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Stereotactic Body Radiotherapy for Spinal Metastases:

What are the Risks and How Do We Minimize Them?

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Abstract

Study Design—Systematic literature review.

Objectives—To summarize the risks of 3 key complications of stereotactic body radiotherapy (SBRT) for spinal metastases, that is, radiation myelopathy (RM), vertebral compression fracture (VCF), and epidural disease progression, and to discuss strategies for minimizing them.

Summary of Background Data—RM, VCF and epidural disease progression are now recognized as important risks following SBRT for spine metastases. It is unclear at this stage exactly how large these risks are and what strategies can be employed to minimize these risks.

Methods—A systematic review of the literature using MEDLINE and a review of the bibliographies of reviewed articles on SBRT for spinal metastases were conducted.

Results—The initial literature search revealed a total of 376 articles, of which 38 were pertinent to the study objectives. The risk of RM following SBRT was found to be dependent on the maximum dose to the spinal cord and estimated to be <5% if the recommended published thecal sac dose constraints are adhered to. The crude risk of VCF was 13.7% (range: 0.7%–40.5%), and, on average, 45% were surgically salvaged. It has been shown that the risk of VCF is dependent on several anatomic and tumor-related factors including the SBRT dose per fraction. The crude risk of local failure at 1 year was 21.4% (range: 12%–27%) of which 67% (range: 38%–96%) occurred within the epidural space. The grade of epidural disease has been shown to be associated with the risk of local failure.

Conclusion—The risk of RM after spinal SBRT is low in particular if recommended dose metrics are adhered to. There is a significant risk of both VCF and epidural disease progression after spinal SBRT. These risks can potentially be minimized by identifying the risk factors for these complications, and performing careful radiotherapy and surgical planning.

Keywords

epidural disease; myelopathy; spine; stereotactic body radiotherapy; vertebral compression fracture

The treatment of spinal metastases is generally aimed at alleviating pain and preserving or restoring neurological function. Following low-dose conventional external beam palliative radiotherapy (cEBRT),¹ several randomized trials and meta-analyses have confirmed complete and overall pain response rates ranging from ~10% to 30% and 50% to 70%, respectively.²

With advanced radiation technology, we are now able to treat spinal metastases with millimetric precision and deliver ablative tumor doses while differentially sparing the adjacent spinal cord to a lower dose exposure. The technique is known as stereotactic body radiotherapy (SBRT) and refers to the delivery of radiotherapy doses that are considered curative in only 1 to 5 fractions. SBRT requires sophisticated technology that allows for highly conformal dose distributions with steep dose gradients.³ These technologies include three-dimensional image-guidance on-board solutions, six degrees-of-freedom (6-DOF) positioning corrections, and integration of magnetic resonance imaging (MRI) for target and organ-at-risk delineation.³ The doses inherent to SBRT, which range from 16 to 24 Gy in 1 fraction, 24 to 27 Gy in 2 to 3 fractions, 30 Gy in 4 fractions, and 30 to 50 Gy in 5 fractions, are typically 3 to 10 times more biologically effective than typical cEBRT practice. The rationale for delivering such doses is to improve upon the low rates of complete pain response and local control observed following cEBRT.

Following the initial systematic review by the Spine Oncology Study Group,⁴ several mature single institution spine SBRT outcomes and multi-institutional studies have been reported. Although the data do suggest greater rates of local control and pain control than otherwise expected with cEBRT, no randomized trials have been completed to date. Importantly, unique adverse outcomes have been observed with spine SBRT such as radiation myelopathy (RM), vertebral compression fracture (VCF), and local recurrence in the epidural space. The aim of this systematic review is to address three specific questions as they pertain to spine SBRT:

1. What is the risk of RM after SBRT for spinal meta-stases, and how do we minimize it?
2. What is the risk of VCF after SBRT for spinal meta-stases and how do we minimize it?
3. What is the risk of epidural disease progression after SBRT for spinal metastases and how do we minimize it?

Materials and Methods

A systematic literature search for clinical outcomes following SBRT for spinal metastases was undertaken. The search was limited to data published from 1996 (to limit data to modern treatment techniques) to 2016 (January). A search on MEDLINE was performed using the keywords “spinal neoplasms,” “spine metastasis,” “radiosurgery,” “stereo-tactic body radiotherapy,” and “radiotherapy, intensity-modulated.” Abstracts were reviewed to identify articles that potentially contained information that could answer the study questions. Full manuscripts were then obtained and analyzed. References from each article were also included in the review. The quality of evidence of the literature was then scored as high, moderate, low, or very low (by JHC and AS) based on the GRADE criteria.⁵ The flow diagram showing the selection process of articles as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines is shown in Figure 1.⁶ Recommendations were then made based on consensus opinion according to GRADE criteria⁷ (Box 1).

Results

A total of 376 studies were identified on an initial search. Studies were restricted to SBRT delivered in one to five fractions for spinal metastases. Case reports or articles describing <10 patients were excluded.

Radiation Myelopathy

Studies reporting spine SBRT outcomes were included if dosimetric data specific to the spinal cord (or a specified surrogate) were reported. Studies were excluded if the dosimetric data for the spinal cord included the cauda equina, or if de novo (no prior radiation) SBRT dosimetric data and outcomes could not be segregated from re-irradiation cohorts. Seven relevant studies were identified for this question^{8,9,22,24–27} (Supplemental Digital Content, Table 1, <http://links.lww.com/BRS/B197>). Two studies were specific to patients who received de novo SBRT, 3 studies were specific to patients who received SBRT as re-irradiation, and 2 studies included both de novo and re-irradiation SBRT with the data segregated. Two studies were well-done observational studies with control groups and graded “low” per GRADE criteria,⁵ and all others were graded as “very low.” Because a variety of different doses and fractionation schedules were used in the different studies, we chose to use the linear-quadratic model (assuming a spinal cord α/β value of 2 Gy) to normalize the dose into the equivalent dose in 2-Gy fractions (EQD2).⁸

Based on the summarized series in Supplemental Digital Content, Table 1, <http://links.lww.com/BRS/B197>, among the non-RM cohorts treated with de novo SBRT, the median EQD2 maximum dose (Dmax) within the contoured spinal cord volume was 37.8 Gy (range: 28–48.7 Gy). This is in contrast to the RM cohort, which was exposed to a greater median EQD2 Dmax of 73.69 Gy. Among the non-RM cohorts treated with re-irradiation SBRT, the median cumulative EQD2 Dmax was 64.8 Gy (range: 41.5–83.4 Gy), as compared to a median of 99.6 Gy (mean 105.8 Gy) in the RM cohort.

Two studies^{8,9} provided specific calculations for the estimated risks of RM in patients with and without previous radiation exposure. Both of these studies used the thecal sac as a surrogate for the spinal cord (which is typically equivalent to the spinal cord plus a 1.5-mm planning organ at risk [PRV] margin) and normalized the dose using the EQD2 formalism.

In de novo patients, dosimetric data for a cohort of nine patients with RM were compared to a control cohort of 66 patients without RM.⁸ The median thecal sac EQD2 Dmax was 35.69 Gy in the control group and 73.69 Gy in the RM group. The authors derived a model based on a logistic regression analysis, and reported that to maintain a risk of RM of 5%, the thecal sac EQD2 Dmax should be restricted to 44.6 Gy. The thecal sac Dmax equivalent doses in one to five fractions specific to de novo SBRT are listed in Supplemental Digital Content, Table 2, <http://links.lww.com/BRS/B197>, and serve as a safe guideline to follow for spinal cord tolerance.

Sahgal et al⁹ also compared dosimetric data for a cohort of five patients with RM and previous radiation exposure, to a control cohort of 13 patients who did not develop RM and re-irradiated with SBRT. The mean thecal sac EQD2 Dmax for the SBRT re-irradiation control cohort was 20.0 Gy (95% confidence interval [CI]: 10.8–29.2), and 67.4 Gy (95% CI: 51.0–83.9) in the RM group. The mean cumulative EQD2 Dmax was 62.3 Gy (95% CI: 50.3–74.3) in the control group, and 105.8 Gy (95% CI: 84.3–127.4) in the RM group. The minimum time interval between initial radiotherapy and re-irradiation in the control group was 5 months. A thecal sac EQD2 Dmax of 25 Gy and a cumulative EQD2 Dmax of 70 Gy were recommended for safe practice based on these findings when re-irradiating with SBRT. The thecal sac Dmax equivalent doses in one to five fractions specific to re-irradiation SBRT are listed in Supplemental Digital Content, Table 2, <http://links.lww.com/BRS/B197>.

Vertebral Compression Fracture

Studies investigating the risk of VCF were included if the incidence of VCF was specified in the series. It was not assumed to be zero if the authors did not state in the Materials and Methods or Results section that VCF was a specific outcome reviewed. This limited the number of relevant studies to 24^{10,12,22,26,28–47} (Supplemental Digital Content, Table 3, <http://links.lww.com/BRS/B197>). Cases of VCF were not included if they occurred in the setting of tumor progression. Patients who received previous surgical stabilization were not included in the total number of treated patients.

All studies were either prospective or retrospective series, none of which had control arms. Therefore, all studies were graded as very low as per GRADE criteria.⁵ Three were prospective cohort studies or phase 1 to 2 clinical trials. Twenty-one studies were retrospective analyses. Seven articles described single fraction SBRT protocols (median 20 Gy, range 15–24 Gy), 3 articles described multifraction SBRT protocols (median 26.4 Gy, range 24–27 Gy in 3 fractions), and the rest used a mixture of fractionation schedules (range, 8–40 Gy in 1–5 fractions). Several institutions published cumulative series based on prolonged follow-up and our approach was to include the most recent report. Seven studies were specific to VCF, analyzing for predictive factors. The remaining studies listed VCF as one of the secondary endpoints without a predictive analysis.

The incidence of VCF was observed to range from 0.7% to 40.5% and the reviewed studies are summarized in Supplemental Digital Content, Table 3, <http://link-s.lww.com/BRS/B197>. Excluding those studies that may have included overlapping patients, the overall risk of VCF was 13.7%. The median time from SBRT to VCF ranged from 1.5 to 25.7 months, and the median of reported medians was 3.3 months. The crude rate of salvage interventions performed in those developing VCF was 45%, of which 50% underwent cement augmentation, 2% percutaneous instrumentation, and 48% decompression and reconstruction.

Epidural Disease Progression

Studies investigating the risk of epidural disease progression were included if they reported the local failure rate (usually defined as failures within or immediately adjacent to the planning target volume), and the incidence of epidural progression following SBRT. This limited the number of relevant studies to 11^{19,21,23,25,29,48–53} (Supplemental Digital Content, Table 4, <http://links.lww.com/BRS/B197>). All studies were either prospective or retrospective series, none of which had control arms. Therefore, all studies were graded “very low” as per GRADE criteria.⁵ Two were prospective cohort studies or phase 1 to 2 clinical trials and nine were retrospective analyses. Several institutions published consecutive cumulative series based on prolonged follow-up, and our approach was to include the most recent report. Five of these articles specifically analyzed for factors that could predict local control. The overall rate of local failure at 1 year was 21.4% (range: 12%–27%). Progression within the epidural compartment was the most common pattern of failure. The overall risk of epidural disease progression was 67% (range: 38%–96%) among local failures.

Discussion

Radiation Myelopathy

Although an initial bolus of complications was observed early in the development of spine SBRT, RM is now regarded as low risk, rare, and should not be a barrier to treatment with SBRT. Likely explanations for initial cases include a lack of understanding of the tolerance of the spinal cord to high dose per fraction SBRT, animal data suggesting potential partial volume tolerance such that small volumes like a point maximum could tolerate much greater doses than otherwise considered safe, variability in the technique with respect to cord delineation, technical migration to more sophisticated technologies of the present, and a lack of understanding of the effect of translational and rotational motions on spinal cord dosimetry. With respect to the latter, for example, Wang et al¹¹ showed that a 2-mm translational error in any direction can result in >5% tumor coverage loss and >25% maximal dose increase to the spinal cord. Ultimately, modern spine SBRT is now a well-defined technique with recommended technical standards for safe practice.

Recommendation 1—Clinicians should apply a strict technical protocol involving near-rigid body immobilization, robotic linear accelerator delivery or sub-centimeter multi-leaf collimator-based linear accelerator delivery, intra-fraction 3D based image-guidance, and 6-DOF repositioning for robust spine SBRT practice.

- Strong recommendation
- Very-low-quality evidence

More recently, owing to a pooled detailed dosimetric analysis of all known RM cases with a comparison to controls, there have been tolerance thresholds for the spinal cord suggested by Sahgal et al for safe practice, and for both de novo and re-irradiation spine SBRT.^{8,9} In reviewing the literature (Supplemental Digital Content, Table 1, <http://links.lww.com/BRS/B197>), it is observed that the majority of practice do indeed fall within those recommended tolerance data. Therefore, in addressing the question of how to minimize the risk of RM, adherence to the Sahgal guidelines (Supplemental Digital Content, Table 2, <http://links.lww.com/BRS/B197>) is a reasonable benchmark for safe practice such that the risk of RM can be kept well below 5%.^{8,9}

Recommendation 2—Clinicians might limit the Dmax to the thecal sac (as a surrogate structure for the spinal cord) for de novo SBRT to an EQD2 of 44.6 Gy.

- Weak recommendation
- Low-quality evidence

Recommendation 3—Clinicians might limit the Dmax to the thecal sac (as a surrogate structure for the spinal cord) for re-irradiation SBRT to an EQD2 of 25 Gy while respecting a cumulative EDQ2 of 70 Gy. The minimum time interval between courses of 5 months is ideal.

- Weak recommendation
- Low-quality evidence

Vertebral Compression Fracture

With the advent of spine SBRT, we are now in an era where routine surveillance of vertebral metastases post-treatment is typically practiced with MRI/CT. We observed a 13.7% (range: 0.7%–40.5%) aggregate risk of VCF. What is not known is whether this high risk of VCF is because of patient selection, or an independent effect of SBRT.

Given that the median time to VCF is typically within months post-SBRT (median, 3.3 months), VCF can be considered an acute to subacute toxicity. However, VCF can also occur much later during follow-up. For example, the median time to VCF was 25 months in the series by Rose et al,¹² reporting a 39% risk of VCF following 18 to 24 Gy in one fraction. This variation in time to VCF may reflect heterogeneity in patient selection. Furthermore, the practice of performing a prophylactic intervention is largely surgeon dependent and, as a result, the patient population within these studies may be dramatically different. Therefore, a center that practiced early stabilization or even prophylactic intervention may be reporting late events rather than early events. Based on this observation of both early and late events, we postulate that there are 2 distinct mechanisms explaining post-SBRT VCF.

The early-onset VCF is likely because of the enhanced biologic effects inherent to SBRT whereby an intense inflammatory and necrotic reaction is induced that destabilizes the

capacity of the vertebral body to withstand the mechanical load, manifesting as VCF. The association of single-fraction SBRT (versus multifraction) with greater pain flare rates,¹³ and emerging evidence of early-onset pseudoprogession¹⁴ are clinical surrogates confirming an early intense inflammatory reaction. Alternatively, we postulate that late-onset VCF is because of the slow induction of necrosis yielding damage to the vertebral body boney and cartilaginous structure that eventually compromises the capacity of the vertebral body to withstand the mechanical load, manifesting as VCF. Al-Omair et al¹⁵ reported on such a case where imaging showed changes suggestive of tumor progression; however, biopsy showed radiation-induced necrosis and fibrosis.

One of the studies reviewed was a pooled multi-institutional analysis of 410 spinal segments treated with SBRT, specifically assessing factors that could potentially be predictive of VCF. 10 Multivariate analysis identified the following factors as significant predictors of VCF: dose per fraction (the risks of VCF for doses per fraction of 24 Gy, 20–23 Gy, and 19 Gy, were 40%, 20%, and 10%, respectively), baseline VCF, lytic tumor, and spinal malalignment.

Recommendation 1—Clinicians might evaluate patients for stabilization prior to SBRT if the following risk factors are observed: baseline VCF, significant lytic tumor burden, spinal malalignment, SINS score indicating potentially or frankly unstable spine, mechanical pain, and/or planned SBRT with 20 Gy per fraction.

- Weak recommendation
- Very-low-quality evidence

The optimal management of SBRT-induced VCF is unknown. Our analysis determined a crude rate of salvage interventions of 45%. However, some series reported a low rate of salvage procedures despite high rates of VCF, whereas others reported the opposite, highlighting the issue of potential bias in the current data. The use and choice of salvage surgical procedures is dependent on several factors including the individual surgeon's judgment, patient preference, multiple competing oncologic priorities, and shifts in goals of therapy to hospice versus active management that may preclude aggressive salvage. Prospective studies are required to investigate these issues further.

Lastly, the optimal strategy for prophylactic stabilization is unknown, as it relates to the timing of SBRT. Gerszten et al¹⁶ performed cement augmentation before SBRT for patients with a baseline VCF, and reported high rates of pain control and local control. However, there may be disadvantages to this approach, as these procedures do place the patient at a small risk of cement extravasation.^{17,18} Newer techniques like percutaneous instrumentation may mitigate these risks, but do represent an escalation on the invasive-ness scale of spine surgeries. The choice of who needs prophylactic stabilization is still surgeon-dependent, and we do not have a robust evidence-based method to stratify patients to SBRT followed by salvage intervention if fracture/symptoms persist/progress, versus upfront stabilization followed by SBRT. Therefore, at this time, no evidence-based recommendation can be made as to which patients should be prophylactically stabilized.

Epidural Disease Progression

This systematic review showed a high rate of epidural disease progression, comprising 67% (range: 38%–96%) of local failures. This observation may be secondary to the relative underdosing of the epidural space to respect spinal cord tolerance. Ultimately, the spinal cord is spared the high dose exposure relative to the prescribed dose. There are data to support higher doses as a means to reduce the risk of local failure. For example, Choi et al¹⁹ reported superior local control rates when the prescribed dose was greater than a single session equivalent dose of 15 Gy. Bishop et al²⁰ reported an association with better local control when the minimum dose in the gross target volume was at least a biologically effective dose (BED) of 33.4 Gy. Whether or not the choice of fractionation scheme can enhance local control is also debatable, and some have reported an association with more favorable local control rates with high-dose per fraction regimens such as 18 to 24 Gy in 1 to 2 fractions, as compared to more fractionated approaches.²¹ These dose-based data were not specific to the epidural space; therefore, at this time, there are insufficient data and quality of evidence to recommend one prescription practice over another, or even dosimetric criteria, to mitigate the risk of local failure. Importantly, in none of the series reviewed has the spinal cord dose exposed been a factor related to local control. Therefore, we can only recommend the principle of maintaining the spinal cord (or surrogate contour) dose exposure to the threshold of safety, and not unnecessarily underdose the epidural space.

Recommendation 1—The spinal cord (or surrogate contour) dose should be maximized to the prespecified safe limits such that the dose within the epidural space is maximized in particular when baseline epidural disease is present.

- Strong recommendation
- Very-low-quality evidence

Studies have shown that tumor within the epidural space is predictive of local failure.^{21,22} If high-grade epidural disease is present at the time of SBRT, then the risk of subsequent progression is increased. This may relate to both a biologic aggressiveness factor given the disease manifested with epidural disease, dose exposure within the epidural space, or both. Al-Omair et al²¹ observed that when high-grade epidural disease (Bilsky 2 or 3) was downgraded to a Bilsky 0 or 1 versus a 2, the rates of local control improved. In their series, the spinal cord dose was not a predictive factor—only the dose-prescribed and postoperative Bilsky grade were predictive. The association with high-grade epidural disease and local control resulted in the authors arguing for aggressive management of epidural disease as a means to mitigate the risk of progression. Surgical strategies will be reviewed in a subsequent article in this series. Ultimately, at this time, we cannot make a strong recommendation to preferably resect high-grade epidural disease. However, consideration can now be made with these data to consider it as a means to improve upon local control post-SBRT.

Recommendation 2—Clinicians might surgically debulk asymptomatic high-grade epidural disease (Bilsky 2 or 3) before SBRT to optimize local control.

- Weak recommendation

- Very-low-quality evidence

Lastly, the issue of conformality may explain this pattern of failure. Spine SBRT is designed not to prophylactically treat the entire epidural space as is practiced with cEBRT. Although the series reporting on patterns of failure have not described marginal miss beyond the baseline epidural disease in the target volume as a risk factor, this is a point of caution. The optimal margin for covering microscopic disease extension beyond epidural disease is currently unknown. In the postoperative series by Chan et al wherein the relationship between preoperative epidural disease location and postoperative epidural disease location was analyzed, the preoperative disease location was a predictor of subsequent failure. Therefore, this implies that when performing postoperative SBRT, careful attention should be paid to preoperative imaging to encompass all areas of potential microscopic residual disease. In intact metastases, we do not have a similar thorough analysis of epidural disease location and site of progression. Therefore, we can only recommend in the postoperative indication to treat any area of epidural involvement present on the preoperative MRI.

Recommendation 3—In postoperative spine SBRT planning, clinicians might encompass any area of epidural disease visualized on preoperative imaging in the clinical target volume, whether resected or not.

- Weak recommendation
- Very-low-quality evidence

Recommendation 4—Where gross epidural disease is present, clinicians might apply a margin for microscopic disease extension radially and craniocaudally.

- Weak recommendation
- Very-low-quality evidence

Conclusion

SBRT for spine metastases is now a mature practice, risks are better understood, and strategies have been developed to minimize these risks. This systematic literature review serves to clarify the risks of RM, VCF, and epidural progression with recommendations to mitigate the risk. However, the evidence is not of sufficient quality that definitive recommendations can be made and high-quality data are needed.

Supplemental digital content is available for this article. Direct URL citations appearing in the printed text are provided in the HTML and PDF version of this article on the journal's Web site (www.spinejournal.com).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1**How to Use and Interpret GRADE Recommendations⁷**

Strength of Recommendation	Interpretation
Strong	Can be confidently applied to all or almost all patients.
	Clinicians apply an intervention in all or almost all circumstances without a thorough review of the evidence and factors, and with an informing, but not necessarily detailed discussion with the patient.
Weak	Can be applied to most patients, but not all patients.
	Clinicians consider fundamental variables such as the quality of evidence, risk and benefit of the intervention, their experience, cost-effectiveness, and most importantly, patient preferences, thus, often resulting in a shared decision-making process with the patient.

Key Points

- The risk of RM can be kept very low (<5%) by following a strict technical protocol for treatment delivery, and adhering to published guidelines regarding spinal cord dose constraints.
- The risk of VCF is significant at 13.7%. This risk can potentially be mitigated by performing appropriate baseline evaluation using the Spinal Instability Neoplastic Score (SINS) criteria, and stabilization procedures in those patients who are at the highest risk of VCF.
- The risk of local failure at 1 year is 21.4%, of which 67% occur in the epidural space. This risk can potentially be mitigated by performing careful radiotherapy planning to ensure that all sites of gross and microscopic disease receive adequate dose, and by considering surgical debulking in those with high-grade epidural disease.

Figure 1.
Flow diagram showing the selection of articles.