Spinal Stereotactic Body Radiotherapy

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Annie Carbonneau, Arjun Sahgal, and G. Laura Masucci

Key Terms

- Stereotactic body radiotherapy (SBRT): the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extracranial body target with doses at least biologically equivalent to a radical course when given over a conventionally fractionated (1.8–3.0 Gy/fraction) schedule.
- Radiation myelopathy: spinal cord injury secondary to radiotherapy, resulting in an alteration of its function.
- Gross tumor volume (GTV): treatment volume including visible tumor on imaging.
- Clinical tumor volume (CTV): treatment volume including GTV with a margin taking into account microscopic disease.
- Planning tumor volume (PTV): treatment volume including CTV with a margin, usually 2–3 mm, to take into account uncertainties relating to positioning.
- Metastatic epidural spinal cord compression (MESCC): spinal cord compression due to tumor involvement with associated neurological symptoms.

Learning Objectives

- Understand the delivery of SBRT to spine.
- Discuss appropriate inclusion and exclusion criteria for spine SBRT.
- Learn about pain relief response and local control rates after spine SBRT.
- Identify most common patterns of relapse after spine SBRT.
- Define target volumes specific to spine SBRT.
- Discuss dose limits for organs at risk, including the spinal cord.
- Discuss the optimal dose and fractionation for spine SBRT.
- Consider acute and late toxicities specific to spine SBRT.
- Use appropriate imaging strategy to evaluate response to spine SBRT and recognize challenges with response interpretation due to specific effects of therapy.

Introduction

It is estimated that nearly 40% of patients diagnosed with cancer will develop spinal metastases at some point during the course of their illness [1]. With improvement in systemic therapies and increasing cancer survivorship, these rates are likely to escalade. Although back pain is the most common initial presenting symptom, patients may also present with mechanical instability and/or neurologic compromise secondary to epidural disease compressing the nerve roots or central neurological structures (spinal cord or thecal sac).

Palliative conventional external beam radiotherapy has had a historical role in the management of spinal metastases with results that are considered suboptimal; partial response

A. Carbonneau
Department of Radiation Oncology, Jewish General Hospital of Montreal, Montreal, QC, Canada

A. Sahgal
Department of Radiation Oncology, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada

G. L. Masucci (✉)
Department of Radiation Oncology, Centre Hospitalier de l'Universite de Montreal (CHUM), Montreal, QC, Canada
e-mail: g.laura.masucci.chum@ssss.gouv.qc.ca

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rates are in the order of 60% [2], and complete pain response rates range from 0% to 14% [3, 4].

Stereotactic body radiotherapy (SBRT) is a novel radiation technique that allows delivery of a high radiation dose, potentially ablative, to spinal tumors while minimizing dose to the spinal cord, cauda equina, and other organs at risk (OAR). The Canadian Association of Radiation Oncology (CARO) defined SBRT as "the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extracranial body target with doses at least biologically equivalent to a radical course when given over a conventionally fractionated (1.8–3.0 Gy/fraction) schedule." [5]. With the intent to maximize pain relief response and local control rates, spine SBRT is increasingly used.

Modern Technical Standard for Practice

Spine SBRT demands extreme precision in radiotherapy delivery to within 1–2 mm. It is only with recent technical advances in the entire radiotherapy process, including image guidance (IGRT), that this level of technical excellence is now achievable.

Technology

CyberKnife

CyberKnife is a robotic nonisocentric X-band dedicated radiosurgery linear accelerator (LINAC) system. Essentially, it is a compact LINAC that is attached to a robotic arm. Initially, the CyberKnife was put into use by 1990s for treatment of only intracranial lesions. Subsequent developments made it possible to extend the facility to extracranial lesions also, thereby making it a whole-body stereotactic radiotherapy system.

Technical Innovations to Adapt LINAC

Most commonly used is an isocentric S-band LINAC using multileaf collimators (MLC). It delivers intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). It uses onboard image-guidance systems, sophisticated immobilization devices, and treatment couches able to move in all six degrees of freedom (6-DOF) to yield extreme precision.

Treatment Delivery Unit Considerations

The dose delivery differs significantly between CyberKnife and LINAC technology. The CyberKnife is a nonisocentric X-band LINAC equipped with circular collimators of fixed diameters. It takes advantage of a highly flexible multijointed robotic arm to move the compact LINAC with six degrees of freedom so that beam placement maximizes target coverage while it minimizes directions in which the OAR are directly in the beam's trajectory. It relies on a set of 1–3 beam paths cross-firing from a large number of beam trajectories and angles (approximately 100–200), and the radiation is shaped by a series of circular collimators with apertures ranging from 0.5 to 6 cm. The flexibility of treatment planning is based on the large number of noncoplanar beam angles. The beam intensity is not modulated, and the additive effect of the individual beams results in a conformal dose distribution. The number of beam apertures is relatively few, and therefore treatment planning is not based on IMRT; this results in significant dose heterogeneity within the target volume. This translates to somewhat higher intratumoral maximum doses compared with other technologies. The technology has recently evolved to allow for MLC-based delivery.

The more common technology is an isocentric S-band LINAC using MLC for beam shaping and intensity modulation. It overlaps a large number (approximately 100–300) of shaped apertures (termed beamlets or beam segmentation) from multiple coplanar and/or noncoplanar beam angles (approximately 7–11) to achieve the desired dose distribution. VMAT (volumetric modulated arc therapy) is a new development in MLC-based LINAC radiation delivery technique in which the dose rate, gantry speed, and beam apertures may continuously change while the treatment is being delivered dynamically in a single- or multi-arc treatment. Treatment planning is achieved with an inverse planning algorithm for the optimization of the beam segment shapes and weight, in which the beam opening is maximal for the target while closing areas to block OAR. A more homogeneous dose distribution is created compared with current nonisocentric CyberKnife technology [6].

Immobilization

Patient immobilization is an important aspect of spine SBRT, in particular for those systems not equipped with near real-time intrafractional image guidance as used in the CyberKnife. Various devices have been used, including a long thermoplastic mask for patients with lesions involving C1 to T3 and near-rigid body immobilization for lesions involving T4 and below. Examples of near-rigid body immobilization devices include the BodyFIX (Medical Intelligence) [7, 8] or in-house, custom-designed device [9, 10]. These immobilization systems serve to minimize potential patient movement, to ensure proper match of the position of the target at time of treatment to that at the time of planning. The aim is to avoid large shift (>2 mm or 2°) as detected with the image-guidance system. Near-rigid body immobilization also reduces the potential for patient

motion while the beam is on (intrafractional variation) and increases delivery accuracy, and this is of critical importance for SBRT.

Image-Guidance System and Online Correction

Image-guided radiotherapy (IGRT) is critical to SBRT. The IGRT system allows 3D imaging of the target just prior to radiation delivery while the patient is immobilized on the treatment couch. It allows the match of the pretreatment position of the tumor to that at the time of simulation and can determine three-dimensionally what corrective actions are required to ensure proper and secure delivery of treatment. Furthermore, because the patient may move while treatment is being delivered, IGRT is used to determine intrafractional positional variations to ensure treatment accuracy. The IGRT systems can be broken down into those based on stereoscopic X-ray- and computed tomography (CT)-based imaging. For spine SBRT, the aim is to ensure precise positioning with an accuracy of 1–2 mm and 1°–2° with either IGRT system [6].

Stereoscopic X-ray imaging, used in the CyberKnife technique, implies simultaneous orthogonal X-ray imaging of the target. The X-rays are processed by software solutions to provide 3D information on the target position indirectly. The position of target is then referenced to that at the time of treatment planning to determine what shifts are required for a match. Bony landmarks are used for spine SBRT. This stereoscopic system allows for fast imaging of the target in near real time and corrects the position of the LINAC to track shifts via the robotic arm while the beam is on.

CT-based imaging results in the direct acquisition of high-quality volumetric images, which provides optimal registration accuracy. Soft tissues and anatomical structures are directly visualized on the transaxial CT images and registered to the corresponding planning CT studies. Necessary shifts for a match are determined. When necessary, shifts are achieved via the robotic couch with up to six degrees of freedom motion. To account for intrafractional variation, interruption of the treatment is necessary to obtain repeat images.

Planning Imaging

CT-simulation requires fine resolution scans with a slice thickness not exceeding 2.5 mm [5]. Magnetic resonance imaging (MRI) of the target vertebrae, and at least one to two vertebrae above and below, is suggested for accurate delineation of the target, paraspinal soft tissue extension, epidural disease as well as the spinal cord/thecal sac. Axial volumetric T1 and T2 sequences without gadolinium are a standard [11]. The use of gadolinium, however, might be advantageous in delineating paraspinal disease, epidural disease, and in differentiating postoperative surgical fluid from residual disease [12].

Specific to postoperative SBRT, fusion of the preoperative MRI axial images is paramount. In patients with metal artifact from hardware obscuring the critical neural structures, a CT myelogram should be obtained [11, 13].

Target Volumes

The International Spine Radiosurgery Consortium has published guidelines for target volume definition in spine SBRT [14]. These propose that the gross tumor volume (GTV) should include all gross tumors, including epidural and paraspinal elements. The clinical target volume (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 tumor. It is recommended that the CTV to planning target volume (PTV) expansion is ≤3 mm and this should be constrained around the spinal cord (Table 46.1).

Recently, a consensus contouring guidelines has been proposed by an international group of experts in the postoperative setting [15]. The GTV is defined as any residual disease visualized on postoperative CT and MRI with attention to residual epidural or paraspinal disease. The CTV should account for the GTV and regions that were involved preoperatively according to CT and MRI. It should

Table 46.1 Summary of GTV, CTV, and PTV contouring guidelines for spine SBRT

Target volume	Guidelines
GTV	• Contour gross tumor using all available imaging • Include epidural and paraspinal components of tumor
CTV	• Include abnormal marrow signal suspicious for microscopic invasion • Include bony CTV expansion to account for subclinical spread • Should contain GTV • Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression
PTV	• Uniform expansion around CTV • CTV to PTV margin ≤3 mm • Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised • Never overlaps with cord • Should contain entire GTV and CTV

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include adjacent anatomic compartments at risk of microscopic disease extension based on preoperative bony and epidural involvement using the International Spine Radiosurgery Consortium anatomic classification as a framework. Indeed, a recent pattern of failure analysis found that the location of preoperative epidural disease was more predictive of subsequent failure than the sites of residual disease postoperatively [16]. It is recommended to use judiciously circumferential CTVs limited to cases of preoperative circumferential or near-circumferential osseous and/or epidural involvement. The surgical incision and instrumentation does not need to be included in the treatment volume unless involved. The expansion of a PTV varies between institutions, ranging from no expansion to 2.5 mm uniform expansion. The PTV should be modified so that it does not extend into the cord avoidance structure for treatment planning.

Given the critical nature of the spinal cord and the impact of uncertainties present in the radiotherapy process, a planning risk volume (PRV) is typically applied to the spinal cord [17]. The margin used for the PRV should be based on a robust evaluation of each center's process. Usually, a margin of 1.5–2 mm is added to the spinal cord to generate cord PRV (Table 46.2).

Table 46.2 Summary of GTV, CTV, and PTV contouring guidelines for postoperative spine SBRT for spinal metastases

Target volume	Guidelines
GTV	• Gross tumor based on postoperative CT MRI with attention to residual epidural or paraspinal disease • Include postoperative residual epidural and paraspinal components of tumor
CTV	• Include the postoperative region and entire anatomic compartment corresponding to all preoperative MRI abnormalities suspicious for tumor involvement • Include entire GTV • Surgical instrumentation and incision not included unless involved • Judicious use of circumferential CTVs limited to cases of preoperative circumferential osseous and/or epidural involvement; however, it can be considered for near-circumferential epidural disease involvement • Modified at reconstructed dural space to account for changes in anatomy after surgery at the discretion of treating physician • Consider additional anatomic expansions of up to 5 mm beyond paraspinal extension and cranio-caudally for epidural disease • Uniform CTV to PTV expansion of up to 2.5 mm • Treating physician may modify expansion at the interface with critical organs at risk
PTV	• May subtract cord avoidance structure from PTV as a modified PTV for planning and does reporting purposes • Include entire GTV and CTV

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Treatment Planning

Treatment planning can be challenging, particularly in situations where multiple OAR are present such as the bowel, kidneys, and esophagus. The basic strategy is often to determine the spinal cord dose to the maximum allowable safe limit and focus on achieving as steep a dose gradient as possible while maximizing coverage within the epidural space.

Typical techniques include 7- to 11-static-field IMRT or VMAT. Standard characteristics of a spine SBRT treatment plan include hotspots in the target in excess of 20–50% beyond the prescription dose, a steep dose gradient between the cord and the target, and 70–90% target coverage (percent volume receiving the prescribed dose) in order to respect strict OAR tolerances [18].

Treatment planning for SBRT in the postoperative setting is complicated by the presence of surgical hardware leading to electron backscatter and photon attenuation. This may not be accurately captured in standard treatment planning algorithms. Therefore, treatment planning algorithm approved by the RTOG for calculation of dose within a medium with heterogeneities should be used for all postoperative spine SBRT cases [19].

Patient Selection

A number of factors are taken into account when deciding whether a patient is a good candidate for spine SBRT.

Epidural Disease Grading

In an effort to standardize the communication of epidural disease extent, a grading system known as the Bilsky grading system has been developed and validated by the Memorial Sloan Kettering Cancer Center group [20]. A schematic representation of the Bilsky grading system is represented in Fig. 46.1. A Bilsky grade 0 implies no extension of the lesion beyond the vertebral body into the epidural space, grade 1A–C refers to epidural disease approaching the spinal cord but not compressing it, grade 2 refers to compression of the spinal cord with cerebrospinal fluid visible in the spinal canal at the level of the compression, and grade 3 refers to complete compression of the spinal cord with no cerebrospinal fluid visible. Spinal metastases graded as a Bilsky 3 should have surgical consultation for consideration of decompression, and if surgery is contraindicated, then conventional EBRT at this time may be most appropriate [21]. For Bilsky 2 tumors, there may be therapeutic benefit to downgrading the epidural disease to a Bilsky 0 or 1 then following with SBRT, as reported by Al-Omair et al.[22]. Otherwise, SBRT for Bilsky 2 disease

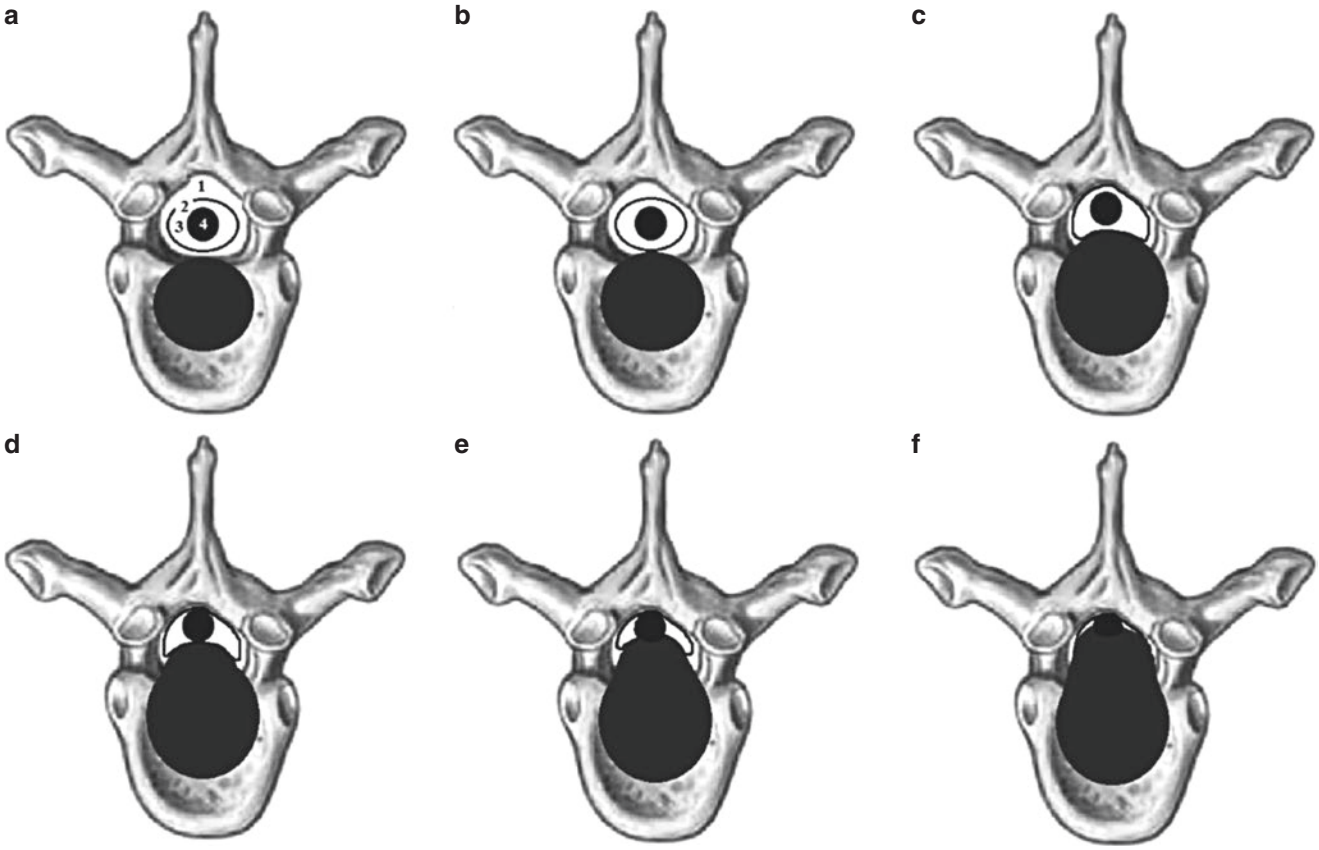

Fig. 46.1 Schematic of Bilsky six-point grading system applied to the thoracic spine depicting epidural spinal cord compression. (**a**) (1) Epidural space, (2) dural sac, (3) cerebrospinal fluid (CSF), (4) spinal cord. Grade 0, bone involvement only; (**b**) grade 1a, epidural impingement without deformation of the thecal sac; (**c**) grade 1b, deformation of the thecal sac without spinal cord abutment; (**d**) grade 1c, deformation of the thecal sac with spinal cord abutment, but without spinal cord compression; (**e**) grade 2, spinal cord compression with CSF visible around the cord; (**f**) grade 3, spinal cord compression without CSF visible around the cord. [Reprinted from Kumar R, Nater A, Hashmi A. et al. The era of stereotactic body radiotherapy for spinal metastases and the multidisciplinary management of complex cases. Neuro Oncol Pract. 2016;3(1):48–58. With permission from Oxford University Press]

remains appropriate as a relative contraindication. Ideally, there should be at least 2–5 mm between the disease and the spinal cord to maximize CTV coverage [23].

Mechanical Instability

The Spinal Instability Neoplastic Score (SINS) provides an objective and validated measure of spinal instability [24]. It considers factors including location, pain quality, posterior element involvement, vertebral body collapse, quality of the metastases (e.g., lytic vs. blastic), and vertebral alignment. The key outcome is categorical, with the condition of patients defined as stable (0–6), potentially unstable (7–12), or unstable (13–18). An experienced surgeon should evaluate potentially unstable or unstable deemed patients to determine whether stabilization prior to SBRT is necessary to minimize posttreatment risk of fracture (Table 46.3).

Neurologic Deficit

Consideration of spine SBRT also requires objective grading of neurologic function. The most accepted score is from the American Spinal Injury Association (ASIA) [25]. An ASIA E rating is normal motor and sensory function, D is incomplete motor impairment with more than half of the key muscles below the affected level having a power of at least 3 out of 5, C is incomplete motor impairment with key muscles below the affected level having a power under 3 out of 5, B is incomplete motor impairment with sensory but no motor function preserved, and A is complete impairment with neither sensory nor motor function preserved. Spinal metastases causing progressive neurologic deficits (ASIA grades A–D), if not definitively responsive to corticosteroids, are considered a strong indication for surgical consultations [13]. ASIA grade A status is usually a contraindication for SBRT [19].

Table 46.3 Spinal instability neoplastic score

Element of SINS	Score
Location	
Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semirigid (T3–T10)	1
Rigid (S2–S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	3
No (occasional pain but not mechanical)	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle, or CV joint fracture or replacement with tumor)	
Bilateral	3
Unilateral	1
None of the above	0

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Life Expectancy

One of the most challenging issues in this clinical setting is to identify patients that will long enough to realize the potential benefits of SBRT as compared to palliative conventional EBRT. Typically, a life expectancy of at least 3 months has been identified as inclusion criteria.

Laufer et al. [26] published a decision framework used at the Memorial Sloan Kettering Cancer Center to select the optimal treatment for patients with spinal metastases. This framework, called NOMS, is based on neurologic, oncologic, mechanical, and systemic parameters. It also incorporates the use of conventional EBRT (cEBRT in Fig. 46.2), spine SBRT, and minimally invasive and open surgical procedures. Following the NOMS decision algorithm, SBRT (SRS in Fig. 46.2) should be mainly delivered in patients presenting a low-grade epidural spinal cord compression score and a radioresistant or previously radiated metastases, without signs of vertebral instability [27].

Chao et al. [28] generated a prognostic index based on the recursive partitioning analysis (RPA) for patients undergoing spine SBRT. The authors used a Kaplan-Meier analysis to detect any correlation between survival and several clinical and technical features (Fig. 46.3). Time from primary diagnosis (< or >30 months) and the Karnofsky Performance Status (< or >70) were determined to be significant parameters to identify patients with a better prognosis and, therefore, most likely to benefit from spine SBRT.

Recently, Tang et al. [29] published a scoring system that stratifies patients based on a secondary analysis of overall survival of two mature phase II prospective trials. Two hundred six patients with a minimal follow-up of 3 years were analyzed. They identified four subgroups of patients characterized by different prognoses ranging from excellent to poor. This prognostic index for spinal metastases (PRISM) was based on a multivariate Cox regression model. Five clinical variables (female sex, Karnofsky Performance Status >60, only one bone metastasis, low number of extra-osseous metastatic sites, and an interval from initial diagnosis to detection of spinal metastasis of more than 5 years) and two therapeutic variables (previous surgery at the SBRT site and a previous radiotherapy at the SBRT site) were found to be statistically predictive of good or excellent prognosis after SBRT.

Indications and Contraindications

Multiple guidelines have been reported detailing appropriate inclusion and exclusion criteria for spine SBRT, including those from the American Society for Therapeutic Radiology and Oncology and the American College of Radiology [11] and from the Canadian Association of Radiation Oncology [5]. In general, patients considered appropriate for spine SBRT have a spinal or paraspinal metastasis from a solid tumor histology in three or less contiguous segments, SINS score revealing a stable or minimally unstable spinal column, low-grade epidural disease, life expectancy of at least 3 months, and a relatively limited systemic disease burden [23]. With respect to the latter, patients with oligometastatic disease are ideal candidates for SBRT given their longer life expectancy and the increasing literature to suggest that a proportion may potentially achieve significant disease-free intervals with aggressive therapy [30]. Furthermore, independent series from various institutions have suggested increased therapeutic benefit in terms of local control and pain relief particularly in tumors stemming from a radioresistant histology such as melanoma, sarcoma, and renal cell carcinoma (RCC) [31–36]. The use of these techniques becomes more critical in a previously irradiated patient in order to deliver a tumoricidal dose and protect critical neural structures simultaneously [23]. A summary of current spine SBRT indications is provided in Table 46.4 and represents an expert opinion considering the data to date and reported consensus.

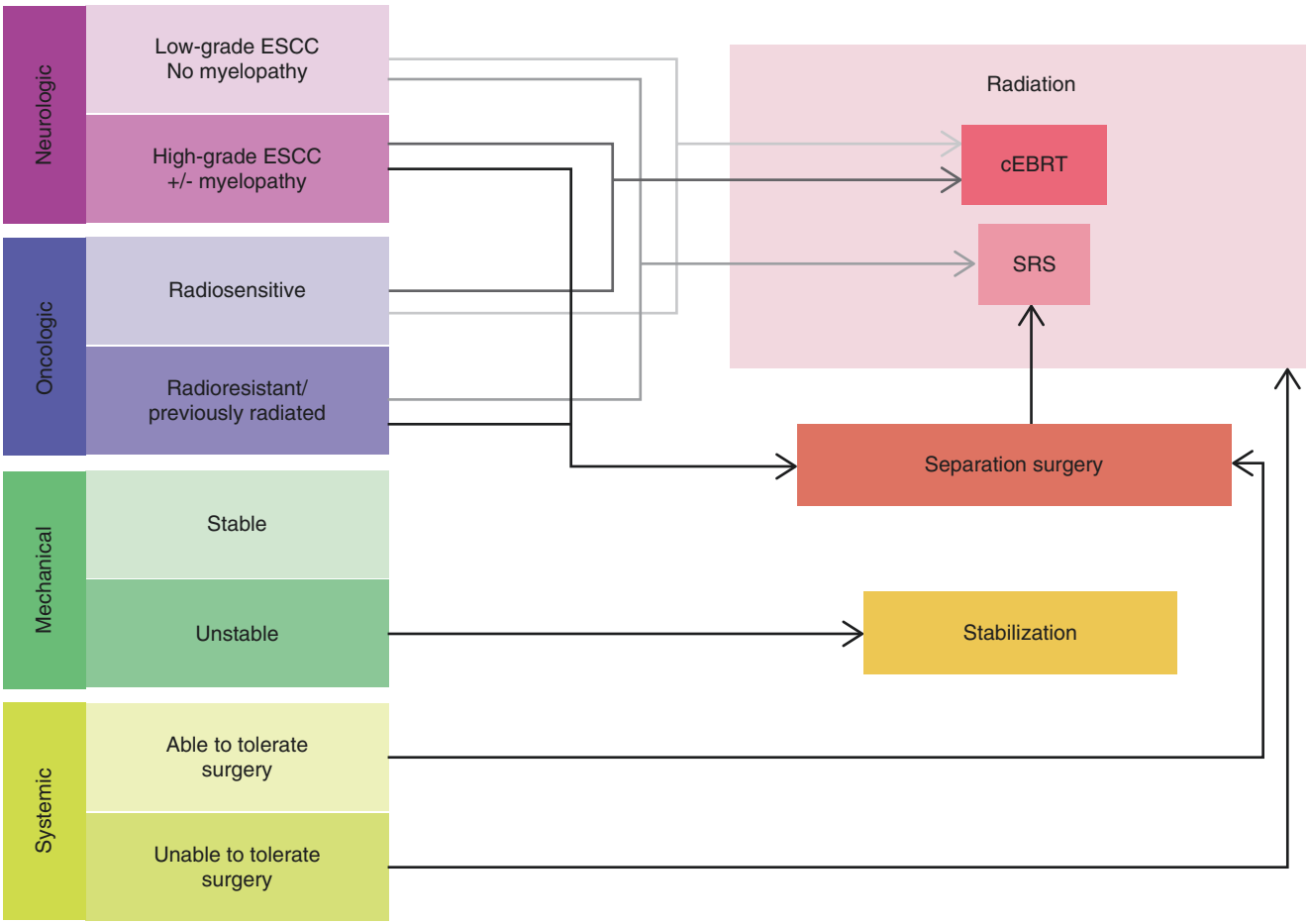

Fig. 46.2 Schematic depiction of the neurologic, oncologic, mechanical, and systemic (NOMS) decision framework. [Reprinted from Bhattacharya IS, Hoskin PJ. Stereotactic body radiotherapy for spinal and bone metastases. Clin Oncol (R Coll Radiol). 2015;27(5):298–306. With permission from Elsevier]

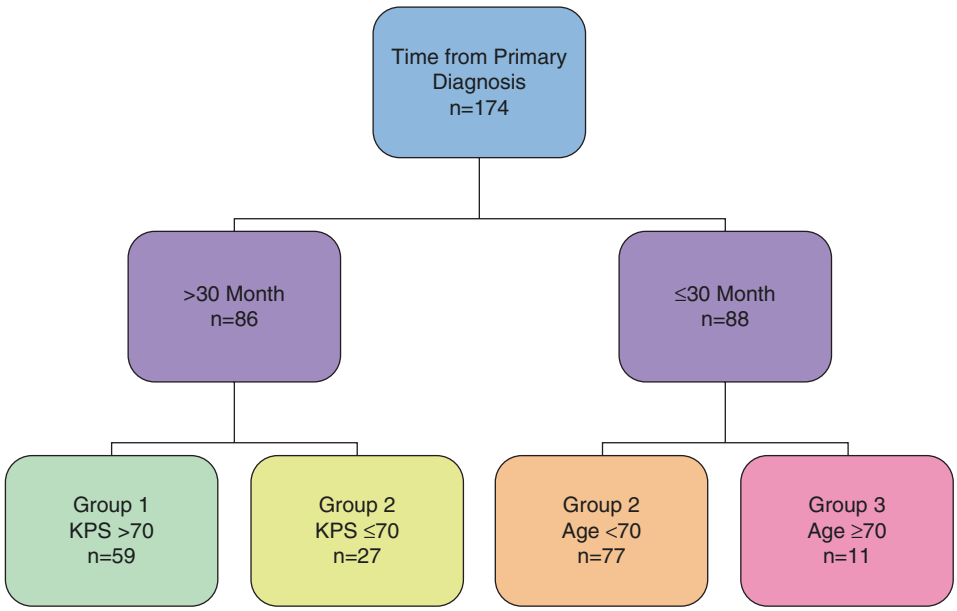

Fig. 46.3 RPA tree for overall survival for patients treated with SBRT to the spine. [Reprinted from Chao ST, Koyfman SA, Woody N, et al. Recursive partitioning analysis index is predictive for overall survival in patients undergoing spine stereotactic body radiation therapy for spinal metastases. Int J Radiat Oncol Biol Phys. 2012;82(5):1738–1743. With permission from Elsevier]

Table 46.4 Inclusion and relative and major contraindication to spine SBRT

Optimal inclusion criteria for spine SBRT	Relative contraindication to spine SBRT	Major contraindications to spine SBRT[a]
• Good to excellent performance status	• Moderate performance status	• Poor performance status (ECOG 3–4; KPS <60)
• Oligometastatic disease (≤5 sites extracranial metastases)	• Oligoprogression in patients with widely metastatic and/or rapidly progressive disease	• Widely metastatic and/or rapidly progressive disease with limited life expectancy
• Oligoprogression in a patient with oligometastatic disease		
• No more than three spinal levels involved (contiguous or noncontiguous)	• >3 spinal levels involved but nondiffuse spine disease and no more than three contiguous segments	• >3 contiguous spinal levels involved or diffuse spine disease
• No or minimal spine instability (SINS 0–6)	• Potential spine instability (SINS 7–12)	• Spine instability (SINS 13–18)
• No or minimal epidural disease (Bilsky 0–1)	• Moderate-grade epidural disease (Bilsky 2)	• High-grade epidural disease (Bilsky 3)
• "Radioresistant" histology	• "Radiosensitive" history	
• No prior cEBRT to affected level or prior cEBRT delivered ≥5 mo of a considered second course of salvage SBRT	• Prior cEBRT delivered 3–5 mo prior to considered course of salvage spine SBRT	• Prior cEBRT <3 mo prior to considered course of salvage spine SBRT
• Spine SBRT delivered ≥5 mo of a considered second course of savage SBRT	• Spine SBRT delivered within 3–5 mo of a considered second course of salvage SBRT	• Spine SBRT delivered <3 mo prior to a considered second course of salvage SBRT
• Robotic LINAC or subcentimeter MLC-based LINAC delivery, CBCT, and/or stereoscopic imaging IGRT; near-rigid body immobilization; fusion of thin-slice MRI sequences for target/CNS contouring; and, in selected postoperative cases, a treatment planning CT myelogram	• If unable to have an MRI, then a treatment planning with CT myelogram for CNS structure contouring provided that the target is identifiable on CT alone with sufficient clinical detail as to paraspinal disease extension/epidural disease extension	• Unable to tolerate near-rigid/supine immobilization • Unable to have a full-spine MRI and/or CT myelogram

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CNS central nervous system (spinal cord, thecal sac), *ECOG* Eastern Cooperative Organization Group, *IGRT* image-guided radiotherapy, *KPS* Karnofsky Performance Status, *MLC* multileaf collimator, *mo* months

[a]Exceptions may exist based on practitioner's experience and clinical scenario

In the postoperative setting, Redmond et al. published a consensus guidelines based on the results of an international survey [19]. Consensus treatment indications included radioresistant primary, 1–2 levels of adjacent disease, and previous radiotherapy. Contraindications included involvement of more than three contiguous vertebral bodies, ASIA grade A status, and postoperative Bilsky grade 3 residual.

Challenges with Response Interpretation

A clear understanding of response to treatment is crucial in order to make appropriate treatment decisions. As suggested by the recently reported SPIne response assessment in Neuro-Oncology (SPINO) group, MRI is the recommended imaging modality for assessment of tumor response following spine SBRT [12]. However, early morphologic changes are poorly understood, and interpretation of the response can be challenging. Traditional metrics such as bidimensional size measurements and RECIST criteria are not optimal to monitor response, especially when changes in tumor dimensions are subtle. Also, a change in signal intensity must be interpreted with caution with the knowledge of the clinical context since it may be not be associated with true progression but due to osteoradionecrosis, fibrosis, as well as non-tumor-related vertebral compression fracture.

Pseudoprogression is a specific treatment response to high-dose radiotherapy such as spine SBRT. It is defined as a treatment-related transient tumor growth that mimics true progression. It was first described in gliomas undergoing high-dose radio- and chemotherapy [37] and has been well documented following brain radiosurgery [38], lung SBRT [39, 40], and liver SBRT [41]. The group from MD Anderson Cancer Center (MDACC) [42] and the one from Montreal University Hospital Center (CHUM) [43] reported a pseudoprogression incidence of 14% and 18%, respectively, occurring at 3- to 6-month time intervals after SBRT. Of note, the latter study demonstrated that tumor growth confined to the 80% prescription isodose line and earlier time to tumor enlargement predicted for pseudoprogression.

The SPINO group suggested defining local progression as gross unequivocal increase in tumor volume or linear dimension, any new or progressive tumor within the epidural space,

or neurological deterioration attributable to preexisting epidural disease with equivocal increased epidural disease dimension on MRI. Images should be interpreted by a radiation oncologist and radiologist. In circumstances where treatment response is unclear, serial imaging with two to three MRIs, 8–12 weeks apart, is recommended by the group. Although there is increasing use of functional imaging such as PET and perfusion MRI, there are insufficient data to recommend these modalities at this time [12].

Clinical Outcomes

The two main therapeutic targets of SBRT for spinal metastasis, namely, pain control and local control, have been explored in a number of retrospective series and few phase I and II studies, but data of phase III studies are not available as of yet. Selected series are summarized in Table 46.5. Of note, these reports largely varied in terms of total dose, dose/fraction, and delivery techniques.

Table 46.5 Results from select series using spine SBRT

Author (year)	Design	No. of tumors/no. of patients	Prescribed dose (range), Gy/no. of fractions (range)	Median follow-up (range), mo	Local control	Overall survival	Pain response
Selected spine SBRT series for spinal metastases with no prior history of radiation (de novo)							
Degen (2005) [44]	Retrospective	72/51	(10–37.5)/3 (1–5)	12 (1–22)	N/A	N/A	VAS: 51.5 (baseline) to 17.5 (12 mo)
Gerszten (2007) [45]	Prospective	500/393	Median, 20 (12.5–25)/1	21 (3–53)	88%	N/A	86% (overall long-term improvement)
Chang (2007) [7]	Phase I/II	74/63	(27–30)/(3–5)	21.3 (0.9–49.6)	84% (1 y)	69.8% (1 y) 24.3 mo median	N/A
Yamada (2008) [9]	Prospective	103/93	Median, 24 (18–24)/1	15 (2–45)	90% (15 mo)	15 mo median	N/A
Gagnon (2009) [46]	Prospective	274/200	(21–37.5)/(3–5)	12 (1–51)	N/A	17 mo median	VAS: 40.1 (baseline) to 28.6 (12 mo)
Nguyen (2010) [36]	Prospective (RCC only)	55/48	(24–30)/(1–5)	13.1 (3.3–54.5)	82% (1 y)	72% (1 y) 22 mo median	BPI: no pain 23% (baseline) to 52% (12 mo)
Wang (2012) [47]	Phase I/II	166/149	(27–30)/3	15.9 (1.0–91.6)	80.5% (1 y) 72.4% (2 y) Tumor progression-free survival	68.5% (1 y) 46.4% (2 y) 23 mo median	BPI: no pain 26% (baseline) to 54% (6 mo)
Garg (2012) [48]	Phase I/II	63/61	(18–24)/1	19.7 (1.2–52.1)	88% (18 mo)	64% (18 mo) 30.4 mo median	BPI: no pain 21% (baseline) to 30% (6 mo)
Guckenberger (2014) [49]	Multicentric retrospective	387/301	Median, 24 (8–60)/3 (1–20)	11.8 (0–105)	89.9% (1 y) 83.9% (2 y)	64.9% (1 y) 43.7% (2 y) 19.5 mo median	BPI: no pain 18.2% (baseline) to 76.8% (11.5 mo)
Selected reirradiation spine SBRT series for spinal metastases							
Sahgal (2009) [50]	Retrospective	37/25	Median, 24 (8–30)/3 (1–5)	7 (1–48)	85% (1 y) 69% (2 y)	45% (2 y) 21 mo median	N/A
Choi (2010) [51]	Retrospective	51/42	Median, 20 (10–30)/2 (1–5)	7 (2–47)	73% (1 y)	68% (1 y)	65%
Damast (2011) [52]	Retrospective	97/94	20/5 (42 tumors) 30/5 (55 tumors)	12.1 (0.2–63.6)	66% (1 y)	52–59% (1 y) 13.6 mo median	85%

(continued)

Table 46.5 (continued)

Author (year)	Design	No. of tumors/no. of patients	Prescribed dose (range), Gy/no. of fractions (range)	Median follow-up (range), mo	Local control	Overall survival	Pain response
Garg (2011) [53]	Prospective	63/59	(27–30)/3 (3–5)	17.6 (0.9–67.5)	76% (1 y)	76% (1 y)	N/A
Mahadevan (2011) [54]	Retrospective	81/60	(24–30)/3 (3–5)	12 (3–39)	93% (crude)	11 mo median	65%
Chang (2012) [55]	Retrospective	54/49	27/3	17.3 (mean)	81% (1 y) 79% (2 y)	11.0 mo median	N/A
Selected postoperative spine SBRT series for spinal metastases							
Gerszten (2005) [56]	Retrospective	26/26	Mean, 18 (16–20)/1	16 (11–24)	N/A	N/A	VAS: 92% long-term improvement
Moulding (2010) [57]	Retrospective	21/21	Median, 24 (18–24)/1	10.2 (1.2–54.0)	90.5% (1 y)	10.2 mo median	N/A
Laufer (2013) [58]	Retrospective	186/186	Median, 24/1 or 27 (24–30)/3 or 30 (18–36)/5	7.6 (1.0–66.4)	83.6% (1 y)	29% (crude) 5.6 mo median	N/A
Al-Omair (2013) [22]	Retrospective	80/80	Median, 24 (18–40)/2 (1–5)	8.3 (0.13–39.1)	84% (1 y)	64% (1 y)	N/A
Tao (2016) [59]	Prospective	69/66	16–24/1 or 27/3 or 30/5	30 (1–145)	85% (1 y) 79% (2 y) 74% (3 y)	74% (1 y) 60% (2 y) 40% (3 y) 30 mo median	N/A

mo month, *y* year, *VAS* visual analog scale, *N/A* not applicable, *BPI* brief pain inventory

De Novo Spine SBRT

Several single-institution retrospective series and few prospective studies have reported high rates of both pain control and local tumor control in previously unirradiated spinal metastases treated with SBRT.

In the prospective phase I/II study reported by Wang et al. [47], 149 patients and 166 lesions were treated to a total dose of 27–30 Gy in three fractions. Pain control was assessed using the validated Brief Pain Inventory (BPI) assessment tool. With a median follow-up of 15.9 months, investigators concluded a mean reduction of 3.4 points based on the BPI, and 54% of patients were completely pain-free 6 months post-SBRT. A concomitant statistically significant decrease in opioid use was also reported. Quality of life outcomes demonstrated improvements in disturbed sleep, drowsiness, sadness, fatigue, distress, lack of appetite, nausea, and memory following spine SBRT. This trial also reported a 1-year actuarial tumor progression-free survival rate of 80.5%. No radiation-related spinal cord myelopathy was reported during the study.

Multiple series corroborate the previous data with radiographic and/or clinical local tumor control rates ranging from 80% to 90% in cohort with mixed tumor histology. Furthermore, at least six series have specifically reported on the outcomes in patients with radioresistant histology such as melanoma, sarcoma, and RCC documenting local tumor control rates of 79–88% [30–35]. More recently, data has been published showing, in patients surviving at least 5 years after treatment, a local recurrence of 9.6% [60].

SBRT is also highly effective at palliation of pain symptoms. In the selected studies summarized in Table 46.5, we observe that complete pain response rates are not often reported but can range up to 86%.

The literature concerning quality of life after SBRT is scarce. However, Degen et al. [44] and Gagnon et al. [46] reported quality of life maintenance after treatment. The 12-item Short Form Health Survey (SF-12) was used to assess quality of life prior to and after treatment. Average SF-12 scores did not vary in either the physical or mental well-being domains throughout follow-up, with assessments at regular intervals from 1 month posttreatment to 18 months posttreatment.

Spine SBRT Following Previous Conventional External Beam Radiation

It is well known that up to 20% of patients will require retreatment due to the recurrence of pain in the previously radiated area in the short term [21]. One of the major indications for spine SBRT has been failure following pallia-

tive conventional EBRT. Equivalent rates of pain and local control in patients with or without prior radiation treated with SBRT are suggested based on a nonrandomized comparison. Selected studies on retreatment with spine SBRT for recurrent spinal metastasis showed 66–93% local control rate over a follow-up period of 7–21 months (Table 46.5). Concerning palliation of pain symptoms, 65–85% of patients experienced a positive response. Another option being studied recently is intraoperative brachytherapy for tumors of the spine involving the dura. It is a useful adjunct to surgical intervention for recurrent spinal metastases, especially in the setting of prior conventional EBRT [61].

Spine SBRT Following Previous SBRT

As the rate of application of spine SBRT continues to rise, salvage of SBRT failures will become increasingly important. A recent review from the University of Toronto examined outcomes in a group of 40 patients with 56 spinal metastases that were treated using a second course of SBRT after local SBRT failure [62]. Furthermore, 43% had received previous conventional EBRT prior to the first SBRT treatment course. The median prescription dose and number of fractions for the second course of SBRT were 30 Gy and four fractions (range 20–35 Gy in two to five fractions). The 1-year local control rate was 81%, and there were no cases of radiation myelopathy. This series is important as it supports the use of aggressive salvage therapy with SBRT despite initial failure, as opposed to strictly palliative approaches for fear of causing complications with a second course of SBRT.

Postoperative Spine SBRT

The historical standard adjuvant therapy to surgical decompression and stabilization has been conventional EBRT. The intent is to deliver sufficient dose to be safe to normal tissues while yielding at least short-term local control and pain palliation. Imaging-based local control after palliative conventional EBRT has not been well defined. Based on the few studies that have been reported, these control rates are modest at best and represent an area for improvement [63, 64]. Innovations in radiation technology and surgery have allowed increasing application of SBRT in postoperative patients, and data are emerging to suggest that outcomes with this technique may be superior to those achieved with conventional EBRT.

Few retrospective series and one recently published prospective study looked at postoperative SBRT in particular. Tao et al. [59] reported 66 patients with 69 tumors treated with SBRT after open spinal decompression. They received 16–24 Gy in one fraction, 27 Gy in three fractions, or 30 Gy in five fractions. After a median follow-up of 30 months, the actuarial 1-year rate of tumor control was 85% and overall survival was 74%. There was no myelopathy reported.

In selected postoperative spine SBRT series, 1-year local control rates range from 83.6% to 90.5%, and pain response rate was reported in one study at 92% (Table 46.5). Posttreatment ambulatory status, although not stated in most series, is 100% in those studies that do report it.

Pattern of Relapse

Failure in epidural space is the most common pattern reported in the SBRT literature occurring in approximately half of the recurrences. Chang et al. [7] reported specific failures in this area in 8 of 17 failures in their series of 74 tumors treated. Nguyen et al. [36] also reported 6 epidural space failures out of 12 failures in their series of 55 RCC metastases treated.

Sahgal et al. [50] reported local failure in 8 of 60 tumors treated and analyzed the potential for treatment failure as the tumor approached the thecal sac. A trend was found when the minimal distance between the target and the thecal sac was <1 mm, and exploratory analysis showed a significant risk of failure for tumors with extensive epidural disease.

Data illustrates the challenge of treating epidural disease with SBRT, because spinal cord constraints simply limit epidural tumor coverage. Therefore, for tumors abutting the critical neural structures, there may be a therapeutic benefit to epidural disease resection with respect to local control as reported by Al-Omair et al. [22].

Failure at other areas due to intentional avoidance or lack of margin beyond the GTV can occur. Failure in the paravertebral tissue has been reported: 4 out of 17 in Chang et al. [7] and 3 out of 12 in Nguyen et al. [36]. It probably results from the practice of applying no margin to paravertebral disease into the adjacent soft tissues. A small margin of 0.5 cm may be reasonable along the paraspinal muscles when involved, to reduce the risk of marginal failure, given that the muscle is not an anatomical barrier to tumor growth. However, optimal margins are unknown [6]. When the posterior elements were deliberately excluded, failures have been reported: 3 out of 7 in Chang et al. [7] and 5 out of 12 in Nguyen et al. [36]. If disease is located only within the vertebral body based on MR imaging, then it is reasonable to exclude the posterior elements, as suggested in the International Spine Radiosurgery Consortium [14]. Progression in adjacent vertebral bodies is rare and supports SBRT treatment of the involved spinal levels only [65].

As observed for unirradiated patients, failure after retreat SBRT most often occurs within, or close to, the epidural space. Also, after postoperative SBRT, the predominant pattern of failure is within the epidural space. It is the only site of failure in two-thirds of cases [22, 59]. A recent patterns

of failure analysis found that the location of preoperative epidural disease was more predictive of subsequent failure than the sites of residual disease postoperatively [16].

Toxicities and Dose Limits for Organs at Risk

In terms of acute toxicity, the treatment appears to be well tolerated, and most reports indicate limited acute toxicities in relation to the surrounding anatomy. Late toxicities are more of a concern, given that we have little experience with dose-volume limits for high-dose-per-fraction exposure of normal tissues. Furthermore, the risk of harmful permanent tissue damage is greater with higher-dose-per-fraction radiotherapy, and it accumulates with time, often manifesting several months to years postradiation.

Pain Flare

Pain flare is defined as a temporary increase in pain in the immediate period after radiation. It was specifically studied after spine SBRT in two studies: Chiang et al. [66] and Pan et al. [67] Incidence reported was 23% and 68%, after a median time up to 5 days after SBRT. The prescription of dexamethasone (most commonly 4 mg orally once daily for the time of the treatment and/or for 5 days after SBRT) resulted in a significant decrease in pain scores. As a matter of fact, dexamethasone has been showed to be efficient in the prophylaxis of radiation-induced pain flare after palliative conventional EBRT for bone metastases [68]. It is not yet standard practice to use dexamethasone as a prophylactic intervention following spine SBRT as many reserve it as a rescue intervention should the pain occur. A randomized trial of dexamethasone in patients treated with spine SBRT has been proposed.

Vertebral Body Compression Fracture (VCF)

VCF after spine SBRT has emerged as the most common adverse effect following SBRT. It includes de novo fracture and fracture progression. The mean time to fracture after SBRT is 3 months. Rates range between 10% and 40% and are more commonly reported after high-dose single-fraction SBRT versus fractionated SBRT. This dose complication relationship is evident. With 24 Gy in a single fraction, the rate of VCF approaches 40%, which was first reported by Rose et al. [69] and later confirmed in a multi-institutional analysis. The risk of VCF is approximately 20% with 20–23 Gy/fraction and 10% with less than 20 Gy/fraction [70]. Other risk factors identified in the literature include spinal misalignment, lytic tumor, baseline fracture, and high SINS [18]. Less than half of all patients require an intervention and, in those that did, a minimally invasive cement augmentation procedure has been applied as opposed to an open spinal surgery [70].

Radiation Myelopathy

Radiation myelopathy is generally the most feared complication of spine SBRT. Fortunately, evidence-based dose constraint guidelines have been published to guide spine SBRT both in the setting of no prior irradiation as well as prior conventional EBRT of the spinal cord.

A report published by the American Association of Physicists in Medicine (AAPM) [71] suggests limiting to 7 Gy, 12.3 Gy, and 14.5 Gy the dose delivered to $\leq$1.2 cc of spinal cord in one, three, and five fractions, respectively. The same report recommends to limit to 10 Gy, 18 Gy, and 23 Gy the dose delivered to $\leq$0.35 cc of spinal cord in one, three, and five fractions, respectively. These recommendations are however not evidence based.

Spinal cord dose limits have been published by Sahgal et al. based on the updated analysis of nine cases of radiation myelopathy specific to spine SBRT and a dosimetric comparison to a multi-institutional control cohort. It was recommended that the point maximum thecal sac dose (typically equivalent to the true cord plus a 1.5 mm PRV) be constrained to 12.4 Gy in a single fraction, 17 Gy in two fractions, 20.3 Gy in three fractions, 23 Gy in four fractions, and 25.3 Gy in five fractions [72]. Using higher doses is a clinical decision in which tumor control is weighed against toxicity. The Memorial Sloan Kettering Cancer Center practice typically allows a maximum point dose up to 14 Gy within the true spinal cord (typically based on myelogram) in a single fraction. They recently published the largest analysis of single-fraction spinal cord dose limits in patients with no prior radiation, using a prospectively collected cohort of dose-volume histogram data, with the longest follow-up time (14.6 months). For 228 patients treated at 259 sites, the median spinal cord maximum point dose was 13.85 Gy. Radiation myelitis occurred in two patients with maximum point dose to the spinal cord of 13.43 and 13.63 Gy, and the authors conclude based on a model that the risk of radiation myelitis with 14 Gy in a single fraction is <1% [73].

GI Toxicity

Case reports and at least one retrospective series have reported gastrointestinal tract complications following SBRT. The most serious include perforation of the esophagus and small bowel. Cox et al. [74] reported the risk of esophageal toxicity following single-fraction SBRT in 182 patients and 204 spinal

segments. Given a median prescription dose of 24 Gy and median follow-up of 12 months, an incidence of acute and late esophageal toxicities of 15% and 12%, respectively, was reported. More specifically, the overall rate of grade 3 or higher late toxicity was 6.8%. In seven cases of grade 4 or higher toxicity, these were associated with radiation recall reactions with chemotherapy regimens such as gemcitabine or doxorubicin or occurred following procedures involving the esophagus. A volume of esophagus receiving 14 Gy or higher (V14) above 2.5 mL was associated with significantly higher toxicity, and the authors recommended maintaining a V14 of less than 2.5 mL as a planning dose constraint and a maximum point dose of 22 Gy or lower. Few reports of esophageal or bowel toxicity have been reported with more fractionated courses of spine SBRT, as fractionation likely mitigates the risk as compared with single-fraction SBRT.

In practice, the limitations published by the AAPM [71] are often used in order to respect normal tissue tolerance. Dose received by a previous radiation treatment has to be taken in consideration.

Toxicity Specific to Spine SBRT Following Previous Radiation

The most common acute side effects include grades 1–2 fatigue (up to 40%) and gastrointestinal effects (up to 10–20%; most often nausea, vomiting, diarrhea, and esophagitis). VCFs were reported in approximately 10% of patients. Serious late neurological effects have been observed, with one patient developing radiation myelopathy and one patient developing grade 3 neurological peripheral nerve toxicity. Although limited to grade 1–2 toxicity, 15 patients developed peripheral nerve injury manifesting as paresthesia and pain along the affected dermatome [75].

A multi-institutional international collaboration [76] led to the publication of reirradiation spinal cord dose limits for spine SBRT. The authors recommended limiting the cumulative nBED to <70 Gy 2/2 as determined by the thecal sac point dose maximum. Additional recommendations included a maximum SBRT nBED of 20–25 Gy 2/2 also determined by thecal sac point dose maximum, a minimum interval of 5 months before reirradiation, and a SBRT point maximum nBED to cumulative point maximum nBED ratio not exceeding 0.5. Table 46.6 summarizes reirradiation SBRT dose limits that satisfy the proposed criteria given common initial conventional EBRT practice.

Toxicity Specific to Postoperative Spine SBRT

The toxicities to adjacent OAR are fundamentally similar to those in patients treated with SBRT for intact metastases. Same spinal cord constraints are applied as de novo SBRT, and no radiation myelopathy has been reported in the limited literature so far. In the recently published consensus guidelines [19], common schemes according to the fractionation schedule and prior radiation doses are provided (Table 46.7).

Toxicities unique to the postoperative setting are wound dehiscence or infection, hardware failure, and VCF. Literature with respect to complications after either postoperative conventional EBRT or SBRT is limited. One series of patients with thyroid cancer managed with surgery with or without conventional EBRT or SBRT noted a 35% rate of postoperative complications [77]. Of 43 patients, 5 (11.6%) required

Table 46.6 Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional radiotherapy (nBED)	Single fraction: SBRT dose to thecal sac P_{max}	Two fractions: SBRT dose to thecal sac P_{max} (Gy)	Three fractions: SBRT dose to thecal sac P_{max} (Gy)	Four fractions: SBRT dose to thecal sac P_{max} (Gy)	Five fractions: SBRT dose to thecal sac P_{max} (Gy)
0	10 Gy	14.5	17.5	20	22
20 Gy in five fractions (30 $Gy_{2/2}$)	9 Gy	12.2	14.5	16.2	18
30 Gy in ten fractions (37.5 $Gy_{2/2}$)	9 Gy	12.2	14.5	16.2	18
37.5 Gy in 15 fractions (42 $Gy_{2/2}$)	9 Gy	12.2	14.5	16.2	18
40 Gy in 20 fractions (40 $Gy_{2/2}$)	N/A	12.2	14.5	16.2	18
45 Gy in 25 fractions (43 $Gy_{2/2}$)	N/A	12.2	14.5	16.2	18
50 Gy in 25 fractions (50 $Gy_{2/2}$)	N/A	11	12.5	14	15.5

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P_{max} dose to a point within the thecal sac that receives the maximum dose, *N/A* not applicable, *nBED* normalized biologically effective doses, *SBRT* stereotactic body radiotherapy

Table 46.7 Common spinal cord constraints that are applied to either true cord or a surrogate of the true cord (cord PRV or thecal sac) according to no prior and common prior radiation dose exposure

Prior conventional RT dose	Single fraction	Two fractions	Three fractions	Four fractions	Five fractions
No prior RT but cord compromise	10–14 Gy D_{max} 10 Gy to <10% cord[a]	17 Gy D_{max}	18–21 Gy D_{max}	23–26 Gy D_{max}	25–30 Gy D_{max}
No prior RT but cord compromise	8–14 Gy D_{max} 10 Gy to <10% cord[a]	17 Gy D_{max}	18–21 Gy D_{max}	23–26 Gy D_{max}	25–28 Gy D_{max}
800 cGy in single fraction	9 Gy D_{max}	12.2 Gy D_{max}	14–21 Gy D_{max}	16.2 Gy D_{max}	17.5–27.5 D_{max}
2000 cGy in five fractions	9–12 Gy D_{max}	12.2 Gy D_{max}	14–21 Gy D_{max}	16.2 Gy D_{max}	15–27.5 Gy D_{max}
3000 cGy in ten fractions	9–12 Gy D_{max}	12.2 Gy D_{max}	14–21 Gy D_{max}	16.2–24 Gy D_{max}	17.5–26 Gy D_{max}
4000 cGy in 20 fractions	9–12 Gy D_{max}	12.2 Gy D_{max}	14–21 Gy D_{max}	16.2 Gy D_{max}	12–25 Gy D_{max}
4500 cGy in 25 fractions	9–12 Gy D_{max}	12.2 Gy D_{max}	14–21 Gy D_{max}	16.2 Gy D_{max}	12–18 Gy D_{max}

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D_{max} maximum point dose
[a]The 10% criterion uses the spinal cord volume 5–6 mm above and below the target volume. Note that these constraints are intended as a summary of practice patterns of experienced spine specialists. However, these constraints are not data driven. They should be utilized with caution and may not be applicable to all clinical scenarios. Evidence-based constraints have been previously published by Sahgal et al. [72, 76]

revision surgery for wound dehiscence or infection. This rate is similar to that recently reported after postoperative conventional EBRT for MESCC (metastatic epidural spinal cord compression), where the overall surgical complication rate was 30% and the rate for risk of wound infection was 10% [78]. Similarly, another recently published article reports the development of wound infections requiring antibiotics postoperatively in 2 of 22 patients (9%) but no new or persistent wound infection after SBRT [79]. It is speculated that SBRT may reduce radiation-related surgical complications as the dose distribution is more conformal, allowing for selective wound sparing. However, it is also important to note that innovations in surgery such as minimally invasive techniques may reduce complications. This was reported in a small series by Massicotte et al. [80], where the time to SBRT after minimally invasive surgery was approximately 1 week. The incision was ≤2 cm, and no wound complications were noted.

It has been hypothesized that SBRT may reduce the rate of hardware failure, limiting the necessity for reoperation. The rationale is that all of the surgical hardware is not exposed to radiotherapy. Only three of the studies reviewed in Table 46.5 specified these data [22, 57, 58]. In aggregate, 6 of 287 patients (2.1%) required revision for hardware failure. This is comparable with the crude cumulative rate of 1.4% reported in the modern study limited to patients receiving conventional EBRT after spine surgery [78].

Similarly, it has been hypothesized that surgical instrumentation may reduce the risk of VCF compared with SBRT for intact vertebral bodies by stabilizing the vertebral column. The risk after SBRT for intact vertebral bodies is well established, ranging from 10% to 40% depending on the dose and fractionation schedule used [69, 70]. One study in Table 46.5 reported cases of VCF specifically in postoperative cases, with 9 of 80 patients (11.3%) having new or progressive loss of vertebral body height [22]. As such, preliminary data suggest that the presence of hardware does not mitigate this risk, although it remains unclear whether the need for intervention may be reduced because of the presence of hardware.

Optimal Dose and Fractionation

The total dose, fractionation, and method of prescribing vary significantly among the series in the summarized literature (Table 46.5). There are no dedicated phase I dose escalation studies, nor are there any randomized studies testing various SBRT dose schemes. Therefore, the optimal practice has not been well established and is a source of controversy.

Retrospective and prospective studies have examined single-fraction SBRT for spinal metastases with excellent local control of 88–90% in the selected literature presented in Table 46.5. Yamada et al. [9] from the Memorial Sloan Kettering Cancer Center analyzed their experience in which the SBRT dose was escalated over time and suggest greater rates of local control with a higher single-fraction total dose, up to 24 Gy in a single fraction.

However, Garg et al. [48] from the MD Anderson Cancer Center described significant neurological toxicity in their series of spinal metastases treated with single-fraction SBRT including two cases of grade 3 or greater neurologic sequelae, specifically hemicord syndrome and foot drop from radiculopathy.

Also, VCF is more commonly reported after high-dose single-fraction SBRT versus fractionated SBRT. This dose-complication relationship is evident; with 24 Gy in a single fraction, the rate of VCF approaches 40%, but it is approximately 20% with 20–23 Gy/fraction and 10% with less than 20 Gy/fraction [70].

Pain flare was also reported to be more frequent with single-fraction spine SBRT. As a matter of fact, recent data of prospective spine SBRT studies found that the only significant predictor of the risk of pain flare was the number of

fractions. In this study, 34% of patients treated with single-fraction spine SBRT experienced this adverse event compared with 20% of patients receiving three fractions and 8% of patients receiving five fractions [67].

At present, there are no prospective randomized studies comparing outcomes following single-fraction versus multiple-fraction spine SBRT. A single retrospective series compared outcomes in 195 spine lesions treated with single session SBRT and 153 lesions treated with multiple sessions of SBRT. The mean doses were 16.3 Gy in one fraction, 20.6 Gy in three fractions, 23.8 Gy in four fractions, and 24.5 Gy in five fractions. This study found that although pain control was significantly improved in patients receiving a single fraction, local control at up to 2 years following treatment was significantly better in patients treated with multiple fractions (96% vs. 70%) [81]. Similarly, the need for retreatment was significantly lower in patients receiving multiple-fraction therapy than following single-fraction treatment. These preliminary data are inconclusive, and future prospective studies will be necessary to evaluate the proposed hypothesis that single-fraction radiosurgery may improve short-term pain control, while fractionated radiosurgery may lead to more durable control with decreased need for retreatment and decreased risk of toxicities including VCF, pain flare, and radiation-induced spinal cord myelopathy.

Since effective prescription doses include 18–24 Gy in a single fraction, 24 Gy in two fractions, 24–30 Gy in three fractions, and 25–40 Gy in five fractions, individual fractionation regimens need to be prescribed on the basis of previous radiation, proximity of the target to the OAR, and volume of the target. Single-fraction SBRT could be considered in selected patients with radioresistant tumors and life expectancies of less than a year and when the main goal of treatment is pain control. Patients to be treated with single-fraction SBRT should have at least 2–3 mm gap between the spinal metastasis and the cord and no risk factors predisposing the patient to vertebral compression fracture, and the treating center should have the appropriate technical capability, expertise, and experience with planning and delivery of single-fraction SBRT [11]. Fractionated SBRT may hold a particular advantage in cases of large or circumferential tumors, in the postoperative setting, or in cases of reirradiation [82].

For previously irradiated cases, the most common practice after initial conventional EBRT has been to prescribe a total dose in the range of 24–35 Gy delivered in two to five fractions. Of note, no dose-response relationship has been clearly demonstrated [75].

In the postoperative setting, there is data suggesting that higher-dose-per-fraction SBRT may be associated with greater rates of local control as compared with lower doses per fraction. The largest series to date from Laufer et al. [58] recently reported on 168 patients after separation surgery, stabilization, and adjuvant postoperative spine SBRT. SBRT was either delivered as 24 Gy in single fraction, hypofractionated with 24–30 Gy in three fractions (high dose), or hypofractionated with 18–36 Gy in five to six fractions (lower dose). Local control at 1 year was 83.6%, and dose was the only predictor of local control. There was a significant improvement in local control with high-dose single-fraction SBRT and high-dose hypofractionated treatment associated with a 9% and 4.1% risk of local progression, respectively, at 1 year. This is compared with 22.6% in patients receiving lower-dose hypofractionated treatment. The series from Al-Omair et al. [22] also reported that dose per fraction may be a predictive factor, with patients receiving 18–26 Gy in one to two fractions having better control rates than those receiving lower-dose-per-fraction regimens of 18–40 Gy over three to five fractions.

Possible dose and fractionation schemes for postoperative spine SBRT include the following: 16–24 in single fraction, 24 Gy in two fractions, 24–30 Gy in three fractions, 30–32 Gy in four fractions, and 30–40 Gy in five fractions [19].

Some practitioners use an integrated boost to areas of residual tumor. Simultaneous integrated boost doses to the GTV are 16–22 Gy in a single fraction for patients with radiosensitive tumors and 18–25 Gy in a single fraction or 50 Gy in five fractions for patients with radioresistant tumors [19].

The optimal timing of postoperative SBRT is largely unknown, but the commonly used is the 4-week postoperative mark [6, 22, 58].

Special Circumstance: Concurrent Spine SBRT with Targeted Therapy

Concerning molecular targeted therapy, tyrosine kinase inhibitors have been shown to potentiate the response to radiotherapy in animal and in vitro models [83]. However, little is known about the combination of molecular targeted therapy and SBRT in terms of toxicity and local tumor control in patients with advanced disease. Few clinical data are emerging concerning safety and efficacy of concurrent spine SBRT and molecular targeted therapy. Three retrospective series reporting spinal metastatic lesions from RCC treated with SBRT and targeted molecular treatments showed promising outcome and acceptable toxicity [84–86].

Although data is limited, fatal toxicities have been observed with combination of SBRT and targeted molecular therapy. Especially with anti-angiogenic therapy, ischemic bowel complication including perforation, tracheoesophageal fistula, and surgical complications have been reported [87, 88]. Therefore, caution must be used in combination of these two therapeutic approaches. No clear recommendation exists concerning the timing between this systemic modality and SBRT.

Cost-Effectiveness

Kim et al. [89] performed a cost-effectiveness analysis to compare single fraction of SBRT and single fraction of conventional EBRT for palliation of vertebral bone metastases. They concluded that selective SBRT used in patients with longer expected survival (11 months and more) might be the most cost-effective approach. Bijlani et al. [90] described and synthesized stereotactic radiosurgery (SRS) and SBRT cost-effectiveness research across several common SRS and SBRT applications including for spinal metastases. He concluded that, from a patient perspective, SRS and SBRT provide patients effective treatment option, while from the payer and provider perspective, SRS and SRT demonstrate cost savings.

Treatment Surveillance and Follow-Up

Prior to treatment, it is essential that the treatment plan undergo strict quality assurance (QA) testing, in accordance with national and international guidelines [5, 11, 71]. Such QA tests include multidisciplinary peer review, physics QA, and pretreatment patient-specific dose measurements. For treatment delivery, online image guidance is critical to ensure the most accurate patient positioning. Image guidance is often based on cone-beam CT (CBCT) for most systems, but near-continuous stereoscopic imaging is also commonly used. Regardless of imaging technique, the entire target volume must be visualized in the field of view. Strict thresholds for repositioning tolerance are demanded because of the close proximity of the spinal cord to the steep dose gradient. For CBCT-based systems, if the treatment time is protracted over more than 15–20 min, it has also been demonstrated that a mid-treatment CBCT serves to correct for intra-fraction motion [91].

As recommended by the SPINO group, spine MRI should be done every 2–3 months after SBRT for the first 12–18 months and every 3–6 months thereafter [12].

Ongoing Studies

Prospective randomized trials are few and still underway. RTOG 0631 is a phase III trial comparing conventional EBRT of 8 Gy in single fraction to SBRT of 16–18 Gy in single fraction (https://clinicaltrials.gov/ct2/show/NCT00922974), and the Canadian SC24 is a phase II randomized trial comparing conventional EBRT of 20 Gy in five fractions to 24 Gy in two fractions of SBRT (https://clinicaltrials.gov/ct2/show/NCT02512965). The Canadian SC24 trial has recently been converted to a phase III trial. A prospective randomized phase III trial at MSKCC in New York compares 24 Gy in a single fraction versus three sessions of 9 Gy (total 27 Gy) in effecting durable local control in oligometastatic tumors, including oligometastatic spine disease (MSKCC 10–154).

Clinical Case Discussion

A 63-year-old patient was referred for an oligometastatic lesion at T8 level. She had a history of breast cancer, stage III, ER/PR+, diagnosed 5 years prior. After being treated with mastectomy and axillary dissection, she underwent chemotherapy and radiotherapy to the breast and lymph nodes and was prescribed hormonotherapy.

She presented with a history of back pain without any neurological symptoms. Bone scan was performed and confirmed the presence of a solitary lesion at T8. A pet scan did not show any evidence of other distant metastases. The presence of the bone lesion in the vertebral body of T8 was confirmed by a MRI (Fig. 46.4) of the spine. Involvement of the right pedicle, lamina, and proximal right transverse process was noted. Epidural disease was present (Bilsky grade 1c); SINS score was evaluated at 5.

In order to maximize local control, the patient was assessed for minimally invasive spinal surgery and underwent resection of the epidural disease. Postoperative MRI did not show any residual disease in the thecal sac (Fig. 46.5).

Patient underwent SBRT treatment after surgery (Fig. 46.6). She received a dose of 24 Gy in two fractions of 12 Gy (Fig. 46.7) using arc therapy. Maximum point dose (D_{max}) received by the spine PRV was 17 Gy and by the esophagus 20 Gy.

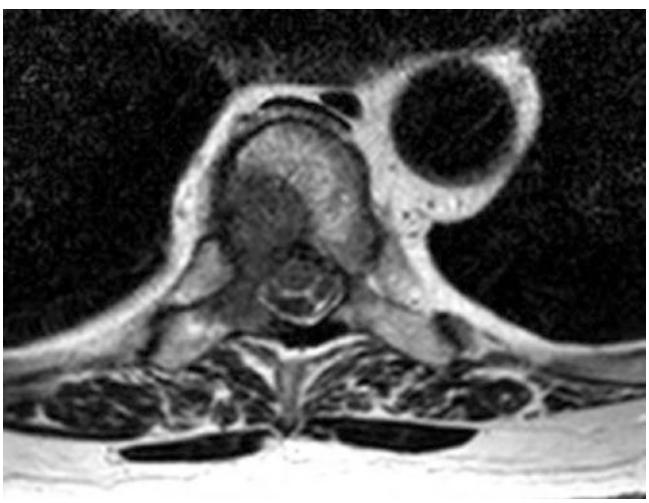

Fig. 46.4 Preoperative MRI, showing epidural disease, Bilsky grade 1c

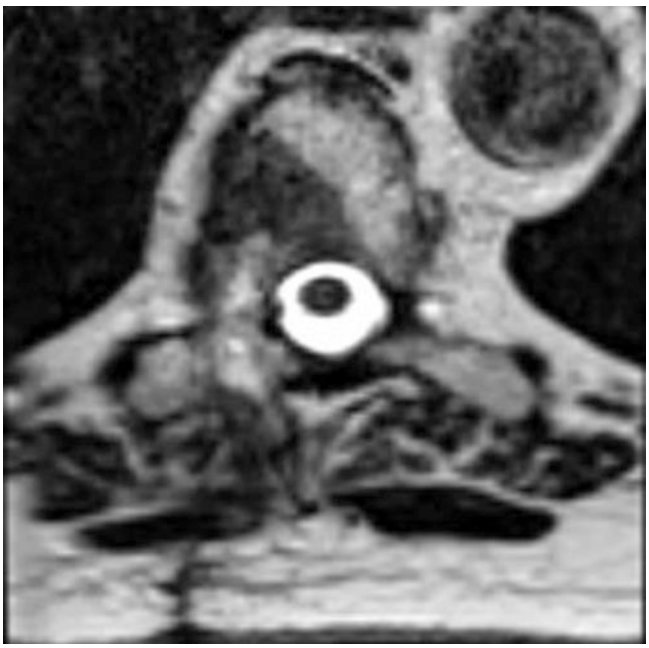

Fig. 46.5 Postoperative MRI

Summary

- Recent technical advances in the entire radiotherapy process, including immobilization, planning imaging with MRI, and image-guidance radiotherapy, are critical to achieve the level of precision required for spine SBRT treatment.
- Guidelines have been published for target volume definition in spine SBRT. In the postoperative setting, a consensus contouring guidelines has also been proposed.
- In general, patients considered appropriate for spine SBRT have a spinal or paraspinal metastasis from a solid tumor histology in three or less contiguous segments, SINS score revealing a stable or minimally unstable spinal column, low-grade epidural disease, life expectancy of at least 3 months, and a relatively limited systemic disease burden.
- In the postoperative setting, treatment indications included radioresistant primary, 1–2 levels of adjacent disease, and previous radiotherapy. Contraindications include involve-

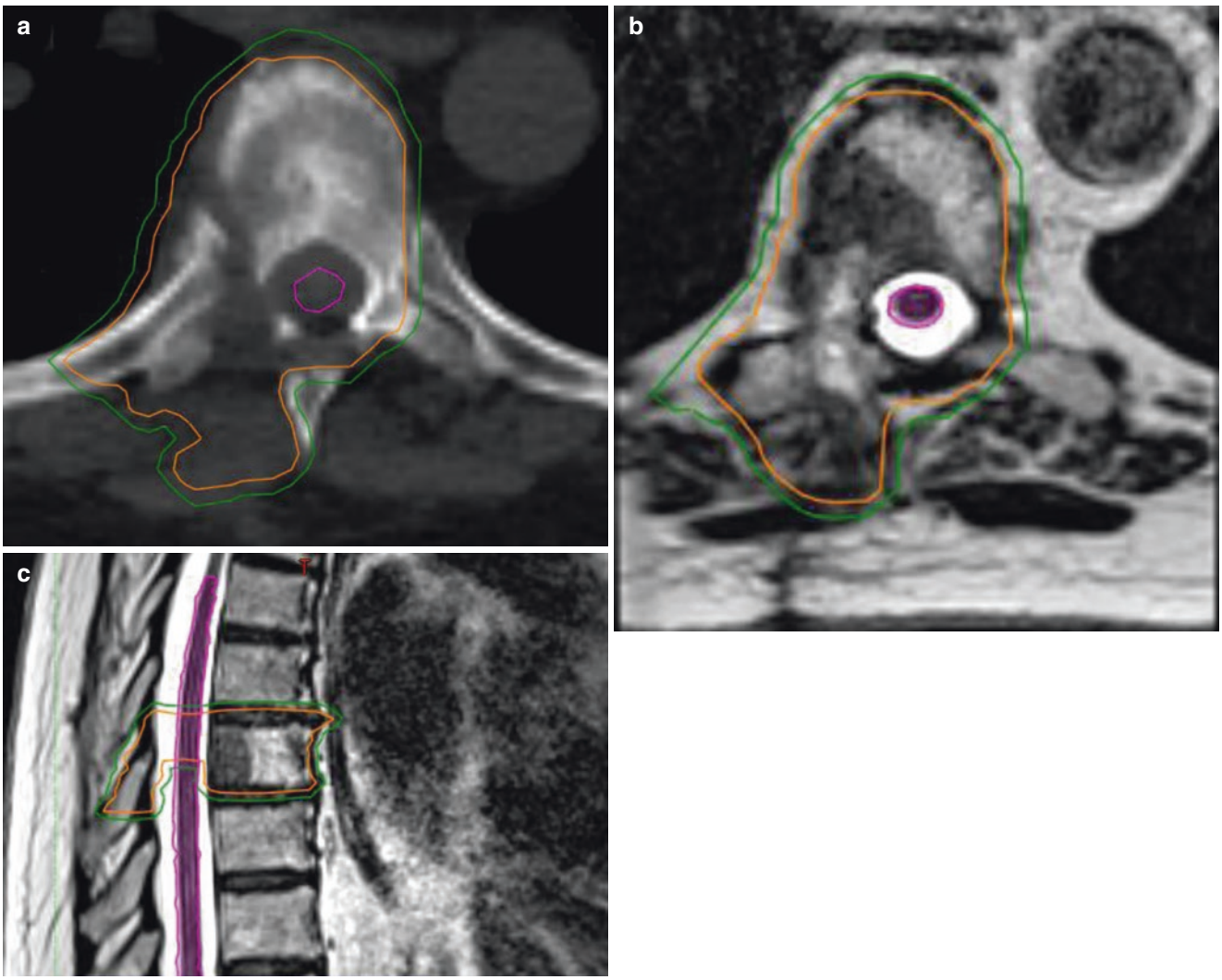

Fig. 46.6 Axial view of CT scan (**a**), axial view (**b**), and sagittal view of planning MRI (**c**) with CTV, PTV, and spinal cord contoured

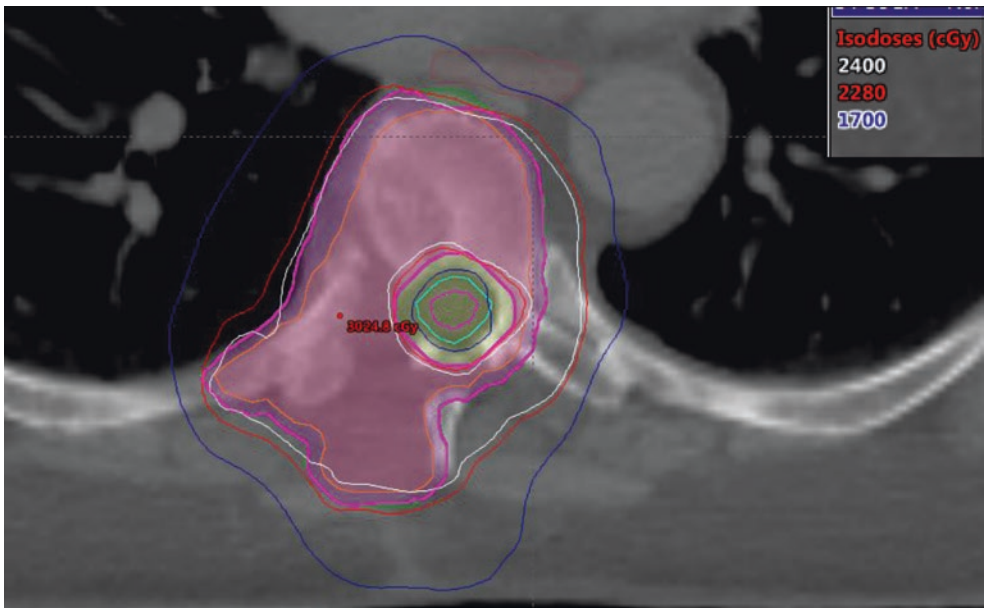

Fig. 46.7 Treatment administered by arc therapy

ment of more than three contiguous vertebral bodies, ASIA grade A status, and postoperative Bilsky grade 3 residual.

- Local progression is defined as gross unequivocal increase in tumor volume or linear dimension, any new or progressive tumor within the epidural space, or neurological deterioration attributable to preexisting epidural disease with equivocal increased epidural disease dimension on MRI.
- Several retrospective series and few prospective studies have reported excellent local tumor control rates (ranging from 80% to 90%). Spine SBRT is also associated with good pain control.
- Failure in the epidural space is the most common pattern of recurrence following spine SBRT occurring in more than half of recurrences.
- Vertebral body compression fracture after spine SBRT is a common adverse effect following SBRT with rates of 10–40%.
- Radiation myelopathy is generally the most feared complication of spine SBRT. Evidence-based dose-constraint guidelines have been published to guide spine SBRT in the setting of both no prior irradiation and prior conventional EBRT of the spinal cord.
- Effective prescription doses include 18–24 Gy in a single fraction, 24 Gy in two fractions, 24–30 Gy in three fractions, and 25–40 Gy in five fractions. Individual fractionation regimens need to be prescribed according to the presence of previous radiation, proximity of the target to the organs at risk, and volume of the target.
- For previously irradiated cases, the most common practice after initial conventional EBRT has been to fractionate treatment, with a total dose in the range of 24–35 Gy delivered in three to five fractions.
- Possible dose and fractionation schemes for postoperative spine SBRT include the following: 16–24 Gy in single fraction, 24 Gy in two fractions, 24–30 Gy in three fractions, 30–32 Gy in four fractions, and 30–40 Gy in five fractions.
- MRI is the recommended imaging modality for assessment of tumor response following spine SBRT. Follow-up spine MRI should be done every 2–3 months after SBRT for the first 12–18 months and every 3–6 months thereafter.

Self-Assessment Questions

1. What is the essential condition for the safe administration of stereotactic body radiotherapy (SBRT) treatment delivery?
   A. Correct volume definition
   B. Image guidance
   C. Correct patient immobilization
   D. All of the above

2. In terms of SBRT doses, higher doses:
   A. Seem to yield better local control results for all patients
   B. Seem to yield better overall survival for all patients
   C. None of the above

3. Recurrence after irradiation occurs most often in:
   A. Paraspinal tissue
   B. Epidural space
   C. Adjacent vertebra

4. Overall survival of patients is influenced by:
   A. Patient Karnofsky Performance Status
   B. Time to reirradiation
   C. Radiosensitive histology
   D. All of the above

5. The risk of vertebral compression fracture depends on:
   A. Dose per fraction
   B. Prior treatment with radiotherapy
   C. Tumor histology

Answers

1. D
2. C
3. B
4. A
5. A

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