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REVIEW

Stereotactic body radiotherapy for the treatment of spinal metastases

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Abstract
Introduction Spine stereotactic body radiation therapy (sSBRT) allows for the delivery of a high dose of radiation to spine metastases while respecting the dose limits of the adjacent spinal cord. In contrast with conventional radiation, the dose to spine metastases is limited by the spinal cord tolerance since the spinal cord is in the treatment field. sSBRT allows for reirradiation of spinal metastases, as well as higher doses to be delivered particularly for radioresistant metastases. It is also being used post laminectomy and decompressive surgery as primary treatment for malignant spinal cord compression instead of conventional external beam radiation therapy. Although experience and evidence are growing, variations in practice remain.
Purpose We review the technical considerations and clinical applications of sSBRT.

Keywords Spine metastasis · Stereotactic radiosurgery · Stereotactic body radiation therapy

Introduction

Stereotactic body radiation therapy (SBRT) is a novel radiation technique that delivers a high dose of radiation to the tumor with great precision, by taking advantage of recent advances in real-time tumor tracking and radiation dose delivery systems [1]. Metastasis to the spine occurs in up to 70 % of all cancer patients, and 10 to 20 % of cancer patients with bony spinal metastasis will develop symptomatic spinal cord compression [2]. Spinal metastases are commonly treated with a fractionated course of external beam radiation therapy

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(EBRT). However, if there is spinal cord compression or vertebral column instability, surgical decompression and spinal stabilization would precede EBRT. In some patients, surgical decompression is not possible due to short overall life expectancy, multiple levels of spinal metastasis, or preexisting medical conditions. In these patients, EBRT is the only available therapeutic option.

One of the main goals of palliative spinal radiotherapy is pain control, and conventional dose fractionated EBRT has a pain response rate of 60 % [3]. Overall, 20 % of patients previously treated with a conventional EBRT dose of 8 Gy in one fraction will require retreatment due to recurrence of pain. This is challenging because with conventional EBRT, the spinal cord within the treated field would have received a substantial dose of radiation, and a further palliative dose of radiotherapy is likely to exceed the spinal cord tolerance. This leads to retreatment with lower biologically effective doses of fractionated EBRT as the cumulative tolerance to the organ at risk (OAR), in this case the spinal cord, decides the dose-fractionation schedule as opposed to tumor control [3].

SBRT delivers a high dose of radiation to the tumor and its vasculature, which can overcome any inherent tumor radioresistance to conventionally fractionated EBRT. Image-guided radiation therapy (IGRT) and intensity modulation radiation therapy (IMRT) have allowed the treated volume in SBRT to minimize dose to the spinal cord. Superior patient immobilization techniques and extreme hypofractionation which is inherent in SBRT, thus making such immobilization practical, has allowed the use of tighter margins. Retreatment pain control rates with SBRT are reported to be 65–85 % [3]. The net result of spine SBRT (sSBRT) is the safe delivery of a very high biologically equivalent dose (BED) of radiation that is spinal cord sparing and may overcome any tumor radioresistance. Given the outcomes achieved with retreatment, it is now being used to treat patients up front, particular in patients with radioresistant histologies. The aim of this review is to provide an overview of the general principles and indications that guide sSBRT and also to discuss the local control rates with this novel radiation technique.

Technical considerations

Spine SBRT is a resource-intensive treatment modality for spinal tumors that utilizes the expertise of radiation oncologists, neurosurgeons, medical physicists, and radiation therapists in delivering precise high-dose radiation in a safe, convenient, and effective manner. Similar to radiosurgical techniques in the brain, sSBRT requires precision radiation delivery in the range of 1–2 mm [4]. To safely and effectively perform sSBRT, the following components are required: a body immobilization system, linear accelerator equipped with a multileaf collimator or circular collimator on robotic arms, a sophisticated treatment planning system with accurate delineation of target and organs at risk, and intrafraction image guidance.

Body immobilization

In sSBRT, the dose gradient is typically very steep outside the target volume in order to spare the spinal cord. Therefore, unlike extraspinal applications of SBRT, sSBRT requires a translational accuracy of <2 mm and a rotational accuracy of <2° [5, 6]. Although respiration has a minimal impact on the motion of spinal tumors, rigid fixation of the spine is not readily achievable. Similar to fixation used for Gamma Knife radiosurgery, Hamilton et al. have described an invasive spinal fixation technique, which is not practical for sSBRT especially if a multifraction treatment plan is developed [7]. Therefore, many centers have utilized a near-rigid immobilization system. At the Cleveland Clinic, we utilize the Elekta BodyFIX stereotactic body frame (Medical Intelligence, Schwabmünchen, Germany) which consists of a carbon fiber base plate, whole-body vacuum cushion, vacuum system, and plastic fixation sheet for thoracic and lumbar lesions [8] (Figs. 1 and 2). The BodyFIX immobilization system is also in use at MD Anderson Cancer Center (MDACC) as well the University of Toronto and multiple other institutions [4, 9]. Some institutions such as Memorial Sloan-Kettering Cancer Center (MSKCC) and the University of Heidelberg, Germany, have developed in-house systems for near-rigid immobilization. Hyde et al. recently evaluated their experience with BodyFIX immobilization system and cone beam computed tomography (CBCT) imaging scan to evaluate setup error and intrafraction motion [10]. They studied 42 consecutive patients with thoracic or lumbar spinal metastases and found that patient positioning errors were relatively small (90 % were within 1 mm

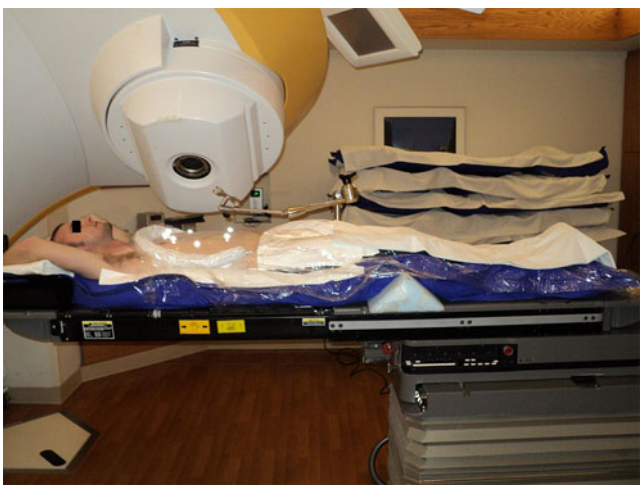

Fig. 1 The Elekta BodyFIX stereotactic body frame (Medical Intelligence, Schwabmünchen, Germany) which consists of a carbon fiber base plate, whole-body vacuum cushion, vacuum system, and plastic fixation sheet for thoracic and lumbar lesions

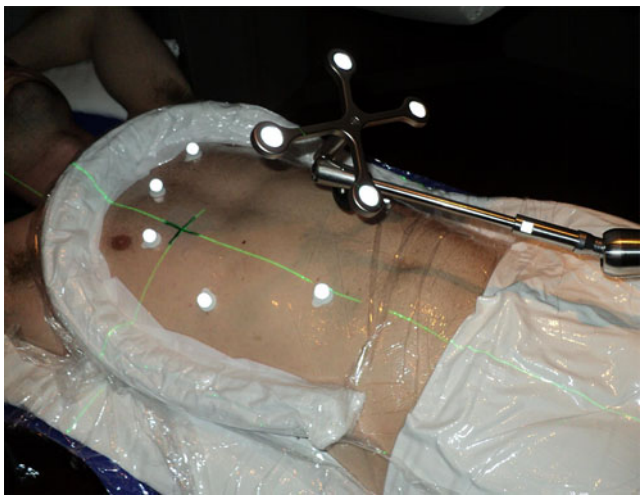

Fig. 2 Infrared fiducials placed on the BodyFIX to track patient motion and correct setup errors. For cervical spine SBRT, a conventional rigid five-point thermoplastic mask is used

and 97 % were within 1°). Larger errors in patient position occurred infrequently. They also analyzed the impact of a stricter threshold for patient repositioning. They found that there was a statistically significant difference in precision if a 1-mm threshold was used instead of a 1.5-mm threshold (intrafraction translational motion was 0.5±0.4 and 0.7±0.5, respectively). This suggested that positioning the patient as precisely as possible reduces subsequent out-of-tolerance motion and improves the overall precision of treatment delivery.

For cervical and upper thoracic spinal lesions above T4, we utilize a five-point thermoplastic head mask similar to several other institutions [9]. If a unit that allows for real-time intrafraction image guidance such as CyberKnife is used, then a regular vacuum cushion or alpha cradle is sufficient [11].

Imaging for treatment delivery

IGRT has allowed for the delivery of complicated SBRT treatment plans with a high degree of accuracy. The patient is imaged while he or she is immobilized on the treatment table, thereby providing the practitioner with the opportunity to match the pretreatment position of the tumor to that at the time of simulation and determining the positioning changes necessary prior to treatment delivery. The IGRT systems can be broken down into those based on stereoscopic x-ray and CT-based imaging systems. Systems such as CyberKnife and Novalis BrainLab (BrainLab AG and Varian Medical Systems) utilize stereoscopic x-ray systems for intrafraction imaging. Orthogonal x-rays are processed by software to generate indirect 3D information regarding the target position. The difference between CyberKnife and Novalis BrainLab lies in the fact that the linear accelerator is mounted on a robotic arm on the CyberKnife system, which can adjust automatically to small changes in patient movement whereas in Novalis BrainLab, the treatment halts until positional changes are manually performed. A kilovoltage-based CT image guidance system mounted onto a linear accelerator has been named CBCT. CBCT offers an important advantage over x-ray-based systems as CBCT imaging results in acquisition of high-quality volumetric imaging of not only the body structures but also soft tissues including the spinal cord and tumor. Although CBCT provides volumetric imaging, its main disadvantage is the time necessary to perform CBCT. The interested reader is referred to a recent review by Dahele et al. which discusses the clinical applications of imaging in sSBRT [12].

Treatment planning

Target volume delineation

The gross tumor volume (GTV) is defined as the radiographically visible tumor based on contrast-enhanced MRI. The clinical target volume (CTV) is defined as the margin applied to the GTV to account for potential microscopic disease in the vicinity of GTV. A margin around the CTV to account for daily patient setup errors is called the planning target volume (PTV). There is considerable variation between centers regarding the volume to which radiation dose is prescribed, and no consensus regarding a standard currently exists. In general, most centers conform to one of two methodologies for delineating the target volume. UCSF, Pittsburgh, and Stanford utilize CT imaging to contour the GTV without any additional margin added to account for microscopic disease similar to target delineation used in radiosurgery for brain metastases (i.e., CTV=GTV) [13–15]. The margins for PTV have ranged from 0 to 10 mm with adjustments for neural contours [4]. Practitioners at Henry Ford Hospital and MDACC utilize MRI to contour the GTV with additional CTV margins added based on anatomic routes of spread within the vertebral segment [16, 17]. A recent study analyzing the differences among five institutions regarding their practice of sSBRT demonstrated that the details of target volume definition are quite different [9]. Table 1 demonstrates the differences between centers and the definition we use at the Cleveland Clinic, and also shows the definition used by the Radiation Therapy Oncology Group (RTOG) phase II/III sSBRT trial (RTOG 0631). At the Cleveland Clinic, we define the target according to the current RTOG study which defines a CTV incorporating the tumor. This CTV is location based to incorporate areas of potential local spread. We do not add a PTV margin.

Spinal cord contouring and dose limits

The most critical OAR in sSBRT is the spinal cord as radiation myelopathy may result in paralysis. Therefore, the spinal cord is the strict dose-limiting structure.

Table 1 Differences between centers and the definition used by the Radiation Therapy Oncology Group (RTOG) phase II/III sSBRT trial (RTOG 0631)

Institution	Imaging modality	Treatment unit	Planning target volume definition
Henry Ford Hospital [16]	CT/MRI fusion	Novalis (BrainLab)	Entire involved spinal segment+gross epidural/paraspinal disease
University of Heidelberg, Germany [38]	CT/MRI fusion	6/15-MV linear accelerator (Siemens)	GTV+entire vertebral body
University of Florida [21]	CT/MRI fusion	Synergy-S (Elekta)	GTV+10-mm bone margin±2-mm extension beyond the bone cortex if GTV is close to the bone surface. No margins added to epidural disease GTV
RTOG 0631 [39]	CT/MRI fusion	Various	GTV±vertebral body±right and left pedicles (depending on GTV location)
Cleveland Clinic [23]	CT/MRI fusion	Novalis (BrainLab)	GTV±vertebral body±right and left pedicles (depending on GTV location)
MDACC [17]	CT	EXaCT Targeting System (Varian)	GTV+entire vertebral body+potential areas of spinal extension
MSKCC [40]	CT	EXaCT Targeting System (Varian)	GTV+10-mm expansion except at the cord
UPMC [14]	CT	CyberKnife	GTV
Stanford [15]	CT	CyberKnife	Target lesion+2-mm margin
UCSF [13]	CT	CyberKnife	GTV

Reirradiation using SBRT is challenging because of the paucity of data regarding the tolerance of the spinal cord. Other OARs in sSBRT to consider include the esophagus, kidneys, and bowel in select patients. The following discussion will focus on differences in spinal cord contouring and spinal cord dose limits between institutions.

Institutional practices regarding contouring of neural critical structures (NCS), which include the spinal cord and cauda equina, are varied among institutions (Table 2). Some examples of delineating the NCS include contouring the spinal cord (±margins for setup errors), the spinal canal, and the thecal sac. At MDACC, the intramedullary spinal cord (and thecal sac for cauda equina) is contoured with no applied margin based on CT imaging post intrathecal administration of iohexol [17]. However, they do add a 2-mm expansion to account for setup and contouring uncertainty. At UCSF, they contour the spinal canal or thecal sac based on CT imaging with 20-mm cranial and caudal margins to account for positional uncertainties [13]. This serves to provide some margins to the actual spinal cord given that radiation delivery in CyberKnife is not coplanar. Intrafraction patient and organ motion may also affect the estimated dose to NCS. This is illustrated by Cai's study which utilized dynamic MRI to show that intrafraction patient movement in the thoracic spinal cord was limited to <0.5 mm [18]. Furthermore, Ma et al. showed that intrafraction motion was greatest in the cervical spinal cord compared to the thoracolumbar cord and that frequent intrafraction imaging was necessary to ensure accurate delivery of the radiation dose [11]. It is also important to note that when MRI and CT fusion are utilized for contouring NCS, it is important to account for fusion uncertainties when determining the margins that need to be added. Guckenberger et al. studied the practices of five institutions and report that four of the institutions utilized MRI for contouring the spinal cord while one institution utilized CT to contour the spinal canal [9]. All five institutions contoured the NCS one vertebral body above and below the PTV and 1- to 2-mm safety margins are applied.

Similar to the differences in NCS contouring, institutional differences in spinal cord and cauda equina dose limits used for treatment planning are extensive and summarized in Table 2. At the Cleveland Clinic, we contour the spinal cord based on MRI–CT fusion and add 6-mm cranial and caudal margins to the spinal cord to account for dose fall off superior and inferior to the region treated. For the cauda equina, we contour the thecal sac with 6-mm cranial and caudal margins as well. We limit the spinal cord to a maximum dose of <14 Gy and limit 10 % of the cord to 10 Gy or more. For the cauda equina, we limit the maximum dose to <16 Gy and limit 10 % of the cauda to 12 Gy or more (Figs. 3, 4, and 5).

Treatment dose and fractionation

Similar to the differences in the definition of a target volume between institutions, there is no consensus regarding radiation dose or fractionation scheme. Currently, most centers use either a single-fraction approach or a hypofractionated regimen. Single-fraction doses tend to range from 12 to 24 Gy. Hypofractionated regimens consist mainly of 25 Gy in five fractions, 30 Gy in five fractions, 24 Gy in three fractions, 24 Gy in two fractions, and 27 Gy in three fractions. Table 3 demonstrates selected fractionation schemes reported in the literature and their reported outcomes. At the Cleveland Clinic, we have

Table 2 Institutional practices regarding contouring of neural critical structures

Institution	Imaging modality	NCS contour definition	Threshold criteria for NCS
Henry Ford Hospital [16]	CT/MRI fusion	Spinal cord: spinal cord+6-mm cranial and caudal extensions	Spinal cord: 10 Gy or more to 10 % or less of PTV; cauda equina: 12 Gy or more to 10 % or less of PTV
University of Heidelberg, Germany [38]	CT/MRI fusion	Spinal cord: spinal cord+2–3 safety margin	Reirradiation: <20 Gy/10 fx/median % of cord >30 % prescribed dose: 23–40.5 %
University of Florida [21]	CT/MRI fusion	Spinal cord or cauda equina with margin of 1 spinal level above and below	No history of RT: 12 Gy to 1 cc; history of prior RT: 5 Gy to 5 cc
RTOG [39]	CT/MRI fusion	Spinal cord: spinal cord+6-mm cranial and caudal extensions	Spinal cord: <10 Gy to 10 % PTV and limit 0.35 cc to <10 Gy and limit 0.03 cc to <14 Gy; cauda equina: limit <0.03 cc to 16 Gy and limit <5 cc to 14 Gy
CCF	CT/MRI fusion	Spinal cord: spinal cord+6-mm cranial and caudal extensions	Spinal cord: 10 Gy or more to 10 % or less of PTV and max dose <14 Gy; cauda equina: 12 Gy or more to 10 % or less and max dose <16 Gy
MDACC [41]	CT (with intrathecal iohexol)	Spinal cord: spinal cord; cauda equina: thecal sac; no applied margin	Max dose=10 Gy
MSKCC [27]	MRI or CT myelogram	Spinal cord: spinal cord; cauda equina: thecal sac	Spinal cord max dose=14 Gy; cauda equina max dose=16 Gy
UPMC [9]	MRI	Spinal cord: spinal cord; cauda equina: thecal sac; margin of 1 spinal level above and below	Spinal cord: max dose=11 Gy (1 fx) or 18 Gy (3 fx); cauda equina: 12 Gy (1 fx) or 18 Gy (3 fx)
Stanford [15]	CT	Spinal cord: spinal cord	Max dose=10 Gy in single fraction
UCSF [13]	CT	Spinal cord: thecal sac; cauda equina: thecal sac; 20-mm margins	Not published

escalated our standard single-fraction dose since the inception of our program from 12 to 18 Gy currently. Given that BED calculations may be inaccurate in the setting of SBRT, comparing different regimens in a scientific manner has been difficult [19]. As a result, accurate mathematical models that are applicable to SBRT are needed in order to compare different fractionation schemes and develop a consensus regarding the optimal treatment strategy for spinal tumors and metastases.

Clinical applications

Indications for spine SBRT

Spine SBRT is typically performed in a single or limited number of fractions and offers the potential for more durable pain control as well as long-term local tumor control. Patients with a long life expectancy, high Karnofsky Performance Score (KPS), resistant histology, limited spinal metastases, and oligometastatic disease are generally considered good candidates for spine SBRT. The patient must also be able to tolerate the treatment, and if they have received prior CRT, a total cord dose of <45 Gy from prior CRT is thought to be ideal. Given the accuracy of most SBRT delivery systems, a separation of at least 3–5 mm between tumor and cord is desirable [4, 6, 20].

Very short life expectancy, low KPS and significant cord compression, mechanical instability of the spine, history of a connective tissue disorder, and prior radiotherapy within the last 3 months are relative contraindications for spine SBRT. Some centers exclude patients that have radiosensitive histologies [9], but at our center, we have offered spine SBRT to select patients with radiosensitive histologies, typically with oligometastatic disease.

Local control and predictors of local control and overall survival

The majority of published studies of spine SBRT are retrospective reviews. Very limited numbers of prospective trials

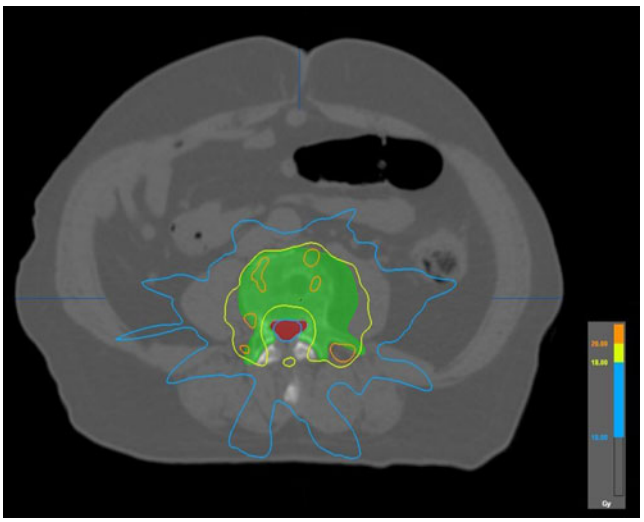

Fig. 3 Vertebral metastasis (L4) from RCC treated with SBRT. The prescription dose to the PTV (*green*) is 18 Gy (*yellow* IDL). The 10 Gy IDL in *blue* is seen sparing the thecal sac. A 14-field IMRT/IGRT was used to deliver a total dose of 18 Gy to the PTV

have been performed. Several articles provide an in-depth review of the spine SBRT literature [3, 4, 6]; here, we provide a summary of select studies.

Chang et al. reported the results of their phase I/II study which included 63 patients with 74 spinal metastases treated with SBRT to a dose of either 30 Gy in five fractions or 27 Gy in three fractions. Seventeen patients developed tumor progression and 37 died. The 1-year actuarial radiographic progression-free survival was 84 % with a median follow-up of 21.3 months [17]. Amdur et al. reported the results of their phase II trial which included 21 patients with 25 spinal metastases who were treated with SBRT to a dose of 15 Gy in one fraction. Local control rate was 95 % with 43 % of patients reporting improvement in pain. One-year overall progression-free survival was 5 % secondary to most patients developing progressive systemic disease [21]. Multiple retrospective studies of SBRT for spinal metastases have demonstrated local control rates ranging from 80 to 100 %. However, important differences exist in the criteria for local control; some studies use pain relief, some use radiographic control, some use clinical control, while others use combined metrics. Although varied endpoints make comparisons difficult, both retrospective and prospective studies have shown spine SBRT to be efficacious at controlling local tumor growth as well as providing pain relief (Table 3).

Several studies have shown that typical patient and tumor factors such as sex, age, KPS, systemic burden of disease, target volume, and various tumor dosimetric data have failed to predict local control. Sahgal et al. suggest that distance separating target volume from spinal cord may be predictive of local control [13]. Choi et al. further suggest that time interval greater than 12 months for retreatment is predictive of superior local control [22]. Chao et al. recently performed a recursive partitioning analysis (RPA) for patients undergoing spinal SBRT [23]. RPA was performed to identify associations between overall survival and a variety of variables including histology, gender, age, KPS, control of primary disease, extraosseous metastases, time from primary diagnosis, SBRT dose (≤14 vs. >14 Gy), extent of spine disease, up front or salvage SBRT, presence of paraspinal extension, and previous surgical intervention. He found that overall survival was predominantly associated with global patient and diseases characteristics. Patients with a KPS >70 and time from primary diagnosis (TPD) >30 months (class 1) had the longest median overall survival of 21.1 months (n=59). Class 2 patients were those that had a KPS ≤70 and TPD >30 months or age <70 years and TPD ≤30 months, and they had a median overall survival of 8.7 months (n=104). Class 3 patients had the lowest median overall survival (2.4 months; n=11) and were ≥70 years old and had TPD ≤30 months. Interestingly, this classification also helps identify those patients that have a short life expectancy and thus are better candidates for conventional radiotherapy [9, 20] (Table 4).

Currently, the first phase III trial, RTOG 0631, tests whether SBRT (single dose of 16 to 18 Gy) improves pain control as compared to conventional external beam radiotherapy (single dose of 8 Gy) and is accruing patients. However, results from this study are not expected to be available in the near future.

Impact of dose on local control

A review of the literature does not reveal a consistent sSBRT dose-fractionation scheme for the treatment of spinal metastases (Table 3); some centers prefer a multifraction

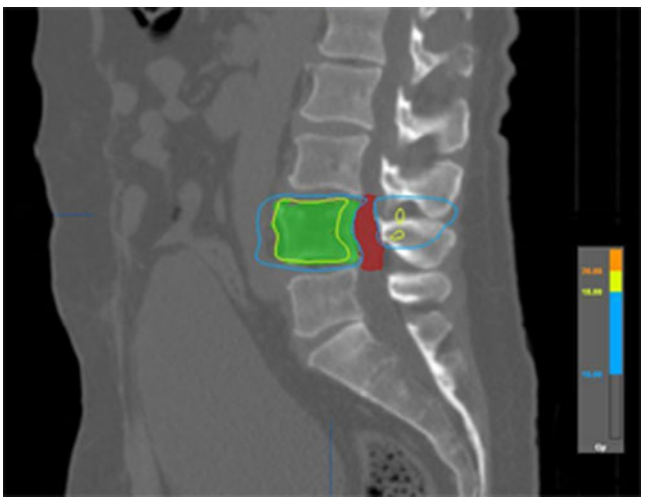

Fig. 4 Coronal view showing PTV in *green* (L4 vertebral body) and thecal sac in *red*. Again, the 10 Gy IDL (in blue) is seen sparing the OAR. A 14-field IMRT/IGRT was used to deliver a total dose of 18 Gy (IDL in yellow-green) to the PTV

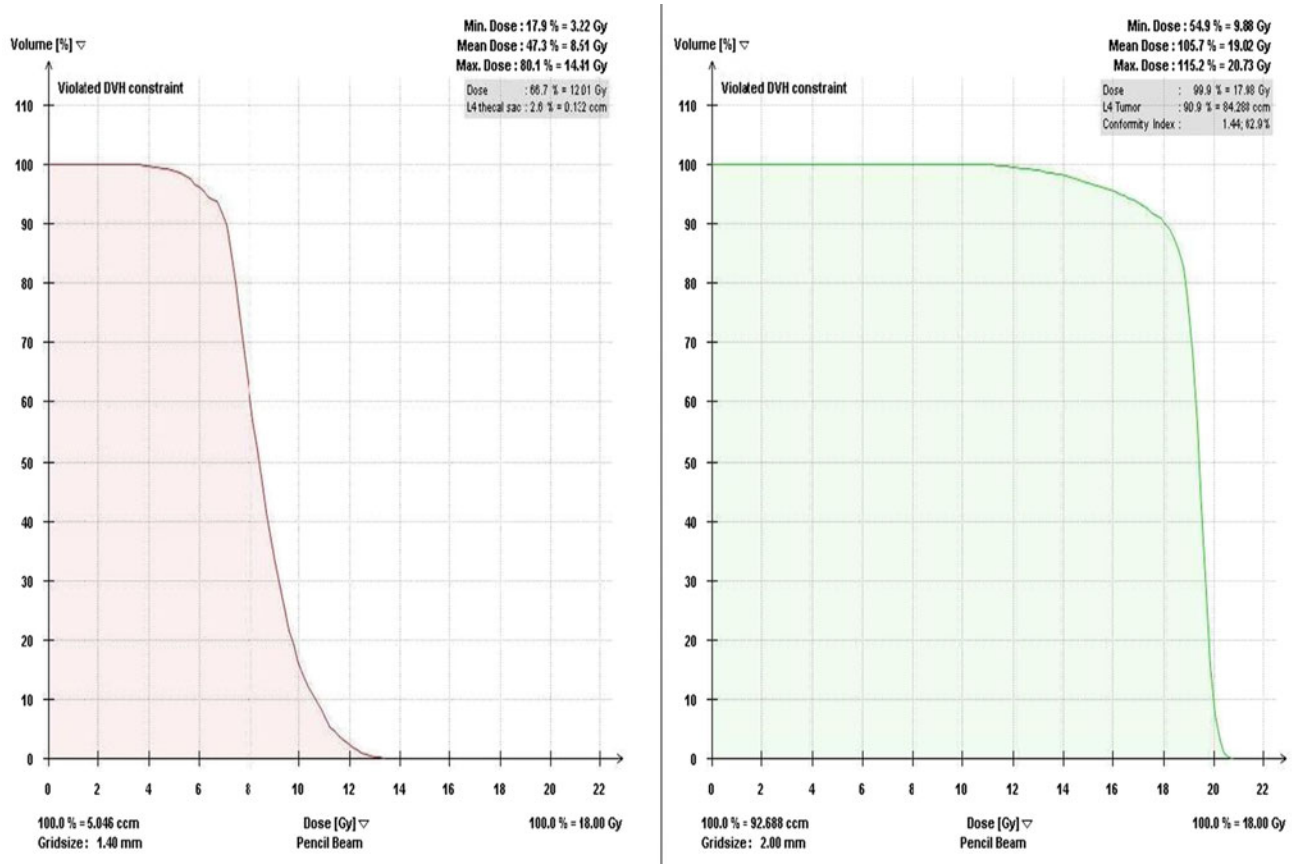

Fig. 5 *Pink* dose–volume histogram (DVH) showing the OAR dose parameters and the *green* DVH showing the same for the PTV. The maximum point dose delivered to the thecal sac using a 14-field IMRT/IGRT is 14.41 Gy (dose constraint, 16 Gy). The mean dose to the PTV is 19.02 Gy, and the prescription dose is 18 Gy

dosing regimen whereas other centers prefer a single-fraction regimen. Several studies have shown that higher SBRT doses lead to better local control irrespective of tumor histology [19]. Yamada and colleagues at MSKCC examined 93 consecutive patients with 103 spinal metastases treated with sSBRT to doses of 18–24 Gy (median, 24 Gy). They found that while tumor histology was not a statistically significant predictor of local control, a higher radiation dose was associated with improved local control (p=0.03) [24]. In a separate analysis, the MSKCC group studied whether local control was dependent on dose insufficiency. They included 91 consecutively treated lesions in 79 patients and studied the correlation between D(min), D(98 %), and D(95 %) of the GTV and local failure. They found that the dosimetric distributions of treatments that resulted in local failure were statistically different from the corresponding distributions of the entire patient population included in the study. Furthermore, they found that no local failures resulted when D(min) was >15 Gy [25]. Garg et al. studied 59 patients with 63 spinal tumors and found that of the tumors that progressed post-sSBRT, 81 % had an epidural component with 5 mm of the spinal cord and many of them eventually developed spinal cord compression [26]. This suggests that dose insufficiency in the epidural space (due to sparing of the spinal cord to prevent radiation myelopathy) leads to local progression. Damast et al. studied patients who were treated with sSBRT after in-field recurrence using a dose of either 4 Gy×5 fractions (n=42) or 6 Gy×5 fractions (n=55). They found that the group treated with the higher dose had a lower rate of local failure than the lower-dose group (26 vs. 45 %, p=0.04, respectively) [27]. Important to note, however, is that the lower-dose group in Damast's study was treated with a dose scheme commonly used in conventional radiotherapy. Choi et al. reviewed their experience with sSBRT in the retreatment setting after in-field recurrence. They reviewed 42 patients with 51 lesions who were treated at a median dose of 20 Gy (range, 10–30) in one to five fractions (median, 2). To compare differing dosing schemes, they used the linear quadratic model (α/β=3 for the spinal cord and α/β=10 for the tumor) to calculate the maximum single-session equivalent dose (SSED). Their analysis showed that tumor recurrence within 12 months of initial radiotherapy and SSED <15 Gy_{10} were significant predictors of local failure [22].

Table 3 Selected fractionation schemes reported in the literature and their reported outcomes

Study	Type of study	No. of pts/no. of tumors	Indication	Prescription dose	Media follow-up	Outcomes
Chang et al. [17]	Phase I/II	63/74	Mixed	30 Gy/5 fx or 27 Gy/3 fx	21.3 months	1 year PFS, 84 %
Amdur et al. [21]	Phase I/II	21/25	Mixed	24 Gy/3fx or 25–30 Gy/5 fx (if PTV touched cord)	8 months	LC=95 %, pain relief=43 %
Gerszten et al. [14]	Retrospective	393/500	Mixed	20 Gy/1 fx (range, 12.5–25 Gy)	21 months	LC=88 %; pain relief=86 %; neurological improvement=85 %
Gibbs et al. [15]	Retrospective	74/102	Mixed	14–25 Gy/1–5 fx	9 months	Pain relief=84 %
Yamada et al. [24]	Retrospective	93/103	Mixed	24 Gy/1 fx (range, 18–24)	15.7 months	Actuarial LC=90 %;
Mahadevan et al. [42]	Retrospective	60/81	Reirradiated	24 Gy/3fx or 25–30 Gy/5 fx (if PTV touched cord)	12 months	R-LC 93 %, 65 % pain control
Damast et al. [27]	Retrospective	97/97	Reirradiated	20 or 30 Gy/5 fx	12.1 months	LC, 20 Gy=55 %; 30 Gy=74 %
Ryu et al. [43]	Retrospective	62/85	Spinal cord compression	24 Gy/1 fx (range, 12–20)	10.3 months	Tumor response rate=80 %; 65 % reduction in tumor volume at 2 months; 63 % of those with neurologic deficits showed improvement

Some other studies have failed to provide significant evidence that a dose response with sSBRT exists. Colleagues at MDACC observed that the local control did not differ between those patients that were treated with 30 Gy in five fractions vs. those patients treated with 27 Gy in three fractions. In one of the first papers showing that sSBRT is safe and effective in patients with prior history of radiation, Sahgal et al. studied 39 consecutive patients with 60 metastases. The median dose prescribed was 24 Gy in three fractions prescribed to the 67 and 60 % isodose for the unirradiated and reirradiated patients, respectively. There was no significant difference in progression-free survival between reirradiated patients vs. all other patients (p=0.31) [13].

No consensus exists regarding which dosing scheme is superior: single fraction or multifraction. Single-fraction SBRT is ideal for small target volumes. However, because of the large dose spill associated with large target volumes, the use of fractionated sSBRT may be considered to avoid excessive dose to the spinal cord by improving the therapeutic ratio. Furthermore, fractionated SBRT offers traditional radiobiological advantages: reoxygenation, reassortment, and repair [19]. However, Kim et al. recently showed in a rat model that fractionation of SBRT leads to decreased tumor kill efficiency [28]. Furthermore, Qutob et al. showed in an in vitro study that cells that received prior fractionated radiation had increased radioresistance in comparison to cells that were radiation-naive independent of intrinsic radiosensitivity of the cells [29]. These studies show that although fractionated radiotherapy offers some advantages in the treatment of large tumors, single-fraction SBRT is likely more effective at achieving superior local control than fractionated SBRT. However, these are preclinical data, and thus far, clinical data showing superiority of single-fraction SBRT to multifraction SBRT do not exist. Further work needs to be done to determine which fractionation scheme is optimal for treating spinal metastases using SBRT.

Patterns of failure

In contrast with conventional radiotherapy, sSBRT is highly focused to the target, and most centers do not add margins to the PTV. The epidural space has been identified as an area at an elevated risk for failure. Multiple series have identified that the closer the proximity of epidural disease to the spinal cord, the higher the risk for failure in the epidural space [13, 22, 26]. It is thought that this could be related to relative underdosing of the target volume in order to spare the spinal cord, due to

Table 4 Recursive partitioning analysis for patients undergoing spinal SBRT [23]

RPA class	Criteria	Overall survival
I	TPD >30 months and KPS >70	21 months
II	TPD >30 months and KPS ≤70 TPD ≤30 months and age <70 y	8.7 months
II	TPD ≤30 months and age ≥70 y	2.4 months

microscopic epidural disease that does not receive the full radiation dose due to lack of margins in the epidural space, or inevitably due to aggressive tumor biology [3].

The risk of failure in the adjacent vertebral body is generally thought to be low [30]. Recently, Koyfman et al. showed that in their experience, failure in the adjacent vertebral body was 12.5 % and was associated with the presence of paraspinal disease and dose <16 Gy [31]. The results of this study suggest that perhaps microscopic disease in the paraspinal area led to failure in the adjacent vertebral body. It is also conceivable that microscopic disease in the epidural space may also be partially responsible for epidural failure. For a more detailed discussion of patterns of failure, we refer the reader to recent a critical review by Sahgal et al. [30].

Toxicities

The most common acute toxicities from sSBRT are grade 1–2 fatigue (up to 40 %) and gastrointestinal effects (up to 10–20 %) [3]. These side effects usually do not result in long-term consequences for patients. However, the most feared toxicity of sSBRT is radiation myelopathy, which is rarely reported with conventional radiotherapy. Development of radiation myelopathy rarely occurs within 6 months of treatment and almost always presents within 3 years of treatment [32]. The incidence of radiation myelopathy from sSBRT has been estimated to be <1 % [33]. Recently, Sahgal et al. performed a multi-institutional study of five cases of radiation myelopathy who had not received prior radiotherapy for spinal metastases and compared it to 19 patients with no radiation myelopathy post-sSBRT [34]. Out of the five patients that developed myelopathy, three patients received a maximum point dose of 10.6, 13.1, and 14.8 Gy in one fraction to the thecal sac. The other two patients received 25.6 Gy in two fractions and 30.9 Gy in three fractions to the thecal sac. His analysis showed that a thecal sac maximum point dose of up to 10 Gy in one fraction is safe. Sahgal et al. also modeled his data using BED and determined that 30–35 2 Gy equivalent BED for up to five fractions was a safe dose range. It is important to note that Sahgal et al. studied the dose to the entire thecal sac rather than the true spinal cord. Radiation myelopathy has also been observed in patients who underwent sSBRT after initial conventional radiotherapy (prior dose ranging from 25.2 Gy in 28 fractions to 51.9 Gy in 28 fractions). sSBRT doses used for these patients were 14 or 16 Gy in one fraction, 20 or 21 Gy in two fractions, or 33 Gy in three fractions [35].

Spinal cord tolerance in the reirradiation setting is also an active area of research, and centers lower the prescribed dose in this setting to decrease the risk of radiation myelopathy. Damast et al. from MSKCC demonstrate that when the dose of sSBRT was increased from 4 to 6 Gy×5 fractions in the reirradiation setting, the local failure rate decreased from 45 to 26 % without increasing the risk of radiation myelopathy (median follow-up=12.1 months) [27]. The major critique of Damast et al.'s study is the short follow-up, and therefore, it is conceivable that many patients did not survive long enough to develop toxicity. Long-term follow-up data are insufficient to calculate a dose–volume relationship especially because of the short survival of patients with spine metastases [33]. Aggregating all the available clinical data on spinal cord myelopathy, Kirkpatrick et al. concluded that 13 Gy in one fraction or 20 Gy in three fractions confers a risk of myelopathy of less than 1 % each [33]. The risk for radiation myelopathy from repeat sSBRT after initial sSBRT is also not known.

Vertebral body fracture is also a significant toxicity of sSBRT and can lead to significant morbidity in patients. Colleagues from MSKCC studied 62 consecutive patients with 71 vertebral bodies treated to a range of doses from 18 to 24 Gy. They reported that 39 % of patients treated with high-dose single-fraction image-guided radiotherapy for spinal metastases developed new or progressive vertebral fractures [36]. Their analysis of risk factors suggested that the following were risk factors for vertebral fractures post-sSBRT: location between T10 and sacrum, lytic appearance, and >40 % vertebral involvement. Furthermore, patients who developed fractures had higher narcotic usage, worse KPS, and higher pain scores [36]. More recently, colleagues from MDACC reported their experience. Boehling et al. studied 123 vertebral bodies in 93 patients with sSBRT dose of one, three, or five fractions for overall median doses of 18, 27, and 30 Gy, respectively. They report a fracture rate of 20 % with age >55 years, preexisting vertebral fractures, and baseline pain as significant risk factors associated with fracture progression [37]. In the Cleveland Clinic series of 57 patients (88 treated vertebral bodies) treated for spinal metastases from renal cell carcinoma with a median dose of 15 Gy in one fraction, we report a 14 % risk of new or progressive vertebral fractures (Balagamwala et al., submitted). Identifying patients at risk for developing vertebral fractures is important as these patients may benefit from prophylactic kyphoplasty or vertebroplasty. Moving forward, it will be important to determine whether sSBRT dose is related to the development of vertebral fractures as dose de-escalation may not necessarily compromise local control but may prevent patients from undergoing additional medical and surgical procedures that may not be otherwise required.

Conclusion and future directions

Spinal SBRT is an emerging radiotherapy technique that could change current clinical practice. Early data from numerous prospective and retrospective case series suggest

that sSBRT is safe and effective. Often, patients considered eligible for sSBRT do not have a surgical option due to extensive metastatic disease burden, poor KPS, or coexisting medical comorbidities. Hence, sSBRT becomes a default option for these patients. Currently, sSBRT remains the only effective nonsurgical treatment option for previously irradiated spinal metastasis. The infrequent outpatient treatment visits and the relative lack of acute side effects together with rapid and durable pain relief make sSBRT an attractive treatment option for this patient population. The decreasing opiate dependence and alleviation of opiate side effects should also be recognized as an added benefit of sSBRT.

Currently, the role of sSBRT post laminectomy and decompressive surgery as primary treatment for malignant spinal cord compression instead of conventional EBRT with corpectomy is being explored at the Cleveland Clinic and other institutions. If patients are well selected, organ-at-risk dose constraints are met, and the PTV encompasses all of the local metastatic disease, the risk of myelopathy, vertebral compression fractures, and epidural disease relapse can be minimized.

Conflict of interest There are no relevant conflicts of interest.

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