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Practice and principles of stereotactic body radiation therapy for spine and non-spine bone metastases

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ABSTRACT

Radiotherapy is the dominant treatment modality for painful spine and non-spine bone metastases (NSBM). Historically, this was achieved with conventional low dose external beam radiotherapy, however, stereotactic body radiotherapy (SBRT) is increasingly applied for these indications. Meta-analyses and randomized clinical trials have demonstrated improved pain response and more durable tumor control with SBRT for spine metastases. However, in the setting of NSBM, there is limited evidence supporting global adoption and large scale randomized clinical trials are in need. SBRT is technically demanding requiring careful consideration of organ at risk tolerance, and strict adherence to technical requirements including immobilization, simulation, contouring and image-guidance procedures. Additional considerations include follow up practices after SBRT, with appropriate imaging playing a critical role in response assessment. Finally, there is renewed research into promising new technologies that may further refine the use of SBRT in both spinal and NSBM in the years to come.

1. Introduction

Radiotherapy plays a critical role in the management of painful spinal and non-spine bone metastases (NSBM). Historically, treatment was based on conventional palliative low dose external beam radiotherapy (cEBRT). Several *meta*-analyses and randomized clinical trials have demonstrated an overall pain response rate of ~ 60 % and complete pain response rates ranging from 8 to 25 % [1,2]. With the intent to improve pain and local control rates, stereotactic body radiotherapy (SBRT) was applied to spinal metastases and more recently to NSBM. SBRT allows for high dose conformal radiotherapy delivered in just a few fractions, intentionally sparing organs at risk with steep dose gradients [3,4]. While cEBRT may remain appropriate in select patients with limited life expectancy, in the setting of advances in systemic therapy and improved survival, dose intensification with SBRT has been shown to be associated with more durable tumor control and pain response [5–7].

Specific to the spine, the International Stereotactic Radiosurgery Society (ISRS) has established practice guidelines to guide patient selection in the use of SBRT for spinal metastases in the de novo, retreatment and postoperative setting [8–10]. In the de novo setting, SBRT has traditionally been recommended in the setting of oligometastases, radioresistant histology and in patients with paraspinal extension contiguous to the spine [8]. The results of a randomized trial reported by Sahgal et al. have extended the indications to include patients with painful spinal metastases with at least a 3 month life expectancy and meets the eligibility criteria of the trial [5]. The rationale for postoperative spine SBRT is to maximize local control after major surgical intervention [3]. When retreating, whether postoperative or not, SBRT should be considered following cEBRT [11] or following prior SBRT [12], upon multidisciplinary discussion. Specifically in settings of high grade epidural spinal cord compression, baseline vertebral compression fracture (VCF) or mechanical instability, a case discussion with a spine surgeon may help formulate a more refined treatment plan that could involve minimally invasive surgical procedures to complement SBRT and, ultimately, provide better functional and patient reported

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outcomes while minimizing oncologic delays that can compromise patient outcomes [9].

2. Spine SBRT

Five randomized clinical trials have compared cEBRT to SBRT in the management of spinal metastases, of which three were specific to spinal metastases and 2 were mixed including spine and NSBM (Table 1).

2.1. Spine specific randomized trials

A randomized single-institution explorative phase 2 trial by Sprave et al. compared single-fraction SBRT (24 Gy) to cEBRT (30 Gy in 10 fractions) [6]. The primary endpoint was at least a 2-point improvement in pain without an increase in analgesic use 3 months following radiotherapy. Other endpoints included complete pain response as defined by International Consensus on Palliative Radiotherapy Endpoints (ICRPE); a worst pain of 0 on the Brief Pain Inventory (BPI) without an increase in daily oral morphine equivalent [13,14]. At 3 months, there were no significant differences in the primary endpoint between arms (70 % in those treated with SBRT and 48 % in those treated with cEBRT, $p = 0.13$), but pain values decreased faster in those treated with SBRT ($p = 0.01$). Specifically for complete pain response, there was a trend towards improved complete pain response rates with SBRT at 3 months (44 % in SBRT arm and 17 % in cEBRT arm, $p = 0.057$), and a significant improvement with SBRT at 6 months (53 % in SBRT arm and 10 % in cEBRT arm, $p = 0.003$) [6].

Sahgal et al. performed a multicentre randomized phase 2/3 trial comparing SBRT (24 Gy in 2 fractions) to cEBRT (20 Gy in 5 fractions) to a painful MRI-confirmed spinal metastasis (target metastasis) [5]. The primary endpoint was complete pain response 3 months after radiotherapy, defined by the ICRPE using BPI [13,14]. Median follow-up in the 229 patients enrolled was 6.7 months. They demonstrated significant improvement of complete pain response at 3 months with the use of SBRT, 35 % in the SBRT arm and 14 % in the cEBRT arm (95 % CI 1.14–1.55, $p = 0.0002$) [5], This improvement in complete pain response persisted at 6 months; 32 % in the SBRT arm and 16 % in the cEBRT arm (95 % CI 1.07–1.44, $p = 0.0036$). The positive result of this trial has resulted in 24 Gy in 2 SBRT fractions as an evidence-based standard of care in the treatment of painful spinal metastases that meet the study inclusion criteria. Fracture rates were equivalent and within expectations and there were few major deviations from the protocol. The trial was designed with appropriate quality assurance measures and was international. Quality of life analyses suggested patient reported financial toxicity was improved with the 2-fraction approach vs. 5 fractions. 24 Gy in 2 fractions is now considered a global standard of care [15].

NRG/RTOG 0631 was a randomized phase 3 trial comparing single fraction SBRT (16 Gy or 18 Gy to involved vertebra) to cEBRT (8 Gy in a single fraction to involved vertebra plus one vertebra above and below) with 353 patients randomized in a 2:1 randomization [7]. The primary endpoint was patient-reported complete pain response at 3 months [16] at the index lesion, defined as a 3-point improvement in Numerical Rating Pain Scale (NRPS), without progressive pain at other sites and no increase in pain medications. The study did not meet its primary endpoint of improved pain relief at 3 months with SBRT (41 % in those treated with SBRT and 61 % in those treated with cEBRT, 1-sided $p = 0.99$) [7]. Similarly, there were no changes in the mean change in pain score from baseline between SBRT and cEBRT. The pain relief in patients treated with SBRT was half of the predicted rate, and there are various reasons why this may have been the case including selection criteria and study conduct.

The inclusion criteria allowed for a wide range of performance status scores resulting in significantly more patients with Zubrod status 2 in the SBRT arm than in the cEBRT arm (22.0 % vs. 10.0 %, $p = 0.02$). Performance status is a predictor of pain response following radiotherapy for bone metastases [17], and their modeling showed a Zubrod score of 0 to be the most predictable factor for pain control [7]. Additionally, the

Table 1
Randomized controlled trials comparing SBRT to cEBRT in the management of both spine metastases and non-spine metastases. Sprave et al., Sahgal et al. and Ryu et al. investigated pain response in spine metastases alone. Sprave et al. and Sahgal et al. defined pain response as a 2-point improvement in pain scores, consistent with International Bone Metastases Consensuses Working Party, whereas Ryu et al. defined this as a 3-point improvement in pain scores. In the setting of non-spine, Nguyen et al. looked at pain response, a combination of partial and complete response, defined by International Consensus Criteria. Piekelnrood et al. and Mercier et al. were in the setting of bone metastases, including both spine and non-spine, with outcomes reported together (they did not separate findings based on spine or non-spine). *Mercier et al. has been only published in abstract form at this time.

Prospective Trial	Phase	Arms	Number of patients	Primary Endpoint	Complete Pain Response	Pain Response
Spine						
Sprave et al.	2	SBRT: 24 Gy in 1 cEBRT: 30 Gy in 10	55	2-point improvement in pain at 3 months	44 % vs. 17 % ($p = 0.057$)	70 % vs. 48 % ($p = 0.13$)
Sahgal et al.	2/3	SBRT: 24 Gy in 2 cEBRT: 20 Gy in 5	229	Complete pain response at 3 months	35 % vs. 14 % ($p = 0.0002$)	53 % vs. 39 %
Ryu et al.	3	SBRT: 16 Gy in 1 18 Gy in 1 cEBRT: 8 Gy in 1	353	Pain response at 3 months		41 % vs. 61 % ($p = 0.99$, 1-sided)
Non-Spine						
Nguyen et al.	2	SBRT: 12 Gy in 1 16 Gy in 1 cEBRT: 30 Gy in 10	160	Pain response (pain score + analgesic use) at 3 months		73 % vs. 49 % ($p = 0.04$)
Mixed: Spine and Non-Spine						
Pielkenrood et al.	2	SBRT: 18 Gy in 1 30 Gy in 3 35 Gy in 5 cEBRT: 8 Gy in 1 20 Gy in 5 30 Gy in 10	89 (49 spine, 40 non-spine)	Pain response at 3 months		40 % vs. 32 % ($p = 0.42$)
Mercier et al.*	3	SBRT: 20 Gy in 1 cEBRT: 8 Gy in 1	126 (145 metastases, 40 spine, 105 non-spine)	Complete pain response at 1 month	37 % vs. 25 % ($p = 0.25$)	

development of the trial predated the use of the Spinal Instability Neoplasia Score (SINS) [18], and some initially high pain scores may have been the result of mechanical pain which does not typically respond as well to radiotherapy [19]. Similarly, the use of spine MRI became standard after the trial opened, and the inclusion criteria were subsequently revised to include patients with clinically occult spinal metastases, which may have confounded reported pain outcomes. Lastly, the lower than anticipated pain response in the SBRT arm may also have been the result of the choice of the primary endpoint for the trial. The International Bone Metastases Consensus Working Party defined pain response as a decrease of at least 2 points at the treated site [14]. This is how complete pain response was defined in other trials [5,6,20], however, NRG/RTOG 0631 defined complete pain response as a 3-point improvement in NRPS [7], which likely contributed to lower pain response scores.

2.2. Mixed cohorts

A phase 2 single-institution randomized trial from Utrecht University Medical Centre was performed, within a prospective cohort (TwiCs), comparing several SBRT regimens (18 Gy in 1 fraction, 30 Gy in 3 fractions or 35 Gy in 5 fractions) to several cEBRT regimens (8 Gy in 1 fraction, 20 Gy in 5 fractions or 30 Gy in 10 fractions) for bone metastases, including spinal metastases [20]. The primary outcome was pain response 3 months after radiotherapy defined by ICRPE using BPI [13,14]. 89 patients were evaluable of which 49 were spinal metastases. Pain response at 3 months was 40 % in those treated with SBRT and 32 % in those treated with cEBRT ($p = 0.42$) [20]. Unfortunately, the trial was underpowered and had a high dropout rate (only 58 % of those offered SBRT actually received it) and radiotherapy doses were non-standardized.

ROBOMET was a multicentre phase 3 trial comparing single fraction SBRT (20 Gy) to cEBRT (8 Gy in a single fraction) in up to 3 painful bone metastases, including spinal metastases (28 % in SBRT arm and 27 % in cEBRT arm) [21]. The primary endpoint was complete pain response one month after radiotherapy. While only reported in abstract form thus far, the study did not meet its primary endpoint with 37 % of patients treated with SBRT having complete pain response at one month and 25 % in the cEBRT arm ($p = 0.25$). However, complete pain response rates by per protocol analysis was significantly improved with SBRT at 3 months (54 % with SBRT and 31 % with cEBRT, $p = 0.048$) [22] and the final report is needed to evaluate this trial before conclusions can be drawn.

2.3. Dose-Response

While no dose–response relationship has been confirmed in the setting of cEBRT for pain relief, dose intensification with SBRT has been shown to improve local control [5,6,22]. In particular, a phase 3 multicenter trial compared 24 Gy in a single fraction to 27 Gy in 3 fractions in the setting of oligometastatic disease to the bone or lymph nodes [23]. 117 patients were included, 62.5 % had spinal metastases. They demonstrated that dose escalation significantly improved local control ($p = 0.0048$), and reduced the cumulative incidence of distant progression ($p = 0.01$) [23]. Specifically in the setting of spine SBRT, Zeng et al. reviewed outcomes in patients treated with 24 Gy in 2 fractions or a dose-intensified 28 Gy in 2 fractions regimen [24]. They identified 646 segments in 323 patients treated with 24 Gy in 2 SBRT fractions, and 301 segments in 159 patients treated with 28 Gy in 2 SBRT fractions. They found that dose escalation significantly reduced local failure at 24 months; 11.1 % with 28 Gy and 17.6 % with 24 Gy ($p = 0.008$). Moreover, these outcomes were consistent with estimated control rates reported by Hypofractionation Treatment Effects in the Clinic (HyTEC) modeling [25] which provides validation of that model. Furthermore, the VCF rates were similar between the two cohorts, and this is consistent with the analyses by Sahgal et al. supporting a dose per fraction under 20 Gy as a mitigation strategy for VCF [26]. Taken together, the current literature suggests a dose–response relationship within spine SBRT practice, but further study is required to validate these observations and determine optimal practice.

2.4. Potential toxicities and organ at risk tolerance

2.4.1. Spinal cord tolerance

The risk of radiation myelopathy is related to total dose, dose per fraction and prior exposure to radiotherapy [27]. With conventional fractionation (1.8–2.0 Gy/day), doses up to and including 50 Gy are associated with a < 0.2 % risk of radiation myelopathy [28,29]. With SBRT, we must account for the uncertainty of how the linear quadratic equation can be applied given the higher doses per fraction and inhomogeneous dose distributions. The rapid dose fall-off around the target, in close proximity to the spinal cord, can result in small volumes of spinal cord receiving much higher point maximum doses than with a homogeneous dose exposure [30].

While there is some debate as to whether the spinal cord is to be considered exclusively as a serial organ, or if there is some inherent redundancy resulting in a dose-volume effect and could be considered a mixed parallel-serial organ [31], current practice is to respect maximum point doses to the spinal cord. The current recommendations by the HyTEC report are the following [32]; 12.4–14.0 Gy in a single fraction, 17.0–19.3 Gy in 2 fractions, 20.3–23.1 Gy in 3 fractions, 23.0–26.2 Gy in 4 fractions and 25.3–28.8 Gy in 5 fractions [32]. These spinal cord dose constraints are associated with a risk of less than 5 % of radiation myelopathy in de novo spine SBRT setting. For re-irradiation of the spine, HyTEC identified factors with a low risk of radiation myelopathy including a minimum interval between irradiation of more than 5 months, cumulative thecal sac or cord planning organ at risk volume (PRV) maximum dose (EQD2 with alpha/beta of 2) less than 70 Gy, thecal sac maximum dose to cumulative maximum dose ratio less than 0.5, and a SBRT thecal sac maximum dose (EQD2) less than 25 Gy [32]. Real-world experience notes the incidence of radiation myelopathy following spine SBRT is only 0.4 % in a pooled analysis of over 1000 patients [33]. The risk remains low even in the setting of re-irradiation, although higher than in the de novo setting at 1.2 % [9].

Appropriate contouring of the spinal cord plays a critical role in mitigating the risk of radiation myelopathy. The spinal cord should be defined based on axial volumetric MRI images [34–37], or with the use of a CT myelogram [34,35] ideally with the patient immobilized in treatment position and at the time of treatment planning CT. CT alone is insufficient as only the spinal canal can be reliably contoured with this approach. As there are setup errors and uncertainties, a safety margin should be used around the true spinal cord [38]. This can either be done using a uniform planning at risk expansion margin (common expansions include 1.0 mm, 1.5 mm and 2.0 mm) around the spinal cord, or by using a surrogate structure such as the thecal sac. The use of the spinal canal is not advised [32], as the CTV either extends to the edge of the spinal canal or into it in the case of epidural disease. Applying constraints to the spinal canal will lead to unnecessary compromise of target coverage [34,39]. Below the level of the spinal cord, the thecal sac is contoured and contouring guidelines have been proposed by Dunne et al. [40]. As initial spinal cord constraints were developed based on the thecal sac contour as a surrogate for the spinal cord, typical practice is to apply those constraints to a safety margin beyond the spinal cord.

2.4.2. Nerve and plexus tolerance

Like radiation myelopathy, the risk of brachial and lumbosacral plexopathy is impacted by the total dose, dose per fraction and prior radiotherapy. Unlike the spinal cord, it is thought that peripheral nerves are either parallel organs or mixed with a possible dose-length effect [41], which may explain why nerve roots are more tolerant than spinal cord tissue.

Proper contouring of the lumbosacral plexus is required to minimize

the chance of lumbosacral plexopathy. Consensus guidelines have been created to properly contour the lumbosacral plexus [42]. Recommended maximum doses to the sacral plexus are 16 Gy in a single fraction, 24 Gy in 3 fractions and 32 Gy in 5 fractions [36]. Much of our understanding of brachial plexus tolerance is from lung SBRT literature [43,44]. Recommended maximum doses to the brachial plexus are 17.5 Gy in a single fraction, 24 Gy in 2 fractions, 30.5 Gy in 5 fractions [36]. Like the lumbosacral plexus, appropriate contouring of the brachial plexus is important in cervical lesions and contouring guidelines are established [45]. The brachial plexus can be contoured on either MRI or CT, with 1 mm slice thickness, starting at the neural foramina down to the level below the clavicular head [45–47].

In a large series of 557 spinal segments treated in 447 patients, there were 14 cases of peripheral nerve injury (2.5 %) [48]. The median time to onset was 10 months after SBRT, with every patient experiencing pain and 93 % experiencing weakness. They found no relationship between SBRT dose and nerve injury [48]. In another series of 79 patients who lived more than 3 years following spine SBRT, there were 6 cases of plexopathy, 1 brachial plexopathy and the other lumbosacral [49]. The 1-, 2-, 3- and 5-year plexopathy rates were 0.74 %, 1.5 %, 2.2 % and 5.1 %, respectively, occurring at a median of 35.7 months. Most of the affected patients had multiple courses of radiotherapy [49]. Lastly, in a series of 159 patients treated with dose escalated 28 Gy in 2 SBRT fractions, only 3 (1.9 %) developed brachial or lumbosacral plexopathy and all were grade 1 or 2 [24].

2.4.3. *Vertebral compression fracture*

The most common adverse event following SBRT spine is vertebral compression fracture (VCF). This can lead to significant pain, deformity, neurologic deficit and, rarely, spinal instability and spinal cord compression [50]. A systematic literature review identified 11 studies addressing risk factors for VCF following SBRT [51]. They found a rate of VCF of 13.9 % in 2911 spinal segments treated with SBRT. They also identified lytic disease, baseline VCF prior to SBRT, higher dose per fraction, spinal deformity, older age and greater than 40 % – 50 % of vertebral body involvement by tumor as risk factors for VCF on multivariate analysis [51].

More recently, an updated systematic review and *meta*-analysis focused on the efficacy and safety of spine SBRT identified 69 studies with 7236 metastases and 5736 patients [52]. They found that the pooled rate of VCF following spine SBRT was 9 % (95 % CI: 4 % – 16 %). They also found that compared to cEBRT, SBRT does not appear to significantly increase the risk of VCF with only 1.7 % of VCF requiring surgical stabilization [52]. Longterm results from patients enrolled in the phase 2/3 multicentre trial by Sahgal et al., however, did show a trend towards increased risk of VCF in those treated with SBRT compared to cEBRT ($p = 0.087$) [53]. Moreover, all VCFs in the cEBRT cohort were managed conservatively but in the SBRT cohort, 4 of the 8 required intervention with 3 requiring surgery and one requiring percutaneous cement augmentation [53].

2.5. *Technical requirements*

Delivery of spine SBRT with close proximity of the spinal cord mandates high precision of the dose delivered and steep dose gradients, therefore, strict adherence to guidelines with respect to immobilization, simulation, contouring and the use of image-guided radiotherapy (IGRT).

2.5.1. *Immobilization*

Accurate setup and immobilization is required to minimize both inter- and intra-fraction motion. For cervical spine and upper thoracic metastases, thermoplastic head and shoulder masks can be used with total body vacuum devices such as the Body-FIX (Elekta AB, Stockholm, Sweden) near-rigid body immobilization system used for mid-thoracic, lumbar and sacral lesions [54,55]. Immobilization with arms above the head results in the lowest intrafraction motion [56,57]. Similarly, a retrospective review [57] found that the least amount of intrafraction motion was seen with a near-rigid body immobilization system. This results in all intrafraction motion less than 2 mm, justifying a 2 mm PTV and planning at risk volume. This is of particular importance as Wang et al. showed that 2 mm translational errors can be associated with more than 5 % loss of tumor coverage and increases of more than 25 % of maximum dose to organs at risk [58].

2.5.2. *Simulation*

Thin slice CT and MRI (1 mm) simulation is required as per SPIne response assessment in Neuro-Oncology (SPINO) guidelines [59] and recent Cancer Care Ontario Guidelines [60]. The use of gadolinium contrast is discouraged as normal bone marrow and tumor both enhance within spinal bone, complicating their differentiation. However, CT and/or MRI contrast may be used to delineate paraspinal and epidural disease, as well as in the postoperative setting to distinguish residual disease from postoperative fluid [59,61].

2.5.3. *Contouring*

Consensus contouring guidelines have been published and incorporated into National Comprehensive Cancer Network Guidelines [62] to guide clinical target volume (CTV) delineation. Current practice has been defined in the setting of the mobile spine, sacrum and postoperative setting [34,35,40]. Fundamental to the approach is the system defined by the International Spine Radiosurgery Consortium (ISRC). The anatomic classification system (Fig. 1) divides each spinal segment into 6 distinct anatomic sectors, inclusion of which in the CTV is based on sector involvement by gross tumor. A report by Chen et al. demonstrated that deviation vs. no deviation from the ISRC contouring guideline, increases the risk of local failure with 1- and 2-year local control rates of 81.1 % (95 % CI: 75.5 %-85.6 %) vs. 70.6 % (95 % CI: 63.2 %-76.8 %), respectively [63]. In the sacrum, deviation from the Dunne et al. consensus guidelines has also been associated with inferior local control; 1-year local failure of 15.1 % vs. 31.4 % in those with no deviation vs. deviation, respectively, in abstract form [64]. These guidelines are specific to boney anatomy. However, epidural and paraspinal disease

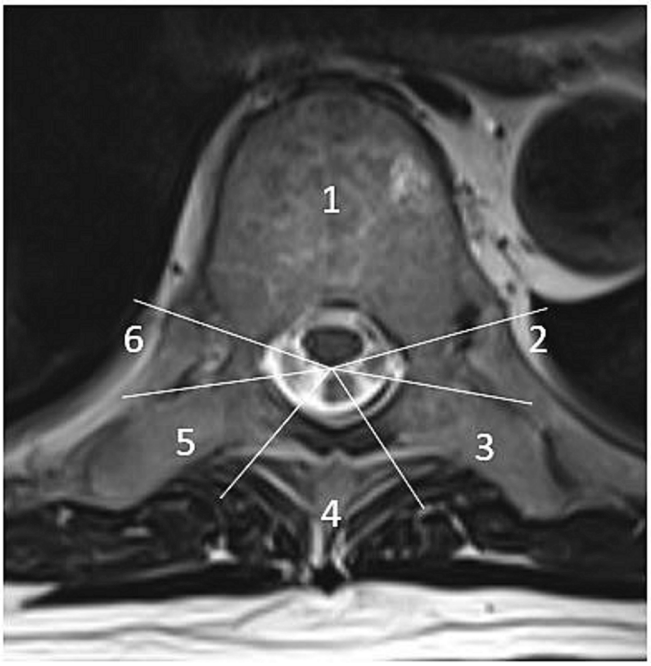

Fig. 1. Axial MRI of a vertebrae with the ISRC sectors (1) vertebral body, (2) left pedicle, (3) left transverse process and lamina, (4) spinous process, (5) right transverse process and lamina, (6) right pedicle.

are to be taken into the CTV. In the SC24 protocol the recommended practice was to apply a 5 mm expansion in all directions, while respecting anatomic boundaries (for example, excluding the spinal cord), beyond epidural and paraspinal disease within the CTV [5].

In the postoperative setting, the CTV should be guided by preoperative imaging. The entire anatomic compartment corresponding to preoperative MRI abnormalities as well as the postoperative region should be included in the CTV, although surgical instrumentation and the incision is to be excluded. Similar to the intact setting, the CTV should include a 5 mm expansion in all directions for any paraspinal disease, and 5 mm cranio-caudal expansion around any epidural component [35].

Local failure following SBRT, particularly in the postoperative setting, typically involves progression within the epidural space [65–68]. Patterns-of-failure analysis of 75 spinal metastases treated with post-operative SBRT [39] demonstrated 25 local recurrences with epidural progression, 24 of which had epidural disease preoperatively. In particular, those with anterior and posterior epidural disease were found to have higher rates of epidural failure, as compared to anterior compartment limited epidural disease alone. This suggests that a "donut" CTV should be used including the entire epidural space when both anterior and posterior epidural disease exists, but selective sparing posteriorly is possible if disease is limited anteriorly. Posterior element alone disease is rare [69] and there were not enough cases to draw conclusions in this circumstance.

2.6. Image-Guided radiotherapy

Image-guided radiotherapy (IGRT) with precise couch motions in all six degrees of freedom is ideal for the accurate and safe delivery of spinal SBRT [37,70]. Common image-guidance protocols include kilovoltage cone-beam computed tomography (CBCT) imaging to correct initial setup errors and a second verification CBCT to assess for residual setup errors [70]. Verification that the patient is not moving beyond safe tolerances during treatment is based on intrafraction imaging, with verification of the overall treatment accuracy based on the post-treatment CBCT [70]. Alternative strategies include the use of stereoscopic x-ray imaging taken before and regularly during treatment, which would be specifically necessary if near-rigid immobilization is not applied [71]. Dahele et al. analyzed translational and rotational positioning accuracy of 18 patients throughout treatment in patients who were not near-rigidly immobilized. Patients had shoulder/arm/head support for lower spine lesions and a thermoplastic head and neck mask for upper spine lesions. According to stereoscopic intrafraction x-ray imaging, positional stability was achieved within 1.5 mm in 94.4 % of fractions delivered and rotational displacements reproducible within 1 degree in 97.6 % of fractions delivered [71]. Another analysis of 42 patients examined initial setup, pre-treatment, mid-treatment and post-treatment CBCTs and found that strict repositioning thresholds in six degrees of freedom (1 mm and 1 degree correction threshold) yields minimal intrafraction motion. They found that with near-rigid immobilization, the translational and rotational errors were small, with 90 % within 1 mm and 97 % within 1 degree of correction [55]. Due to the inherently inhogomogenous dose distributions seen with spine SBRT, and the close proximity of the spinal cord, even small motions can be dosimetrically significant [54,58]. These studies highlight that with image-guided radiotherapy and strict immobilization, spine SBRT can be delivered safely with minimal PTV and PRV margins.

2.7. The role of emerging technology

With several prospective trials demonstrating improved pain control with the use of SBRT compared to cEBRT [5,6,22] and excellent long term local control [53], the use of SBRT for spinal metastases is increasing globally. There is renewed research into the application of new technologies that may further refine spine SBRT practice. MR-Linac (MRL) technology has been evaluated in various sites including glioblastoma [72], brain metastases [73], pelvic nodal metastases [74] and more recently in the spine [75]. MRL may further enhance the efficacy of spine SBRT where target coverage is often compromised to meet constraints on adjacent bowel, as the position of the bowel can vary as illustrated in Fig. 2.

The feasibility of spine SBRT with MRL has been investigated in the setting of lumbar and thoracic spines with the use of phantoms, comparing the delivery of spine SBRT with 1.5 T MRL to a conventional Linac [75]. They found that the dose to GTV was +/-3% on both MRL and conventional Linac plans. The dose to the spinal cord was closer to the measured dose using MRL; −0.6 % with MRL and + 1.8 % with conventional Linac in the lumbar spine and + 3.9 % with MRL and + 6.9 % with conventional Linac in the thoracic spine [75]. This is consistent with other studies comparing various MRL and conventional Linac planning softwares [76,77] While the feasibility has been demonstrated in phantom studies, much work still needs to be done to demonstrate its feasibility and then efficacy with online adaptive plans in patients.

Another strategy may be the use of charged particle radiotherapy such as proton therapy or carbon ion therapy. A dosimetric study, in 3 patients previously treated for spinal metastases and planned for single fraction spine SBRT was performed, comparing plans generated using step-and-shoot intensity modulated radiotherapy (IMRT), carbon ion radiotherapy and proton radiotherapy [78]. They were planned so that 90 % of the PTV received at least 18 Gy and plans were compared with respect to PTV coverage, organ at risk sparing and treatment time. There were no differences in PTV coverage between particle radiotherapy and IMRT. There were no differences in spinal cord doses in the thoracic region; however, they found that the maximum dose, dose to 1 %, and the spinal cord volume receiving 5 Gy was lower with particle radiotherapy for the cervical and lumbar lesion cases. They also reported shorter estimated delivery times with particle radiotherapy (6–7 min vs. 12–14 min with IMRT) [78]. Dosimetrically, proton and carbon ion therapy SBRT may be feasible, however, safety and efficacy data are needed.

2.8. Response assessment

Imaging is an integral part of the follow up and assessment of response following spine SBRT [59]. Several imaging-based guidelines have been used, each with its own limitations [59,79–81]. In particular, Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 is limited in this setting as only the extraosseous component of lytic metastases can potentially be measureable and sclerotic metastases are non-measurable [79]. In addition, if a metastatic lesion involves posterior elements of the vertebral body, it may not be feasible to measure the largest linear representative dimensions of the tumor on a single orthogonal plane, given the complex three dimensional shape of vertebral bodies [82]. SPINO guidelines which have been specifically developed for spine SBRT have defined progression as unequivocal increase in the size of the tumor [83]. However, no measurement threshold has been defined by SPINO guidelines. There is a need for data driven thresholds for imaging-based response assessment following spine SBRT. As per SPINO, MRI is the imaging modality of choice for assessment of response following spine SBRT [59]. It has been shown that in the setting of spine SBRT, a 10.9 % change in GTV is the minimum detectable difference that can be reliably captured on standard follow up MRI [84]. A recent single-centre study has proposed the feasibility of a model where each vertebral body is divided into different sectors and linear-based measurements are used in each sector to predict response [82]. However, this needs to be validated in prospective multicenter studies.

Physiologic imaging such as dynamic contrast enhanced (DCE) MR perfusion has been used in several small studies for response assessment [85–87]. While the plasma volume, a parameter derived from DCE perfusion, has shown promise in response assessment [86], the complex technique, post-processing and lack of validated parameter thresholds

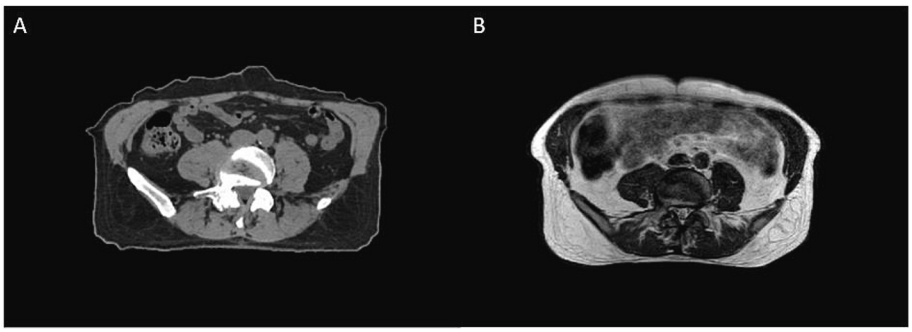

Fig. 2. A patient treated with SBRT spine for a L5 metastasis underwent volunteer MRL imaging. The CT simulation scan (A) shows a different positioning of the bowel than his MRL (B) scan in the same treatment position, highlighting the potential utility of MRL with variation in the position of bowel that impacts target coverage.

have limited its use in everyday practice. Direct metabolic imaging such as positron emission tomography (PET) has also been investigated is few small studies [88,89]. Another appealing feature of PET is that there is less image degradation related to spine metallic hardware. Access to PET, availability and reimbursement models limit this technique at present. In addition, it is still unclear at what time points DCE MRI or PET should be used for optimal results and resource utilization. Prospective multicentre trials are needed to provide robust and practical evidence to integrate DCE MR perfusion and PET in post-SBRT care in the management of spine metastases.

Another issue is the optimal follow up imaging interval following spine SBRT. SPINO's recommendation is to perform MRI every 2–3 months following SBRT for 12–18 months, and then every 3–6 months after [59]. This, however, is based on expert consensus and not data-driven studies or clinical trials. In addition, considerations such as epidural or paraspinal disease, SINS category and tumor histology can potentially affect the risk of recurrence and, therefore, the optimal follow up imaging interval. Research studies are currently underway to address this issue.

Finally, another challenging aspect of imaging-based response assessment is the issue of pseudoprogression. This is defined by SPINO as transient increase in the size of the tumor [59] and is similar to pseudoprogression following radiation to brain gliomas. There are few reports in the literature addressing pseudoprogression with a reported incidence of 14–37 % [90–92], and time of onset of 3 weeks to 3 months following SBRT [93,94]. These wide ranges are due to lack of measurement cut offs to define pseudoprogression. In addition, the onset of pseudoprogression is affected by the histology of the primary tumor [90]. There are no consensus guidelines regarding how to best image suspected pseudoprogression in spine following SBRT. While DCE MRI and PET are very promising, data regarding their use in clinical practice is not yet available.

3. Non-Spine bone metastases

NSBM are common in patients with metastatic cancer, and their presence can have a significant impact on quality of life and survival. cEBRT has been well established as an approach to palliating symptomatic NSBM but with the evolution of systemic therapies, its role in long-term disease control is unclear [1,2]. With the advent of SBRT, implementation of higher ablative doses in NSBM is becoming increasingly common for the purposes of achieving improved complete pain response and local control in the settings of oligometastases or oligoprogression [95–97]. While randomized data regarding SBRT in NSBM is more limited compared to spinal metastases, there is a growing body of evidence supporting its use in these scenarios, with recent guidelines directing technical specifications.

3.1. SBRT indications

When approaching patients with NSBM, a comprehensive evaluation is vital to select those who would most benefit from SBRT. In the absence of phase 3 data, patient selection can be driven by consensus guidelines for NSBM. Memorial Sloan Kettering Cancer Center (MSKCC) conducted a modified Delphi process among an expert multidisciplinary panel to establish consensus for management of NSBM [98]. There was high agreement that in symptomatic patients, SBRT can be considered for those with KPS $\geq$ 70, tumors with radioresistant histology or in the setting of re-treatment when more conformal therapy is needed to avoid exceeding dose constraints. For asymptomatic patients in the oligometastatic setting, enrollment on a clinical trial is preferred until phase 3 data is available. Similarly, consensus guidelines from GETUG indicates that SBRT for NSBM is appropriate for those with a life expectancy of $\geq$ 6 months and WHO performance status $\leq$ 2 [99].

Patients with impending or existing pathologic fracture (PF) require rapid surgical assessment for consideration of fixation, as those who undergo prophylactic surgery are shown to have improved functional outcomes and lower postoperative mortality compared to intervention in the post-fracture setting [100–102]. Evaluating risk of PF is multifactorial, involving both patient and lesion characteristics. A commonly used criteria is the Mirels' score, which is a 4-factor classification system to predict risk of fracture based on lesion location, size, radiographic appearance and pain severity [103]. This score can help guide clinicians in determining those who require assessment for upfront prophylactic surgical fixation, though it has not been validated for assessing risk of PF post-SBRT. More recent data highlights the importance of circumferential cortical involvement of the lesion, and a cut-off of $>$ 30 mm has been shown to be indicative of a high risk of fracture with a high sensitivity and specificity [104,105]. In addition, Howard et al. found that the inability to load at least 85 % of a patient's weight on the affected limb was predictive of fracture [106]. In the MSKCC consensus paper, there was majority agreement to consider referral for surgical consultation if patients have any of the following: lytic long bone or pelvic lesions with pain worsened with activity, any significant lesion in the femur that is either lytic or painful, progressive growth after radiation, or failure of palliation with radiation [98].

3.2. Overview of evidence

Given the higher biological effective doses associated with SBRT, and potential benefits in symptomatic response, there has been emerging data evaluating the efficacy of this approach in NSBM for the purposes of pain relief and local control.

MD Anderson Cancer Center (MDACC) conducted a prospective phase 2 noninferiority trial (Table 1), enrolling patients with painful bone metastases with a life expectancy of $>$ 3 months [107]. Patients were randomized between single-fraction SBRT (12 Gy or 16 Gy in 1

fraction) or cEBRT (30 Gy in 10 fractions). In the per-protocol analysis, the SBRT group had more complete and partial pain responders than the cEBRT cohort at 2 weeks (62 % vs. 36 %; p = 0.01), 3 months (72 % vs. 49 %; p = 0.03), and 9 months (77 % vs. 46 %; p = 0.04). At 2 years, local progression-free survival rates were higher in the SBRT arm compared to the cEBRT arm (100 % vs. 75.6 %; p = 0.01). There was no significant difference in toxicity between the two cohorts. This study supports utilizing stereotactic techniques to deliver higher single-fraction doses for patients who have more favorable prognosis and longer survival. In addition, Ito et al. conducted a single-arm phase 2 trial to evaluate the efficacy of SBRT for painful NSBM [108]. In the per-protocol analysis, complete or partial pain response at 3 and 6 months was 78 % and 75 %, respectively, and local control at 6 months was 92 %.

As previously discussed, the ROBOMET phase 3 randomized controlled trial compared single-fraction SBRT of 20 Gy to cEBRT with 8 Gy for painful bone metastases (Table 1), including 105 NSBM [22]. While the study did not meet its primary endpoint, per-protocol analysis for patients evaluable after 3 months showed a significantly higher complete pain response after SBRT (54 %) compared to cEBRT (31 %) (p = 0.048). There was no difference in treatment toxicity with a PF rate of 2 % in both cohorts.

Conversely, Pielkenrood et al. (Table 1) showed less favorable results for pain relief which included 40 NSBM [20]. In the intention-to-treat analysis, there was no significant difference in pain response between treatment arms, and there was no grade 3–4 toxicity reported. However, only 26 patients in the SBRT arm completed treatment as allocated and the pain questionnaire completion rate was only 39 % in trial participants significantly limiting the assessment of pain response in this group.

Recently, Nguyen et al. published the largest single retrospective cohort study on 505 NSBM treated with SBRT, showing favorable rates of local failure (LF) and PF [109]. On multivariate analysis, lytic lesions, a lower prescription biological effective dose (BED) and a larger PTV were significant predictors of LF. Patients who had a PTV of $\geq$ 54 cc had a significantly higher LF compared to those with a smaller PTV. For PF those with lytic lesions, mixed lytic/sclerotic lesions and rib metastases were at a significantly greater risk on multivariate analysis.

3.3. Dose-fractionation

Currently, the optimal SBRT dose-fractionation for NSBM remains unknown. Nguyen et al. conducted an international survey among experts, and found a wide variation in dose prescriptions recommended by participants, ranging from single-fraction doses (18–24 Gy) up to 10 fraction (42–50 Gy) regimens [110]. All prescriptions had a BED of $\leq$ 100 Gy_{10} and 58 % had a BED of 60 Gy_{10}. Overall, 35 Gy in 5 fractions was the most common fractionation scheme. Other common schedules included 20 Gy in 1 fraction, 30 Gy in 3 fractions and 30 Gy in 5 fractions.

A simultaneous integrated boost (SIB) approach can be considered when treating larger volumes or sensitive anatomical locations where the aim is to minimize treatment toxicity. A portion of experts used a SIB prescription with 2 dose volumes, most commonly 15–24 Gy in 3 fractions with a boost to 30 Gy in 3 fractions. This technique was suggested for a femur metastasis involving a large, destructive mass with soft tissue component [111].

GETUG conducted a survey among radiation oncologists to establish guidelines for treating bone metastases with SBRT [99]. For NSBM, there was consensus that multi-fraction SBRT should be favored over ultra high-dose single-fraction regimens. Furthermore, the same prescription schemes utilized in spine SBRT can be employed in NSBM.

There is evidence supporting the correlation between prescription dose and local control. Thomas et al. found that a prescribed $BED_{10} \geq 50$ Gy was associated with a reduced risk of LF (HR 0.68; p < 0.03) in oligometastatic lesions [112]. Similarly, Cao et al. reported that each 1 Gy increase in BED_{10} was associated with a 1 % decreased risk of LF (p = 0.031) [113]. Previous literature has shown radioresistant histologies to have a higher rate of LF, prompting clinicians to favor dose escalation in these scenarios. Data from Amini et al. suggest that a BED $\geq$ 80 Gy and a dose per fraction of $\geq$ 9 Gy are associated with improved local control when treating renal cell carcinoma bone metastases with SBRT [114]. Conversely, Dove et al. showed no significant difference in 1-year local control rates between 30 Gy or 40 Gy in 5 fractions for treatment of RCC bone metastases (90 % vs. 83.7 %; p = 0.553), though sample size was limited [115].

In regards to PF following NSBM SBRT, reported rates in current literature vary. In the MDACC phase 2 trial, the SBRT arm had a PF rate of 1.2 % [107]. Thomas et al. also reported a PF rate of 1.2 % overall in their cohort, while Nguyen et al. described 12.3 % of patients having PF post-SBRT [109,112]. In a Japanese phase 2 trial there were 7 patients with PF following SBRT (17 %), all of which were lytic or mixed lytic/sclerotic in nature [108]. Madani et al. conducted an international analysis across 7 centers, evaluating 114 metastatic lesions in the femur, humerus and tibia treated with SBRT [116]. Rate of PF was 7 %, suggesting that SBRT for metastases in long bones is safe in appropriately selected patients.

In the survey conducted by Nguyen et al., most experts dose de-escalate when treating a weight-bearing bone or long bones to mitigate the risk of fracture, especially in the settings of retreatment or with moderate-to-severe cortical erosion [110]. Correlation between dose and fracture risk is well demonstrated in the spine metastases data, and MSKCC showed a 39 % rate of VCF when using single-fraction SBRT for spine lesions [117]. Likewise, for lung SBRT, dose- and volume-response analysis showed that rib fracture risk was associated with an increase in dose [118].

Ultimately, the optimal dose-fractionation for NSBM SBRT that balances local control and toxicity is yet to be described. Untildedicated phase 3 data are available, dose and fractionation scheme for NSBM remains up to clinician preference based on the size of target lesion, anatomical location, and patient's overall prognosis.

3.4. Technical requirements

3.4.1. Immobilization

For NSBM SBRT, personalized immobilization devices are mandatory in order to maximize repositioning accuracy and intrafraction stability [119,120]. Alternatively, an image-guided tracking robotic system that minimizes intrafraction motion can be used [99]. Based on the location of the NSBM, the appropriate immobilization device should be employed. For example, a thermoplastic mask is used for lesions located cranial to T5, a Blue-BAG vacuum cushion (Elekta AB, Stockholm, Sweden) for NSBM in the pelvis, a Blue-BAG vacuum cushion (Elekta AB, Stockholm, Sweden) with an abdominal compression plate for rib metastases, or the complete BodyFIX dual vacuum system (Elekta AB, Stockholm, Sweden) based on physician preference [120]. For treatment of lesions in the extremities, a vacuum cushion should be used to minimize limb rotation [119].

3.4.2. Simulation

Planning CT simulation is acquired with 1–2 mm slice thickness with appropriate margins to include organs at risk in close proximity to the target. For NSBM in locations that may be susceptible to respiratory motion, such as the ribs and sternum, 4-dimensional CT (4DCT) planning can be considered to maximize target coverage [36].

Precise target localization while minimizing organ at risk doses is vital to ensure safe and effective delivery of SBRT. From the imaging perspective, MRI has been shown to be significantly more accurate than CT alone for delineation of bone metastases, and there is emerging utility of MRI fusion for the purposes of accurate contouring of NSBM [121,122]. Nguyen et al. showed that 5 experts used MRI fusion routinely for NSBM contouring, and 2 used MRI in cases where the target

was not well visualized on CT [110].

When coupled with standard CT simulation, MRI T1 images reduced inter-observer variability among radiation oncologists in delineating NSBM [123–125]. Agreement between the clinician and radiologist was also improved with the addition of MRI images [123]. Data has shown that the use of MRI fusion resulting in significantly larger contoured lesions compared to using CT alone, suggesting underestimation of true disease extent with CT alone [124,126]. Prins et al. found these differences were mainly observed in lesions with bone marrow involvement and soft tissue extension. Conversely, de la Pinta et al. found inter-observer variance in NSBM was equal when MRI was compared to CT, and was felt to be a result of the relatively lower experience of radiation oncologists in delineating targets on MRI [122]. This highlights the importance of establishing standardization, training, and consensus guidelines for NSBM MRI contouring.

A recent study examined the effect of both MRI and PET-CT fusion on inter-observer variability in contouring of NSBM compared to using planning CT alone [127]. Within a cohort of patients with predominantly osteoblastic prostate cancer metastases, the contoured CTV was significantly larger when using a combination of MRI and PET-CT fusion with planning CT. Furthermore, there was statistically more inter-observer agreement with PET-CT fusion as well both MRI and PET-CT fusion compared to CT alone. PET-CT fusion was found to have superior agreement when directly compared to MRI fusion, suggesting PET-CT to be a suitable method of fusion-based target delineation for planning of NSBM SBRT.

3.4.3. Contouring

Recently, Nguyen et al. published consensus contouring guidelines for NSBM SBRT [111]. These recommendations were based on an expert survey and directional margin analysis from the contours of 9 international radiation oncologists and the final guidelines generated 100 % agreement. In summary, an intraosseous CTV margin of 5–10 mm within contiguous bone should be used, and extraosseous CTV margin of 5–10 mm in cases of soft tissue disease and/or significant cortical bone disruption. All CTVs should be modified to respect the natural anatomic barriers to spread including uninvolved joint spaces, uninvolved organs and risk, peritoneal cavity, pleura and intact cortical bone. Most experts preferred an intraosseous or extraosseous CTV margin of 5 mm when MRI fusion was used, opting for a larger CTV margin of up to 10 mm when MRI was not available. PTV margin should be based on location of the target, patient immobilization, available motion management, image guidance and local expertise. For NSBM SBRT this generally ranges from 2 to 5 mm. An example of a metastases to the distal femur at the level of the knee is shown in Fig. 3.

When treating mobile targets such as ribs, an ITV should be generated from the different phases of a 4DCT [99]. For SIB approaches, 2 target volumes are delineated, with a smaller CTV (typically GTV or GTV + 2 mm) receiving the higher dose, and a larger CTV receiving the lower dose [110,116].

3.4.5. Treatment

Patients should be treated using intensity-modulated radiotherapy or volumetric modulated art therapy. A conformal plan should be generated with the goal of achieving $\geq$ 95 % PTV coverage with 100 % of the prescription dose while maintaining organ at risk dose limits that minimize toxicity [99,119,120]. Treatment is to be delivered using 3D kilovoltage (kV) CBCT image guidance for each fraction and a robotic couch permitting 6 degrees-of-freedom positional corrections. If available, technology to assess intrafraction motion such as tumor tracking (ExacTrac or orthogonal kV imaging) or gating can be implemented [99,112,119]. Intrafraction CBCT should be considered if treatment delivery length is $>$ 20 min or there is suspected patient movement, and an optional post-treatment CBCT can be used to document stability of the target during treatment [55,99,128].

3.5. Emerging technology

The advent of MR-Linac technology has shown promise within the scope of bone metastases [129]. In particular, it has been explored as a method of rapid palliative treatment, integrating MRI-only simulation and adaptive planning capabilities in order to allow for same-day treatment [130]. In addition, the MR-Linac allows use of diffusion weighted imaging to correlate imaging response after radiation treatment delivery with outcome. Use of this workflow is being evaluated for spine SBRT, and could be a potential approach for NSBM in the future with MRI biomarkers to assess response after SBRT across disease sites [131].

Proton therapy has also been explored as an approach to treating painful bone lesions. The FAST-01 trial examined the use of proton radiotherapy for symptomatic bone metastases using FLASH, an ultra-high-dose-rate proton treatment delivering $\geq$ 40 Gy/second using a single-transmission proton beam [132]. In this study, 10 patients with 12 metastatic lesions were treated with a dose of 8 Gy in 1, with a nominal dose rate of 60 Gy/second. With a median follow-up of 4.8 months, 67 % of treated sites had pain relief, and 50 % had complete response. Pain flare occurred in 33 % of treated sites, and 2 patients had a pathologic fracture. This early evidence shows that this approach is clinically feasible though further data is necessary to support its implementation into routine practice.

3.6. Response assessment

Response assessment following NSBM SBRT is challenging and there is yet to be consensus or well-established criteria for osseous metastases. While RECIST can be used, this system was designed for soft tissue

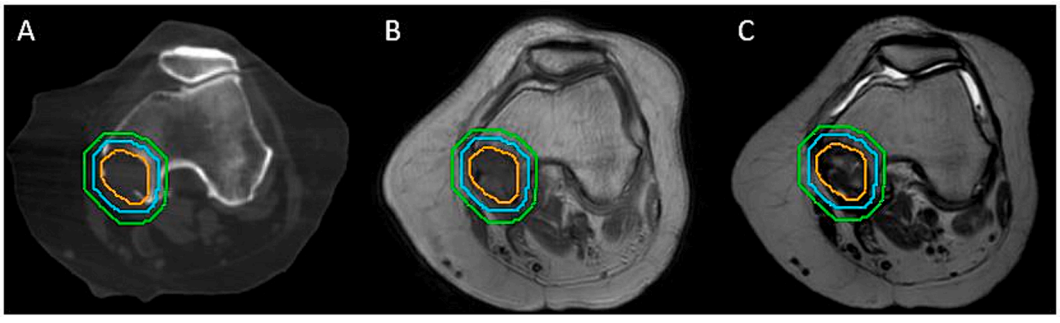

Fig. 3. A painful metastasis to the right knee treated with 30 Gy in 5 fractions with GTV in orange. The CTV is in blue and is a 5 mm intraosseous expansion from GTV within contiguous bone and, given cortical disruption, a 5 mm extraosseous expansion was also added, as per contouring guidelines by Nguyen et al. The PTV is in green and is also a 5 mm expansion, as per institutional policy. These are displayed on the following sequences A) CT simulation B) T1-weighted MRI C) T2-weighted MRI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lesions and is not applicable for NSBM since bone metastases are often identified as non-measurable targets [133]. Interpretation of imaging in follow-up is difficult as post-treatment changes to bone can complicate accurate radiographic assessment and obscure evidence of progressive disease [134]. With these confounding factors, the MDACC study used clinical responses defined by the International Pain Consensus Criteria taking into account pain response and narcotic utilization to report clinical response after radiation treatment [107]. The authors also correlated serial radiographic scans with PET/CT, MRI and diagnostic CT scans at follow up to assess response after radiation therapy.

Data from the spine metastases population has established MRI as the ideal imaging modality for assessment of bone metastases following SBRT and is necessary to determine development of pseudoprogression [37,59,93,135]. Correira et al. conducted a radiological assessment in 35 patients with 43 bone metastases post-SBRT, 21 of which were NSBM, and performed contrast-CT, MRI and PET/CT in follow-up [136]. A statistically significant difference was found between the target width parameter and imaging method which was increased in CT, stable in MRI and decreased in PET/CT, suggesting advanced imaging can potentially impact post-treatment response assessment. Furthermore, selecting appropriate endpoints for NSBM SBRT is equally important for effective clinical response assessment. Ito et al. proposed a pathophysiology-based classification system for patients receiving SBRT for bone metastases, categorizing NSBM patients into oligometastatic scenarios, de novo treatment for pain and re-irradiation for pain [137]. For oligometastatic patients treated with radical intent, authors suggested overall survival should be used as the ideal primary endpoint, while palliative approaches for symptomatic relief should be assessed using quality of life measures and clinical symptoms such as pain. These guidelines may help to inform clinical assessment and trial design.

4. SBRT in oligometastatic spine and non-spine bone metastases

With the known local control benefits of SBRT [5,6] together with confirmation of its overall survival benefits in the setting of oligometastatic disease [138,139], there is increased interest in the role SBRT in the setting of oligometastases to the spine and NSB. In fact, these are common sites treated in the oligometastatic paradigm, with a survey of over 1000 radiation oncologists finding spine and NSB were among the four most common sties treated with SBRT, other than brain, in the setting of oligometastases [140].

An international pooled analysis of 288 spine and 233 NSB lesions treated in 236 patients found low rates of local recurrence of 12.6 % and 19.3 % at 1- and 2-year, respectively [113]. They also found that 3 years after SBRT, 59.1 % of patients were alive, highlighting the potential benefit of SBRT in well selected patients [113]. Specifically in the setting of oligometastases to the spine, a multicentre retrospective series identified 183 lesions in 177 patients with oligometastatic disease [141]. They found excellent rates of local control; 90.3 %, 84.3 % and 84.3 % at 1-, 2- and 3-years, respectively. Additionally, they found that 1-, 2- and 3-year polymetastases-free survival rates were 57.8 %, 43.4 % and 32.4 % and median overall survival was 18 months [141]. These highlight that SBRT is an effective treatment option with promising results in oligometastatic spinal metastases and NSBM, the impact of which on the natural history of metastatic disease needs to be confirmed in large scale and histology-specific randomized trials.

5. Conclusion

Spine SBRT is now well established and an evidence-based treatment for spinal metastases. Further refinements in dose selection, integration with surgical procedures and approach to the peripheral nerves will only enhance the field further. The recent ESTRO guideline for spine SBRT represents a major advance to standardize practice. For NSBM, further evidence evaluating SBRT is required with large scale randomized trials needed to shift the paradigm. Overall SBRT is making considerable advances for patients with spine and NSBM with better palliation of pain and disease control.

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