with 22 % in the 27 Gy in 3 fraction group. It is worth noting that the biologically effective dose (BED10) of 24 Gy in 1 fraction (81.6 Gy) is much higher than 27 Gy in 3 fractions (51.3 Gy) across a range of alpha/beta ratios, and so the superior local control is not surprising, even assuming the linear-quadratic model holds true for such schedules. The results of that study are hypotheses generating and require validation.

A patterns of practice survey of international experts in non-spine bone SBRT demonstrated marked variability in preferred dose fractionation schedules [17]. The most common schedules chosen by ≥ 3 experts were 35 Gy in 5 fractions (BED10 = 60 Gy), 20 Gy in 1 (BED10 = 60 Gy) fraction, 30 Gy in 3 fractions (BED10 = 60 Gy) and 30 Gy in 5 (BED10 = 48 Gy) fractions. The GETUG Delphi consensus survey recommended fractioned SBRT doses rather than a single fraction schedule and favored 3 fractions (total dose 27 Gy-30 Gy) over 5 fractions (30–35 Gy) [20]. The SEOR SBRT guidelines also preferred shorter schedules and while supporting 1, 3 and 5 fraction regimens, favored single fraction (20–24 Gy) [19]. The panel agrees with the principle of minimizing the number of fractions where possible, but also acknowledges that 1, 3 or 5 fraction schedules are all reasonable options and there may be institutional and practitioner preferences based on local protocols and clinical experience. There was expert consensus for the following dose fractionation schedules: 18–24 Gy/1, 27–30 Gy/3 and 30–35 Gy/5 (Table 4). Given the heterogeneity in the location and local anatomy of NSBM, dose selection should be tailored to the target in question and the clinical indication. The panel suggests considering dose de-escalation, whether by reducing the total dose and/or increasing the number of fractions, in weight-bearing bones [17,19], where there is moderate or worse cortical bone erosion (>=1/3) [17,19] or if there is associated extraosseous disease [27]. Dose escalation to maximally tolerated dose based on nearby organ-at-risk constraints might be considered in situations where local control is prioritized, such as with oligometastatic disease and/or radioresistant histologies (Fig. 6). For example, a breast cancer bone metastasis may be treated to a dose of 20 Gy in 1 fraction, whereas a renal cell bone metastasis may be dose escalated to 24 Gy in 1 fraction. The optimal maximal dose is not clear, particularly for 5 fraction dose schedules. These dose fractionations had the most variability across included studies, ranging from 30 Gy in 5 fractions to a maximum of 50 Gy in 5 fractions. The study from Cao et al had as many as 20 % of included patients treated to 50 Gy in 5 fractions. There remains uncertainties regarding the safety and incremental benefit of this maximum dose given the limited number of patients treated at this dose and a lack of details around the individual patient and tumor characteristics of each case. When dose escalation is desired, the panel supports increasing dose beyond 35 Gy in 5 fractions, but the optimal maximum dose is not clear.

Despite the concerns regarding fracture following NSBM SBRT, patient series to date have demonstrated modest fracture rates and an overall low toxicity profile. The most robust characterization of fracture risk in this setting is a pooled multi-disciplinary retrospective review of

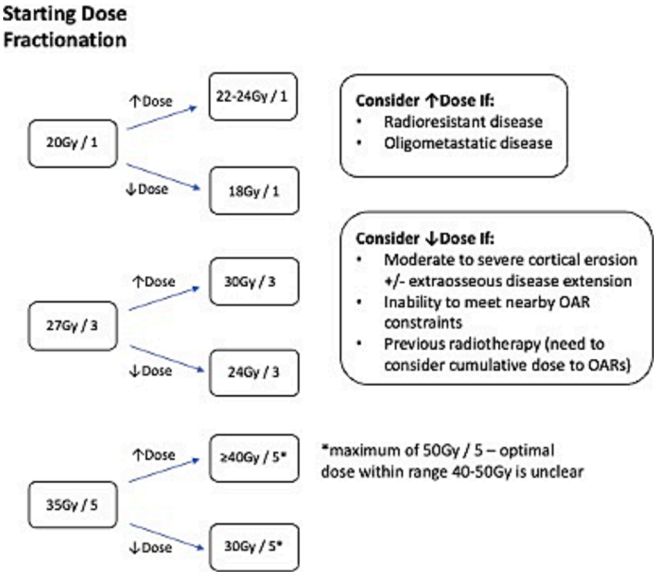

Fig. 6. Algorithm for Dose Selection for NSBM SBRT.

111 patients looking exclusively at long bone metastases, which are sites that often carry the most concern for fracture [27]. In this study, Madani et al reported a fracture rate of 7 % which is similar to the rates of vertebral compression fracture after spine SBRT which tend to range between 10–20 % [45,46]. In the cases with post-treatment fracture, 5 targets were in the femur, 2 in the tibia, and 1 in the humerus. Notably, the dose delivered in these cases was 25–35 Gy in 5 fractions (median BED 48 Gy, range 38 Gy to 61 Gy), which is on the lower end of the 5-fraction regimens included (range 30–50 Gy/5 fractions) and on the lower end of BED across all dose schedules (1-,2-,3-, 4-,5- and 10-fraction schedules; range 34.6 Gy to 100 Gy). Furthermore, multivariable analysis did not establish dose as predictive of fracture. Instead, the presence of extraosseous extension was the only statistically significant predictor for fracture. This suggests that standard fractionated SBRT schedules may be a safe and reasonable choice for NSBM in weight-bearing long bones and may not necessitate dose de-escalation to mitigate the risk of fracture as much as other factors, such as extraosseous extension. Predicting post-treatment fracture using baseline clinical or radiological features needs further investigation. In case of significant cortical erosion in weight-bearing bones, an opinion from orthopedic surgery may be beneficial prior to proceeding with radiotherapy. A Mirels score of ≥ 8 has also been a useful threshold to prompt consultation with an orthopedic surgeon [47]. Overall fracture rates are lower than those observed after spine SBRT, typically in the order of 10–15 % with fractionated treatment.

Two recently published *meta*-analyses have shown concordant findings to our analysis. Moraes et al reported favorable local failure (7 %) and fracture rates (5.3 %) at one year, in a similar but smaller group of patients. Similar to our conclusions, they did not report a higher rate of fracture in long bone NSBM and the highest observed fracture rate was seen for rib metastases. In their analysis, a larger PTV was correlated with fracture risk, so the authors urge caution in treating large lesions (note the median PTV for patients with a fracture was 113.5 cc). No relationship was found between local failure and the PTV, dose delivered, or radiosensitivity of the underlying histology. The second *meta*-analysis included 9 studies and reported similar 1 year incidence of LF (5.4 %) and pooled fracture rates (3.1 %) [48]. Meta-regression was not performed due to heterogeneity across the included studies. Unique to this study was the inclusion of pain response outcomes which was only reported in 4 of the studies they examined. Based on the available data, the estimated combined partial and complete pain response rate was 87.7 %.

The recommendations proposed in this guideline were limited by the available published data at the time of manuscript preparation. There continues to be a need for prospective studies to better understand how to maximize the effectiveness of SBRT for NSBM. Gaps in the literature include ideal dose fractionation (e.g. optimal total dose, number of fractions), the relationship between SBRT dose and pain relief, and the impact of anatomical bony sites on fracture risk and tumor control. In addition, these recommendations were shaped by the invited experts. While there were efforts to recruit an international panel to provide diverse perspectives, there may still be inherent biases that may not be truly reflective of worldwide practice.

Conclusion

SBRT for NSBM can be delivered safely, with low levels of side effects, whilst achieving a very high local control rate and encouraging overall survival. This international consensus offers guidelines for safe practice in the treatment of NSBM.

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusions, and recommendations contained in this report.

CRediT authorship contribution statement

Timothy K. Nguyen: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Alexander V. Louie:** Writing – review & editing, Supervision, Conceptualization. **Rupesh Kotecha:** Writing – review & editing, Supervision, Methodology. **Anshul Saxena:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Yanjia Zhang:** Writing – review & editing, Formal analysis. **Matthias Guckenberger:** Writing – review & editing, Methodology, Data curation. **Mi-Sook Kim:** Writing – review & editing, Data curation. **Marta Scorsetti:** Writing – review & editing, Data curation. **Ben J. Slotman:** Writing – review & editing, Data curation. **Simon S. Lo:** Writing – review & editing, Data curation. **Arjun Sahgal:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Alison C. Tree:** Writing – review & editing, Supervision, Methodology, Data curation.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110717.

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