



Overview

Stereotactic Body Radiotherapy for Spinal and Bone Metastases



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Abstract

Stereotactic body radiotherapy (SBRT) can deliver high radiation doses to small volumes with very tight margins, which has significant advantages when treating tumours close to the spinal cord or at sites of retreatment. When treating spinal tumours, meticulous quality control is essential with effective immobilisation, as dose gradients at the edge of the spinal cord will be steep and excessive movements can be catastrophic. A range of dose-fractionation schedules have been used from single doses of 15–24 Gy to fractionated schedules delivering 15–35 Gy in three to five fractions. Indications include solitary or up to three vertebral metastases and primary tumours, in particular chordomas or bone sarcomas. Pain relief from metastatic disease is seen in over 80%, with similar rates of objective local control. Local control can be achieved in primary tumours of the spine in up to 95% and similar response rates are seen in non-spinal bone metastases. Toxicity rates are low, even in series that have delivered re-irradiation with myelopathy in <1%, although later vertebral fracture may occur. Further prospective studies are required to formally evaluate patient selection and optimal dose and fractionation alongside an evaluation of cost-effectiveness.

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Key words: Bone metastases; chordoma; palliative; SBRT; spine; stereotactic body radiotherapy

Statement of Search Strategies Used and Sources of Information

A Medline search was used with the terms: stereotactic body radiotherapy, SBRT, cyberknife, Brainlab, bone metastases, spinal metastases, spinal cord compression, spinal tumours, chordoma, spinal cord tolerance, re-irradiation. All citations were evaluated for relevant content and validity.

Background

Stereotactic body radiotherapy (SBRT) has emerged as a novel treatment modality for spinal and bone metastases, particularly in the setting of oligometastatic disease, but also a treatment option for primary malignant spinal tumours. SBRT enables the delivery of potentially ablative radiation doses while respecting normal tissue constraints.

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Stereotactic Body Radiotherapy Delivery

There are several commercially available platforms capable of delivering SBRT and some provide near real-time positional adjustment during treatment [1,2]. CyberKnife is a linear accelerator that is attached to a robotic arm and allows for near real-time tracking of target motion using implanted fiducials or, in the case of the spine, using bony landmarks. The Novalis Tx unit allows for near real-time positional assessment via a stereoscopic X-ray image guidance system. However, if corrections for intrafractional motion are required, the treatment must be stopped and couch shifts applied. Other delivery systems are based on computed tomography image guidance and achieve intrafractional imaging by stopping treatment and re-acquiring a computed tomography image during treatment. Each system has strengths and weaknesses. Regardless of the treatment unit used, the key to high-quality SBRT delivery is the experience of the treatment team and the quality assurance of the entire process [3]. Methods of SBRT have not been standardised between various centres. A survey of spine SBRT methods at five international institutions found that despite close agreement in many steps of spine SBRT,

prospective and retrospective studies are required to refine the details of safety and efficacy [4]. Appropriate institutional credentialing by clinicians and medical physicists is essential for the safe and effective delivery of spinal SBRT. A multinational report has identified key methodologies for the safe implementation and credentialing of spinal SBRT [5].

Spinal Stereotactic Body Radiotherapy

Spinal radiation dose is limited by spinal cord and cauda equina tolerance. SBRT allows delivery of a high radiation dose to spinal metastases using between one and five fractions while sparing these and other organs at risk [6,7]. The delivery of a higher biologically equivalent dose of radiation may provide improved pain and local tumour control [8]. SBRT may also have a role in the retreatment of spinal regions that have previously received palliative doses of radiation when retreatment rates of up to 20% are expected, particularly after a single dose [9].

Patient Selection and Clinical Applications

As with any radical treatment, patients should have a good performance status (ECOG 0–2) and be able to comply with the requirements for treatment. Further considerations will relate to the setting, whether a primary or metastatic tumour and primary or postoperative treatment. A prognostic index using a recursive partitioning analysis index has been developed that is predictive of overall survival. This is based on three parameters: time from primary diagnosis $<>30$ months, Karnofsky performance status $<>70$ and age $<>70$ years, as shown in Figure 1. The median survival for groups 1, 2 and 3 are 21.1, 8.7 and 2.4 months, respectively. Although this was derived in a relatively small cohort of only 174 patients and has yet to be independently validated, it provides a simple means of selection for patients being considered for spinal SBRT [10].

An alternative approach uses the NOMS framework developed by Memorial Sloan-Kettering, which includes four parameters of disease (neurologic, oncologic,

mechanical and systemic) to select patients for appropriate treatment when presenting with spinal metastases, as shown in Figure 2 [11].

Contraindications include spinal cord or bone compression, for which surgical decompression would be more appropriate, and instability of the spine when surgical fixation should be considered. The effect of previous radiotherapy will also have to be taken into account with regard to spinal cord tolerance [12,13]. In general, lesions >5 cm will not be suitable for SBRT and multiple levels of involvement are also a relative contraindication. One study of SBRT in renal cell carcinoma spinal metastases found that multilevel involvement with more than five levels was an independent risk factor for radiographic failure and progression of pain [12,14].

Technique

In most circumstances the most stable set-up will be achieved by the patient in the supine position. Rigid fixation of the spine is not feasible. Patient immobilisation may be achieved using vacuum bags or simpler devices to prevent rotational movement. Planning computed tomography acquiring no greater than 3 mm (typically 1–2 mm) image slices should be obtained and a planning magnetic resonance imaging scan with at least T1 and T2 image sequences through the target volume is desirable. Image registration will then allow accurate localisation of the gross tumour volume and the clinical target volume (CTV) as well as important organs at risk, such as the spinal cord. The international spine radiosurgery consortium have published guidelines for target volume definition in spinal SBRT [15]. These propose that the gross tumour volume should include all gross tumour, including epidural and paraspinal elements. The CTV should include the entire vertebral body, particularly including all areas of abnormal bone marrow signal, but should avoid encircling the cord unless there is invasion of the pedicles or extensive epidural tumour. It is recommended that the CTV to planning target volume expansion is ≤ 3 mm and this should be constrained around the spinal cord.

The most critical organs at risk for the spine are the spinal cord and cauda equina. Using high-dose gradients, SBRT has additional risks over conventional fixed-field treatments in that deviations in the target position of 1–2 mm may substantially increase the spinal cord dose and thus the risk of radiation-induced myelopathy. Definition of a planning organ at risk volume around the cord is therefore important to allow for this using an expansion of 1–2 mm. This is then assigned a planning organ at risk volume dose constraint for optimisation [3]. A set of class solutions have been developed for spinal SBRT, which includes a pCTV metric for plan evaluation while obtaining improved treatment plans with higher planning efficiency [16]. A typical dose volume histogram with tabulated doses achieved is shown in Figure 3 and an isodose distribution can be seen in Figure 4.

Safe delivery of spine SBRT is dependent on verifying the target position while the patient is immobilised before

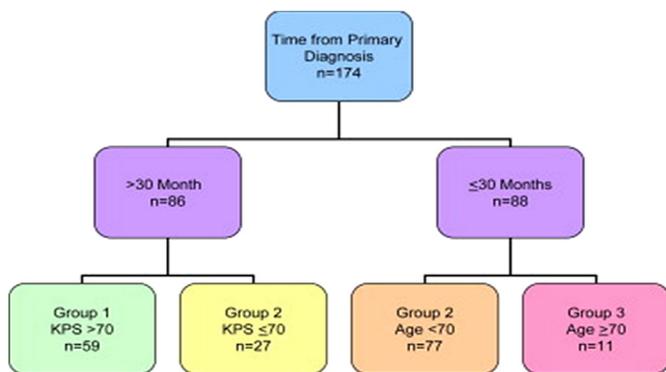


Fig 1. Recursive Partitioning analysis tree for overall survival for patients treated with stereotactic body radiotherapy to the spine. Reproduced with permission from [10].

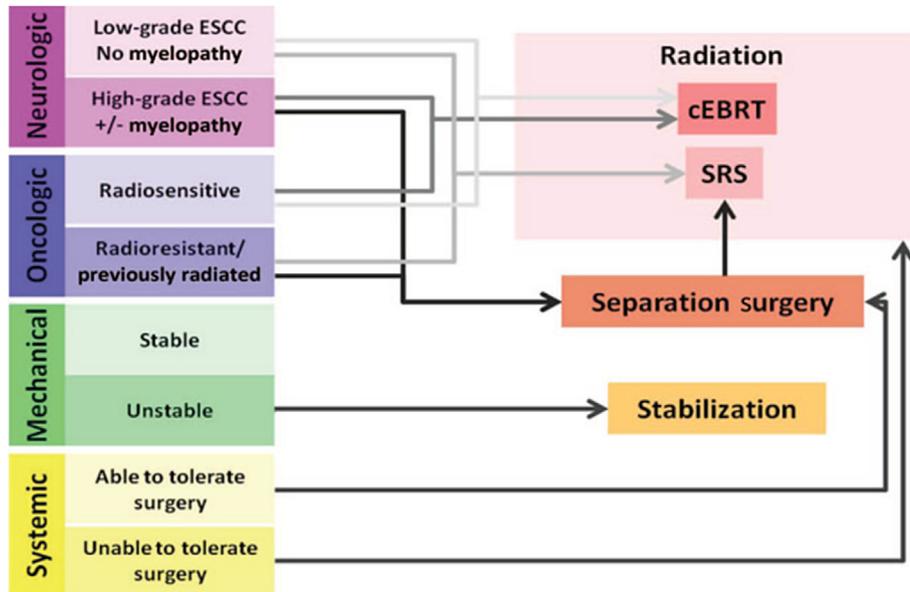


Fig 2. Schematic depiction of the neurologic, oncological, mechanical and systemic (NOMS) decision framework. cEBRT, conventional external beam radiation; SRS, stereotactic radiosurgery. Reproduced with permission from [11].

treatment delivery and again ensuring the target is in the same position to that at the time of treatment planning. To facilitate this, an on-board image guidance system is important, with online corrections being made [1,3,7]. This will also allow the detection of intrafractional motion. Corrections can be achieved by a robotic couch with up to six degrees of freedom movement capability, or by moving the linac itself via a robotic arm, as used with CyberKnife.

Dose and Fractionation for Spinal Stereotactic Body Radiotherapy

There is no consensus on the radiation dose for spinal SBRT. This will depend upon the indication (primary or metastatic), setting (radical or palliative) and the effect of any previous radiation exposure. The American College of Radiology have identified three main prescription groups:

single doses of 12–18 Gy, three-fraction schedules of 21–27 Gy and five-fraction schedules of 20–30 Gy [17]. It is not clear where the optimal approach lies and dose schedules outside these ranges are also found in the literature. One retrospective review from two centres examined the clinical outcomes of 348 lesions in 228 patients. A single dose was delivered to 195 lesions (mean 16.3 Gy) and 153 lesions were treated using a fractionated regimen (mean 20.6 Gy/three fractions, 23.8 Gy/four fractions, 24.5 Gy/five fractions). Pain control was significantly improved in the single dose group for all measured time points up to 1 year after treatment (100% versus 88%). Toxicity rates and neurological deficit improvement were not statistically different. Local tumour control was significantly better in the fractionated regimen group up to 2 years after treatment (96% versus 70%). Similarly, the need for retreatment was significantly lower in the fractionated regimen group

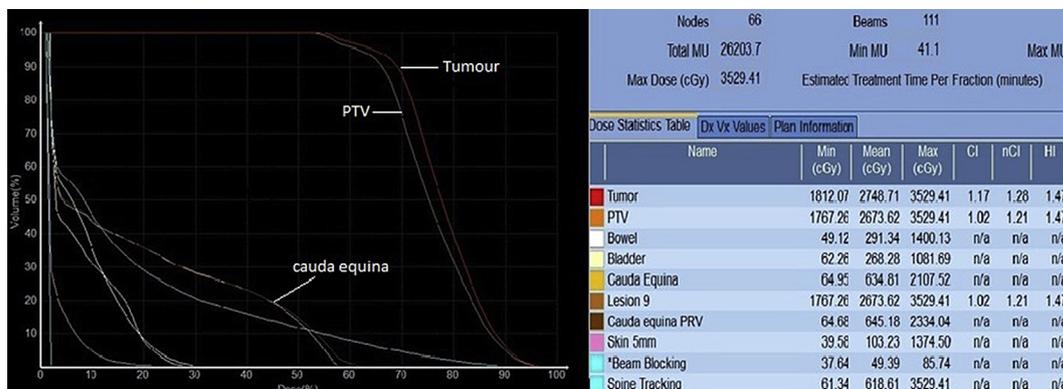


Fig 3. Dose volume histogram and associated achieved doses for a spinal stereotactic body radiotherapy plan to the lumbar spine.

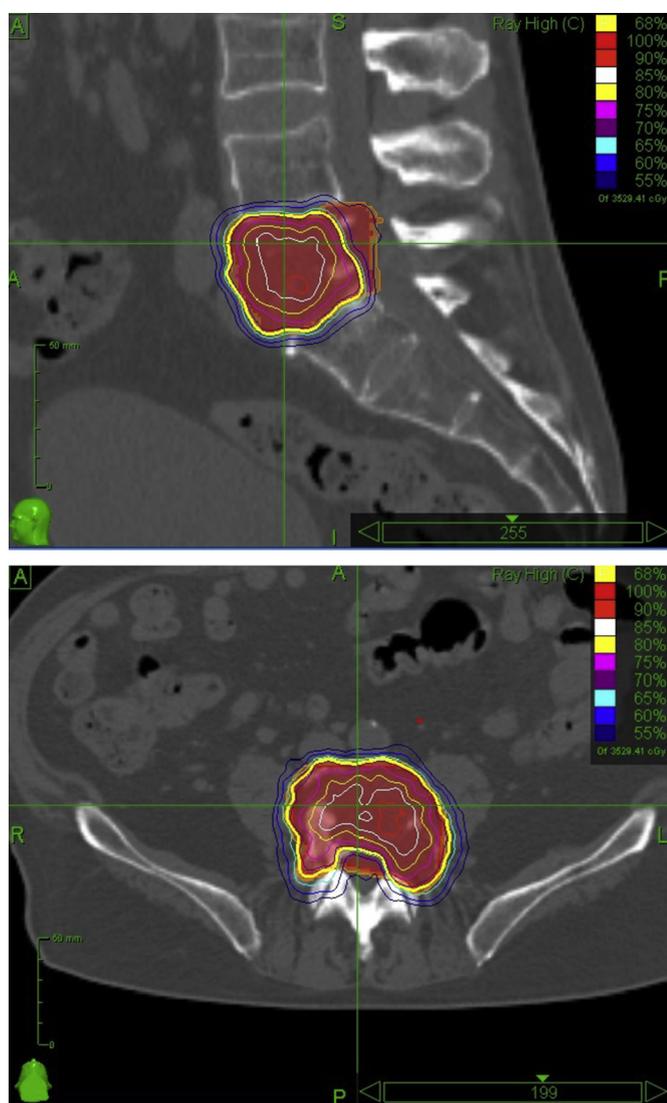


Fig 4. Isodose distribution for localised stereotactic body radiotherapy to lumbar vertebra.

(1% versus 13%) and 1 year overall survival was significantly greater in the fractionated treatment group (63% versus 46%) [18]. However, the results of a retrospective non-randomised analysis such as this should be regarded with caution.

Re-irradiation

SBRT is an attractive treatment option when re-irradiation is required [19]. One phase I/II trial where 56% of 63 patients had received previous radiotherapy reported that no patients developed grade 3 or greater neurological toxicity. The 1 year actuarial progression-free rate was 84%, with a median follow-up of 21 months. Treatment failure was found to be either with recurrence in the bone adjacent to the site of previous treatment or within the epidural space adjacent to the spinal cord [20]. A further study of 37 spinal metastases re-irradiated with SBRT using a median prescribed dose of 24 Gy in three fractions reported a 1 year

progression-free probability of 96% after a median follow-up of 7 months. There was no radiation-induced myelopathy or radiculopathy seen [8]. Another study re-treated 42 patients with 51 spinal metastases with 10–30 Gy in one to five fractions and reported 6 and 12 month actuarial local control rates of 87 and 73%, respectively. One case of radiation myelopathy was seen with a median follow-up of 7 months; the median spinal cord maximum single-session equivalent dose was 12.1 Gy [3,21]. Data from these and other studies show that it is possible to re-irradiate spinal metastases in well-selected patients if treatment is carefully planned and delivered.

Results of Spinal Stereotactic Body Radiotherapy

Primary Spinal Tumours

Radiotherapy for primary spinal tumours is limited by spinal cord tolerance and in children issues related to bone growth must be considered. Stereotactic radiotherapy therefore has significant advantages over conventional fixed beam treatment in enabling ablative doses to be delivered with sparing of the contents of the spinal canal. The tumours in question will be mainly chordomas or sarcomas and therefore the ability to reach high doses is important in achieving durable local control, both in the postoperative setting and in the less common instance of primary or salvage radiotherapy alone [12,22,23]. No consensus on dose fractionation emerges from the current literature, with a range of single doses and hypofractionated schedules in use. Biological equivalent doses are quoted typically around 60 Gy EQD2, but little detail on the parameters used for the calculation is provided; a simple linear quadratic equation in this setting may well be misleading. There are currently no comparative data to evaluate the advantages of this approach, but single series report comparable if not better local control rates with SBRT, with local control of 60–70% in chordomas and a progression-free survival of 56 months [12,24,25].

There are few data published on the use of SBRT for other spinal primary tumours; one small series of spinal sarcomas including both primary and metastatic tumours reported a local control rate of 78.3% at 1 year [22], whereas another that included both primary and postoperative patients reported local control in 73.4% at a mean of 33 months [23].

Spinal Metastases

Current evidence includes three prospective trials and a number of case series. The first prospective trial is a phase I/II trial of 61 patients (63 non-cervical spine tumours) receiving single-fraction SBRT for previously unirradiated spinal metastases. The actuarial 18 month imaging local control rate was 88%, the actuarial 18 month overall survival rate for all patients was 64% and the median survival for all patients was 30 months [26].

The second is the phase II component of the RTOG 0631, which assessed the feasibility and safety of spine SBRT for localised spine metastases (44 patients) in a cooperative group setting. Patients with one to three spine metastases received a 16 Gy single-fraction SBRT. It showed the feasibility of SBRT to treat spinal metastases with high standards of quality control, in a cooperative group setting. The phase III RTOG 0631 will proceed to compare pain relief and quality of life between SBRT and external beam radiotherapy [27].

Finally, a prospective, phase II study of 25 patients receiving a single fraction SBRT for spinal metastases reported local control in 95%, with a 1 year progression-free survival of only 5%. It was concluded that SBRT was an option for patients with symptomatic spine metastases in previously irradiated areas. However, in those patients without previous irradiation, the biology of metastatic cancer limits the ability of spine SBRT to improve outcome [28]. Clearly careful case selection is imperative in this group.

Table 1 shows SBRT reported series of spinal metastases from 2005 to 2014, which include more than 50 treated sites [14,18,20,29–37]. An analysis that pooled case series [38] to result in a total of 1388 patients with 1775 lesions who underwent spinal SBRT has been reported. The weighted (based on number of patients in each series) mean value of the median follow-up times for patients on all the series was just over 15 months. Where pain relief was examined, 79% of patients ($n = 902$) experienced some reduction in discomfort associated with their spinal lesions. The weighted overall local control rate defined as lack of progression of the gross disease on surveillance imaging was 90%. There was an extremely low crude incidence of

myelopathy at less than 0.5%. This pooled analysis further shows the safety and efficacy of spinal SBRT. Recently, a multi-institutional analysis (which included eight centres and 387 patients) has been published looking at the safety and efficacy of SBRT as a primary treatment for vertebral metastases. The median overall survival was 19.5 months and local tumour control at 2 years was 83.9% [39].

Stereotactic Body Radiotherapy in Spinal Cord Compression

SBRT has been used in spinal cord compression, but spinal cord compression remains an oncological emergency requiring urgent decompression to avoid further neurological damage and reverse neurological deficits. SBRT delivery requires lengthy and meticulous preparation beginning with complex patient immobilisation, treatment planning, quality assurance, treatment set-up and ultimately treatment delivery. This is a time-consuming process, which may result in a significant delay in treatment initiation, compromising functional outcome [3].

A study of 62 patients with a total of 85 lesions of metastatic epidural compression were treated with SBRT. The mean epidural tumour volume reduction was $65 \pm 14\%$ at 2 months after SBRT. The epidural tumour area at the level of the most severe spinal cord compression was $0.82 \pm 0.08 \text{ cm}^2$ before radiosurgery and $0.41 \pm 0.06 \text{ cm}^2$ after radiosurgery ($P < 0.001$). The thecal sac patency improved from $55 \pm 4\%$ to $76 \pm 3\%$ ($P < 0.001$). Neurological function improved in 81% [40]. In a smaller series, 24 patients with 31 lesions presented with spinal cord compression and received SBRT with a single median dose

Table 1

Published stereotactic body radiotherapy (SBRT) series treating spinal metastases, including more than 50 treated sites with outcome data

Reference	Number of sites + tumour sites	Retreat (%)	Dose	Local control (%)	Follow-up (median months)	Myelopathy (%)
[29]	72: various*	53%	21 Gy/1 fraction	96%	12	0
[20]	74: various	56%	30 Gy/5 fractions 27 Gy/3 fractions	84%	21	0
[30]	103: various	0%	24 Gy/1 fraction	90%	15	0
[31]	55: renal	58%	24 Gy/1 fraction 27–30 Gy/3–5 fractions	82%	13	0
[32]	70: various		18 Gy/1 fraction	76%	14.5	2
[33]	85: various	26%	24 Gy/3 fractions	88%	8.2	0
[14]	88: renal	21%	15 Gy/1 fraction	77%	5.4	0
[34]	185: various	29%	51 Gy/10 fractions	79% (retreatment) 90% (first treatment)	21.8 (mean)	0
[26]	63: various		16–24 Gy/1 fraction	88%	20	0
[18]	348: various	55% 57%	16.3 Gy/1 fraction 20.6–23.8 Gy/3–5 fractions	70% 96%	12 12	0 0
[35]	166: various	53%	27–30 Gy/3 fractions	72%	16	0
[36]	120: sarcoma	10%	24 Gy 28.5 Gy/3–6 fractions	90.8% 84.1%	12	0
[37]	71: renal	15%	24 Gy/2 fractions	83%	12	0

* Includes 14 primary spinal tumours.

of 16 Gy. The median follow-up was 11.2 months. Eighty-six per cent had complete pain relief and 71% of patients who presented with neurological deficits had improved or normalised neurological function [41].

The largest series of metastatic spinal cord compression reported on 186 patients treated after initial surgical decompression; in 91 of these they were deemed to have failed previous radiotherapy [42]. Local control was achieved in 83.6%. Various dose schedules were used, including: 24 Gy/one fraction; 24–30 Gy/three fractions; 18–36 Gy/five to six fractions. The hypofractionated three-fraction schedules were superior in multivariate analysis. No toxicity data were reported.

Toxicity of Spinal Stereotactic Body Radiotherapy

Acute reactions from spinal radiotherapy are well recognised and will include skin erythema, gastrointestinal symptoms from dorso-lumbar treatment and dysphagia with local mucositis from cervico-thoracic treatment. These are self-limiting and resolve with supportive symptomatic treatment. Although bone marrow will be ablated within the treated volume, this is not expected to affect overall function or peripheral blood counts. Pain flare is well recognised after irradiation to bone metastases and is usually self-limiting.

Late effects are of greater concern. The most critical structure is the spinal cord. There is an extensive literature on spinal cord tolerance with conventionally fractionated radiotherapy (1.8–2 Gy/fraction) [3]. However, this is based on homogeneous spinal cord dose exposure involving relatively long lengths of the spinal cord, unlike SBRT, where small sections may receive very high doses and in large doses per fraction. There is no consensus on partial volume tolerance of the spinal cord, as the spinal cord is typically regarded as a serial organ. In one study, the dosimetric data of five patients who developed radiation-induced myelopathy after SBRT were examined. The thecal sac was contoured as the spinal cord. Radiation myelopathy was seen with maximum point doses of 25.6 Gy in two fractions, 30.9 Gy in three fractions and 14.8, 13.1 and 10.6 Gy in one fraction. This suggests that 10 Gy in two fractions is safe; which equates to a normalised 2 Gy equivalent biological equivalent dose of 35 Gy using an α/β ratio of 2, well within conventional tolerance levels [43]. It has been estimated that 13 Gy in a single fraction or 20 Gy in three fractions is associated with a less than 1% risk of myelopathy in previously unirradiated patients [12,44]. In a case–control study that included five cases of myelopathy and 14 controls who were retreated with SBRT after conventional radiotherapy to the spine, a retreatment thecal sac point maximum dose of greater than 20–25 Gy as a 2 Gy equivalent dose (EQD2, α/β ratio of 2) was associated with myelopathy. No cases were seen below this threshold provided the total EQD2 dose from both treatments (at least 5 months apart) was less than 70 Gy and the normalised thecal point dose for retreatment was less than 50% of the

total. In this setting the point maximum equated to a volume of $1 \times 1 \times 1.25$ mm [45].

Although bone is usually relatively resistant to late radiation effects after high radiation doses, late damage and fracture are well recognised. The true incidence is unknown as many will be asymptomatic and only identified on imaging. In addition, the dose received from SBRT is inhomogeneous and it is not clear what the critical components of the vertebra are that predict for fracture and collapse. One multi-institutional analysis of 252 patients with 410 spinal segments treated with SBRT reported 57 fractures, of which 47% were new and 53% were progression of previous fractures. The median time to vertebral compression fracture progression was 2.46 months (range 0.03–43.01 months), with two thirds occurring within 4 months [46]. In another cohort receiving single-dose SBRT, the incidence was 39%, with a median time to fracture of 25 months [47]. Various predictive factors for fracture have been defined, including lytic lesions, spinal misalignment and vertebral compression fracture. It has also been reported that SBRT to vertebrae below T10 is associated with a 4.6-fold greater likelihood of fracture than treatment above this level [12,47].

Non-spinal Bone Metastases

Non-spinal bone metastases are a common feature of many solid tumours, resulting in significant morbidity, reduced function and impaired quality of life. Conventional external beam radiotherapy is recommended as the treatment of choice in this setting, with 90% experiencing partial relief and up to 54% having complete resolution of pain [48,49].

Several randomised prospective trials show no difference in effectiveness between single and multifraction treatment regimens [50–54]. A meta-analysis of 25 randomised trials compared single-fraction versus multifraction treatment schedules for painful bone metastases [55]. It concluded that there is no significant difference between single and multifraction schedules in terms of bone pain relief. There was, however, a significant increase in retreatment rates in patients who received a single fraction.

The role of SBRT against this background is unclear. Selected patients with oligometastatic disease or those requiring retreatment may benefit from the potential for improved local control. An example of a solitary pubic ramus metastases treated with SBRT is shown in Figure 5. SBRT may provide faster and more durable pain relief in comparison with conventional radiotherapy [56,57]. There are, however, disadvantages of SBRT in the setting of bone metastases. The immobilisation and treatment planning process is time consuming and may delay the initiation of treatment in a patient with severe bone pain. The treatment delivery times are often prolonged and some patients may not be able to tolerate this. Patients must be able to lie immobilised and still for an extended period and have a sufficiently good performance status. The delivery of ablative doses may result in severe skin or soft tissue reactions



Fig 5. Isodose distribution for stereotactic body radiotherapy to isolated pubic bone metastasis.

for bone lesions in close proximity to the skin and long-term compromise the integrity of the bone resulting in pathological fracture.

A review of 74 patients (85 lesions) with oligometastatic non-spine bone metastases of different histologies included 31% with prostate cancer and 65% lesions were in the pelvis. Local recurrence occurred in seven patients and the median time to failure was 2.8 months. Local control was 91.8% at 1 year. The median follow-up was 7.6 months. The median SBRT-specific overall survival was 9.3 months and progression-free survival was 9.7 months. Eighteen patients developed acute toxicity, including grade 1 and 2 fatigue and acute pain flare. Nine patients developed grade 1–2 late toxicities. Two patients developed asymptomatic pathological fractures [58].

Two studies have reported on the use of SBRT for sacral metastases [59,60]. The first reported retrospectively on their experience with three sacral lesions treated with 18 Gy/one fraction [59]. No long-term side-effects were reported; 2/3 patients had received previous conventional radiotherapy in the SBRT field. The second treated 18 patients with a mean dose of 15 Gy/one fraction and pain relief was achieved in all 13 symptomatic patients [60]. No toxicity was reported in the 6 month follow-up period.

Another study of 48 cases (32 patients) investigated the use of SBRT in bony oligometastases (including spine) from prostate cancer. Patients were treated with fraction doses of 6–15 Gy (total doses of 6–45 Gy). Prostate-specific antigen (PSA) before the treatment varied from 0.01 to 387 ng/ml (mean 28.67; median 3.12). PSA concentration decreased to 0.0–22.4 ng/ml (mean 5.8; median 4.4) during the first month of follow-up. There was a linear correlation between the total dose delivered, PSA concentration and pain relief. There was complete pain relief in 28 patients and partial relief in 16 patients [61].

At the Mount Vernon Cancer Centre, 22 patients have been treated with SBRT for bone and spinal metastases over

a 3.6 year period. The median follow-up was 12.3 months. Doses varied from 19.5 to 40 Gy/three to five fractions. Eight patients received SBRT in a previously irradiated field. Local control was 91%. Overall survival at 1 year was 94.7% and at 2 years was 63.3%. Progression-free survival at 1 year was 45.1% and at 2 years was 19.7%. One patient had only local progression, 13 had distant progression and one patient had both local and distant progression. The median time to progression was 7.6 months. There were no significant toxicities reported [62].

Conclusion

SBRT has been shown in prospective trials and numerous case series to be safe and effective in spinal and bone lesions, as well as primary bone tumours. Despite extensive experience, particularly in the USA, there are as yet no prospective comparative data from randomised trials, without which it is difficult to provide clear guidelines for its use alongside more conventional approaches. RTOG 0631, comparing image-guided radiosurgery or SBRT with external beam radiotherapy in patients with localised spine metastases, is currently in progress [27].

Health economic evaluation of this more complex treatment is also urgently required to define its place in the management of patients with spinal and other bone metastases. One comparison of the palliative efficacy and cost-effectiveness of external beam radiation therapy compared with SBRT as a primary treatment for spinal metastases found that patients treated with external beam radiotherapy had increased acute toxicities and there was a higher likelihood of them requiring further intervention at the treated sites. Although SBRT was more costly, there were comparable rates of pain control and late toxicity [63]. A review of the current SBRT clinical and health economic literature found SBRT to be a clinically effective treatment option from the patient's perspective. SBRT also provided a clinically effective treatment option for patients from the payer and provider's perspective and cost savings were shown [64].

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