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Critical Review

Stereotactic Radiosurgery for Postoperative Spine Malignancy: A Systematic Review and International Stereotactic Radiosurgery Society Practice Guidelines

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Abstract

Purpose: To determine safety and efficacy of postoperative spine stereotactic body radiation therapy (SBRT) in the published literature, and to present practice recommendations on behalf of the International Stereotactic Radiosurgery Society.

Methods and Materials: A systematic review of the literature was performed, specific to postoperative spine SBRT, using PubMed and Embase databases. A meta-analysis for 1-year local control (LC), overall survival (OS), and vertebral compression fracture probability was conducted.

Results: The literature search revealed 251 potentially relevant articles after duplicates were removed. Of these 56 were reviewed in-depth for eligibility and 12 met all the inclusion criteria for analysis. 7 studies were retrospective, 2 prospective observational and 3 were

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prospective phase 1 and 2 clinical trials. Outcomes for a total of 461 patients and 499 spinal segments were reported. Ten studies used a magnetic resonance imaging (MRI) scan fused to computed tomography (CT) simulation for treatment planning, and 2 investigations reported on all patients receiving a CT-myelogram at the time of planning. Meta-analysis for 1 year LC and OS was 88.9% and 57%, respectively. The crude reported vertebral compression fracture rate was 5.6%. One case of myelopathy was described in a patient with a previously irradiated spinal segment. One patient developed an esophageal fistula requiring surgical repair.

Conclusions: Postoperative spine SBRT delivers a high 1-year LC with acceptably low toxicity. Patients who may benefit from this include those with oligometastatic disease, radioresistant histology, paraspinal masses, or those with a history of prior irradiation to the affected spinal segment. The International Stereotactic Radiosurgery Society recommends a minimum interval of 8 to 14 days after invasive surgery before simulation for SBRT, with initiation of radiation therapy within 4 weeks of surgery. An MRI fused to the planning CT, or the use of a CT-myelogram, are necessary for target and organ-at-risk delineation. A planning organ-at-risk volume (PRV) of 1.5 to 2 mm for the spinal cord is advised.

Introduction

Spine metastases are frequent in the natural history of patients with cancer, and treatment options include surgery, systemic therapy, radiation therapy, or a combination of these modalities. A subset of these patients requires surgical intervention for high-grade epidural disease or mechanical instability to preserve or improve pain, neurologic outcomes, and quality of life. Surgery can also be used reduce the burden of epidural disease allowing for better dosimetry with spine stereotactic body radiation therapy (SBRT) and can reduce the risk of instability with SBRT in the appropriately selected patient.[1]

In the landmark study by Patchell et al, patients with symptomatic malignant epidural spinal cord compression (MESCC) were randomized to receive either surgery followed by radiation therapy or radiation therapy alone.[2] Eighty-four percent of patients in the surgery group, compared with 57% of patients receiving radiation therapy alone, were able to walk after treatment. Patients in the surgical arm also retained their ability to walk for significantly longer than the radiation therapy alone arm. This study established the role for surgery in patients with a single symptomatic level of MESCC. More recently, the prospective multicenter North American AOSpine MESCC study confirmed that in patients with symptomatic MESCC, surgical intervention provided an immediate and sustained improvement in postoperative ambulatory status, health related quality of life outcomes, and pain scores.[3]

Surgery is also indicated for mechanical instability, as the pain caused by instability is not palliated effectively by radiation alone.[4] More recently, the Spinal Instability Neoplastic Score (SINS) was developed as a tool to determine which patients should have a consultation for surgical stabilization (Table 1). This tool has been validated among surgeons and radiation oncologists and has gained acceptance in the oncologic community including incorporation into clinical trials.[5] SINS provides a classification for patients with stable, potentially unstable and frankly unstable metastases.[6] The potentially unstable group is one where there is a lack of outcome data with respect to pain control after either surgery or radiation to clarify optimal treatment. Versteeg et al recently reported prospective outcomes in patients with a SINS of 7 to 12 without evidence of symptomatic MESCC and showed the utility of surgery with statistically significant improvements in pain and quality of life outcomes up to 1 year postsurgery.[7] Although comparisons to the radiation therapy cohort are not valid due to the inherent differences in the baseline characteristics, the study showed that patients with at least vertebral compression fracture (VCF) and

Table 1 Spinal instability neoplastic score

SINS components	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi rigid (T3-T10)	1
Pain	
Mechanical	3
Occasional pain but not mechanical	1
None	0
Bone lesion type	
Lytic	2
Mixed (lytic and blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation	4
Kyphosis/scoliosis	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% of body involved by tumor	1
None of the above	0
Posterolateral involvement of spinal elements	
Bilateral	3
Unilateral	1
None of the above	0

Abbreviation: SINS = Spinal Instability Neoplastic Score.
Final score: 0 to 6, stable; 7 to 12, potentially unstable; 13 to 18, unstable.

mechanical pain should be considered for some form of stabilization before, or after, radiation.

With respect to adjuvant postoperative radiation, conventional external beam radiation therapy (cEBRT) is the standard of care. The intent of treatment is to provide local control and palliate pain or other neurologic symptoms. Dose and fractionation regimens have varied widely and include 8 Gy in 1 fraction (fx), 20 Gy in 5 fx, and 30 to 40 Gy in 10 to 20 fx. A recent review by Redmond et al estimated the crude local control rate for patients treated with postoperative conventional RT for spinal metastases to range from 4% to 79%, with a median of 72% in the included studies.[8] However, it is important to recognize that published series on these patients are limited in their assessment of local control due to a lack of rigorous imaging based follow-up and clinical follow-up in general.

Given the advances in systemic therapy during the past 2 decades and promising results of trials for patients with oligometastatic disease, local-control is an increasingly relevant endpoint in patients with spine metastases.[9-12] This, coupled with the development of the techniques of spine stereotactic body radiation therapy (SBRT), has led practitioners to offer patients a higher dose of adjuvant radiation with SBRT. If patients are subjected to an aggressive management strategy involving spine surgery, an equally aggressive adjuvant treatment to improve and sustain local tumor control and potentially symptom control should be considered. Although spine SBRT was recently shown to be superior to conventional radiation in the phase 3 randomized study by Sahgal et al, which enrolled patients with painful de novo spinal metastases and was limited to 6 months of follow-up, this study does not inform the role of spine SBRT in postoperative patients.[13] Therefore, the aim of this systematic review was to summarize the literature for the treatment of postoperative spinal metastases with SBRT and to provide recommendations for treatment and patient selection on behalf of the International Stereotactic Radiosurgery Society (ISRS) Guidelines Committee.

Methods and Materials

A systematic review of the literature was performed to select articles that reported on patients treated with postoperative SBRT according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1). To be eligible, patients must have received radiation therapy using SBRT technique and doses (≥5 Gy per fx), local control must have been reported, and sample size should have included at least 5 patients. Studies that did not define the local control in postoperative patients specifically were excluded. Case reports and abstracts without an accompanying article were also excluded.

The PubMed and Embase databases were searched for relevant publications between the dates of January 2005 and June 2018. Search terms included "postoperative spine radiosurgery," "postoperative spine SBRT," "postoperative spine stereotactic body radiation therapy," and "postoperative spine stereotactic body radiotherapy." A total of 557 articles were initially identified, and another 8 were added from other sources. After removing duplicates, 251 remained and were further screened with title or abstract review. Fifty-six publications were selected for full-text review, and of these 44 were excluded based on the above criteria. Twele studies met all inclusion criteria (Fig. 1). Due to the heterogeneity of studies, guidelines are based on the systematic review of the literature rather than the meta-analysis. Variables extracted from each study for the purpose of the meta-analysis included the number of patients and spinal segments treated, SBRT dose and fractionation, information related to local control (LC), overall survival (OS), toxicity, and follow-up.

The meta-analysis was performed using the "metafor" package (version 2.4-0) in R (version 4.0.2×64; R Foundation for Statistical Computing). One-year OS, LC, and VCF probabilities were arcsine transformed and summarized using inverse variance-weighted DerSimonian-Laird random effects models. The arcsine transformation was used for better stability at the extremes of the range of proportions. Estimates were generated using the restricted maximum likelihood method. Heterogeneity was assessed using I^2 and the statistical significance of the Q statistics. Publication bias was assessed using the Egger test and funnel plots. Leave-one-out sensitivity analyses were performed to assess for the outlier studies that were influential to the heterogeneity of the meta-analyses. A P value threshold of .05 was used for statistical significance.

Results

A total of 461 patients and 499 segments treated across 12 studies were included in this analysis.[14-25] Surgical techniques were heterogenous, and a description of technique used per study is outlined in Table 2. Seven studies were retrospective by design, 2 were prospective observational, and 3 were prospective phase 1 or 2 clinical trials. Median follow-up ranged from 7.2 months to 30 months. All included studies were published between 2009 and 2019.

Ten studies predominantly used a magnetic resonance imaging (MRI) scan fused to the computed tomography (CT) simulation for cord and target delineation, with CT-myelogram reserved for patients with significant artifact or high-grade epidural disease. Two investigations reported on all patients receiving a CT-myelogram at the time of planning. Four studies used a 1.5 mm planning organ-at-risk volume (PRV) for spinal cord, one study

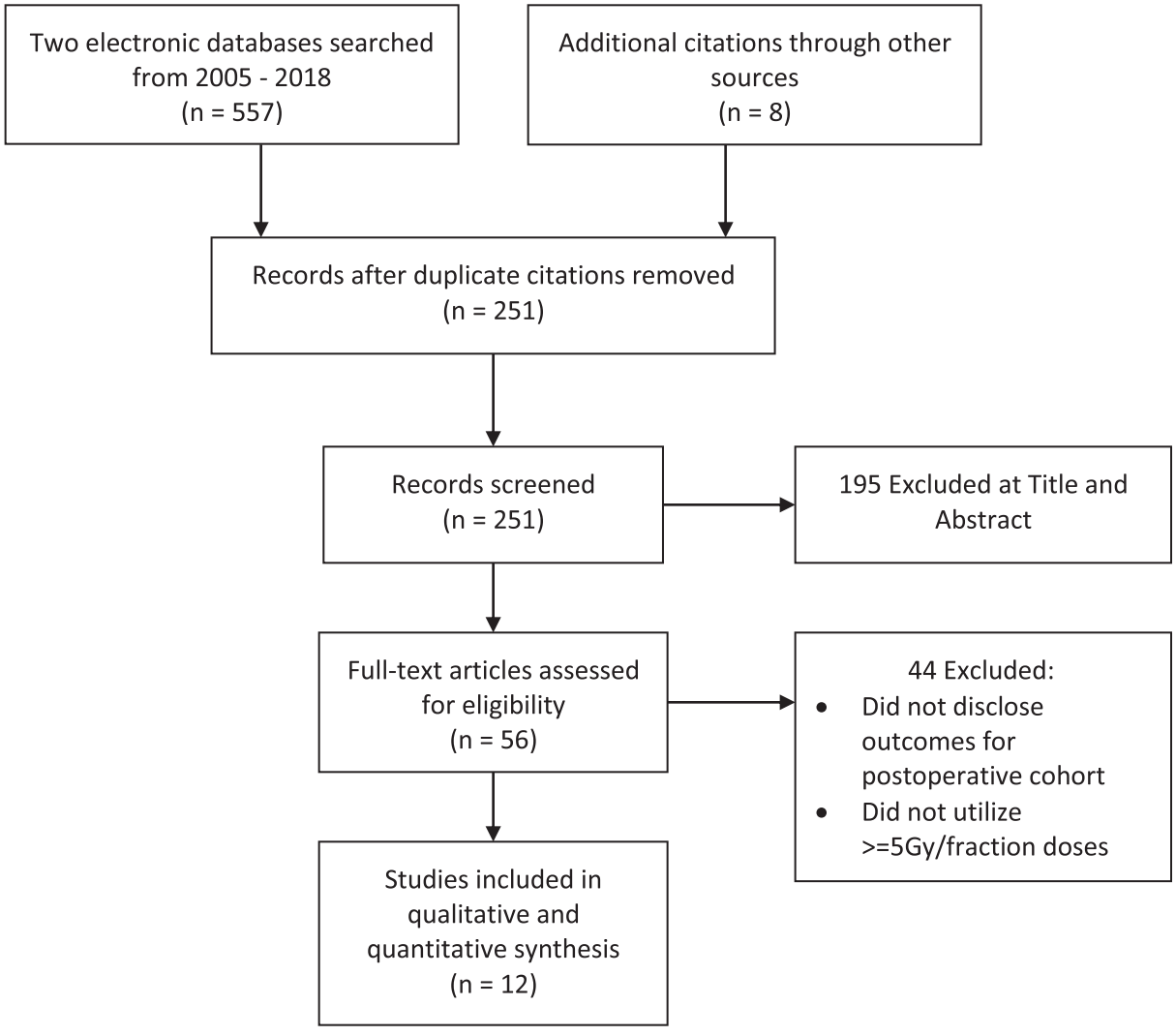

Figure 1 Preferred reporting items for systematic reviews and meta-analyses diagram.

used a 2 mm PRV and 7 studies did not comment on whether a PRV was used.

Dose and fractionation

Dose and fractionation varied considerably, with 5 studies using primarily a single fraction approach and a median/mean total dose range from 15 Gy to 24 Gy. Three used a median total dose of 24 Gy delivered in 2 fractions. Four of the included studies treated patients with a median total dose of 24 Gy to 30 Gy delivered in 3 to 5 fractions. Garg et al was the only study that reported using a simultaneous integrated boost approach with the gross tumor volume (GTV) prescribed 18 Gy and the clinical target volume (CTV) prescribed 16 Gy in a single fraction.

Local control and overall survival

The 1-year LC rate was reported in 9 of the included studies and ranged from 70% to 95.7%. Eight of these studies reported a 1-year LC of 83% or greater. Meta-analysis for local control at 1 year was 88.9% (95% CI: 82.9-93.8%; Fig. 2). There was a moderate amount of between-study heterogeneity (I^2 = 49.9%, P = .041). Sensitivity analysis indicated the study by Garg et al to be a potential outlier.[18] Exclusion of this study resulted in a 1-year LC estimate of 87.3% (95% CI, 82.0%-91.8%), with low heterogeneity (I^2 = 28.6%, P = .22). There was no LC-related publication bias (P = .70).

Pattern of failure was epidural progression in most patients, as described by Al-Omair et al (71%),[15] Redmond et al[24] (100%), and Tao et al (65%).[25] Alghamdi et al[14] reported a 20% pattern of failure confined to the epidural space; however, 60% of patients with multicompartment progression had failure involving both epidural space and bone.

Seven studies reported OS outcomes with the 1-year OS ranging between 55% and 74%. The median OS rates ranged from 10 months to 16.7 months. Meta-analysis for OS at 1-year was 57% (95% CI, 45.9%-67.8%). There

Table 2 Summary of postoperative spine SBRT studies

Studies	Study design	No. of postop pts	Surgical technique	Contouring technique	Median SBRT dose/fraction (range)	Local control	Overall Survival	Pain or neurologic outcomes	Toxicity	Median follow-up (mo)
Alghamdi et al (2019)[14]	Retrospective	47 (83 target volumes)	MIS in 13% of segments of which 73% were stabilization alone and 28% decompression alone. Open approach was used in 87% of segments of which 13% underwent stabilization alone, 19% underwent decompression alone, and 68% underwent both.	Planning MRI consisting of volumetric 1-2 mm slice thickness T1 and T2 axial fused with 1 mm planning CT. CT myelogram for patients with metal artifact obscuring cord. 5 mm cranio-caudal margin along canal if epidural disease. 1.5 mm CordPRV and 2 mm PTV margins.	24 Gy/2 fx (24-30 Gy/2-5 fx)	1 y 83%	1 y 55%	NR	1 radiculopathy (2.1%) 3 VCF (3.6% of segments treated).	11.7
Redmond et al (2020)[24]	Prospective phase 2	33 (35 target volumes)	Heterogeneous surgical techniques.	MRI T1 with gad, T2 and STIR Axial and Sagittal sequences fused with CT (contrast added if paraspinal extension). CT myelogram used if metal artifact. Target delineation according to consensus guidelines. PRV was 2 mm expansion on cord.	30 Gy/5 fx	1 y 90%	Median 14.3 mo	VAS score reduction in 52.2% and stable in 12.5%. Increased by 1 point in 8.3% and by 2 or more points in 25%.	No grade 3 or higher.	10.5
Barzilai et al (2018)[16]	Prospective	111	Posterolateral approach separation surgery without extensive cytoreductive tumor excision. 101 underwent posterior instrumented fusion; 10 had previous instrumentation and underwent separation surgery.	All patients underwent simulation with CT-myelogram. Dura and epidural space were included in the treatment volume to account for microscopic spread. GTV was the entire preoperative tumor volume and CTV was expansion to include adjacent marrow compartments at risk.	27 Gy/3 fx (24-30 Gy/1-5 fx)	1 y 95.7%	Median 16.7mo	BPI: Worst pain 6.3 baseline vs 4.5 at 3 mo ($P <$ .0001). General activity 5.9 baseline vs 4.0 at 3 mo ($P = .0002$).	8 patients (7.2%) had VCF, 2 of which required kyphoplasty. 2 pts (2%) required revision surgery (for wound excision and postop hematoma).	7.2
Ito et al (2018)[21]	Retrospective	28	All patients underwent angiography and embolization of segmental arteries preop. Mostly posterior approach procedures with decompression and fixation.	MRI fused with CT for planning. CTV included residual disease, preoperative extent of bony epidural disease, spinal instrumentation, surgical incision plus immediate adjacent anatomic compartments at risk as per guidelines. PTV was 2 mm margin on CTV, 1.5 mm cord PRV margin and no thecal sac margin.	24 Gy/2 fx	1 y 70%	1 y 63%	Ambulatory function 1 y after SBRT: 20% improvement, 25% worsening and 55% no change.	10% VCF 3.5% myelopathy	13
Harel et al (2016)[20]	Retrospective	17	Open surgery with dorsal and/or ventral approach. Decompression or instrumented fusion performed.	CT with MRI fusion used for planning; if MR not possible CT myelogram was performed. No PTV margins were added.	Mean 14.6 Gy/1 fx (12-16 Gy/1 fx)	91% RECIST criteria (crude) 81% WHO criteria (crude)	NR	88% clinical response to treatment, and 11.7% had a clinical progression.	Postop and pre-SBRT: 5% urinary tract and 9% superficial wound infection. None post-SBRT.	Mean 12.6

(*Continued*)

Table 2 (*Continued*)

Studies	Study design	No. of postop pts	Surgical technique	Contouring technique	Median SBRT dose/fraction (range)	Local control	Overall Survival	Pain or neurologic outcomes	Toxicity	Median follow-up (mo)
Tao et al (2016)[25]	Prospective phase I/II	66	Laminectomy, vertebrectomy or a combination of these techniques.	Pre- and postoperative MRI fused with CT. CT myelogram used if instrumentation caused artifacts. GTV included any residual disease, postoperative tumor bed or both. Extent of preop disease was contoured with preop MRI. CTV included a 5 mm margin in the soft tissue around the GTV. The cord and surgical scar were excluded from CTV, no PTV expansion.	27 Gy/3 fx (16-30 Gy/1-5 fx)	1 y 85%	1 y 74%		8% gr 1 and 5% gr 2 neurologic toxicity. 15% gr 1 and 12% gr 2 GI toxicity. 30% gr 1-2 fatigue, 18% gr 1-2 pain, 5% gr 1 skin pigmentation and 3% gr 1 alopecia. 5% gr 3 pain. No myelopathy.	30
Bate et al (2015)[17]	Retrospective	21	Separation surgery with epidural tumor debulking, vertebrectomy from a posterolateral approach. Pedicle and/or lateral mass screw fixation and titanium cage and methyl methacrylate as indicated.	MRI fused to CT for planning and CT myelography performed postoperatively if high-grade epidural disease. GTV included any residual disease. CTV contoured to preoperative tumor volume and contiguous elements of diseased vertebral body. CTV received 80% prescription of GTV.	22 Gy/1 fx (16-30 Gy/1-5 fx)	1 y 90.5%	NR	NR	No cases of VCF or myelopathy. 2 cases (9.5%) of durotomy.	13.7
Al-Omair et al (2013)[15]	Retrospective	80	Heterogeneous surgical techniques.	Postoperative MRI was fused to the treatment planning CT. CT myelogram used if hardware obscured visualization on MRI. GTV defined preoperatively. 90% had variation of "donut" type CTV.	24 Gy/2 fx (18-40 Gy/1-5 fx)	1 y 84%	1 y 64%	NR	11.25% had VCF 3.75% had grade 1 GI and GU toxicities respectively. 8.75% had a pain flare. 1.25% developed hardware failure. No cases of radiation-induced myelopathy or wound breakdown.	8.3
Garg et al (2012)[18]	Prospective phase I/II	16	Corpectomy (81%) and other procedures.	Immobilized using BodyFix. CT myelogram performed on a case-specific basis. GTV defined on MRI and CTV defined as GTV plus contiguous bone marrow space at risk. No PTV used.	Mean GTV prescribed to 18 Gy and mean CTV received 16 Gy/1 fx	1 y 100% 94% (crude)	NR	NR	NR	17.8

(*Continued*)

Table 2 (*Continued*)

Studies	Study design	No. of postop pts	Surgical technique	Contouring technique	Median SBRT dose/fraction (range)	Local control	Overall Survival	Pain or neurologic outcomes	Toxicity	Median follow-up (mo)
Massicotte et al (2012)[22]	Retrospective	10	Minimal Access Spine Surgery based on a tubular retraction system to gain access for decompression and mechanical stabilization using methyl-methacrylate under direct visualization.	CT simulation with noncontrast MRI fusion. GTV contoured as visible tumor, CTV included pathway for microscopic spread and the ipsilateral trajectory of the tube. 1.5 mm PRV expansion for the cord, no expansion on cauda equina or thecal sac. PTV of 2 mm.	24 Gy/3 fx (18-35 Gy/1-5 fx)	70% (crude)	NR	Of 8 initially symptomatic patients, at 1 mo median improvement of 1 point and at 5 months median improvement of 6 points on VAS.	30% rate of progressive VCF 20% rate of pain flare. 0% myelopathy rate.	13
Moulding et al (2010)[23]	Retrospective	21	All patients underwent posterolateral decompression and instrumentation with the goal of epidural tumor decompression and spinal fixation.	Preoperative MRI was used along with postoperative CT myelography to contour a GTV that includes all epidural and paraspinal disease. GTV contoured to the preoperative tumor volume. CTV expansion for microscopic disease. PTV contoured to the dural margin, 2-3 mm expansion on CTV.	24 Gy/1 fx (18-24 Gy/1 fx)	1 y 90.5% 81% (crude)	Median 10mo	NR	3 pts (14%) each had a grade 1 skin reaction and grade 2 esophagitis. 1 pt (5%) developed grade 4 esophagitis requiring surgical repair of fistula. 1 pt (5%) had acute neuritic pain.	11.3
Gerszten et al (2009)[19]	Prospective	11	Percutaneous transpedicular coblation corpectomy immediately followed by balloon kyphoplasty.	MRI used for GTV delineation. Entire vertebral body and any adjacent tumor extension were included within radiosurgical treatment volume (CTV).	Mean 19 Gy/1 fx (16-22.5 Gy/1 fx)	100% (crude)	NR	Long-term improvement in back pain in all patients. Mean baseline pain score 8, reduced to 3 at last follow-up (10 pt VAS).	No radiation-induced or surgical toxicity. No myelopathy.	11

Abbreviations: BPI = brief pain inventory; CT = computed tomography; CTV = clinical target volume; fx = fraction(s); GI = gastrointestinal; GTV = gross tumor volume; GU = genitourinary; MIS = minimally invasive surgery; MRI = magnetic resonance imaging; NR = not reported; PRV = planning organ-at-risk volume; PTV = planning target volume; RECIST = response evaluation criteria in solid tumors; SBRT = stereotactic body radiation therapy; STIR = short-TI inversion recovery; VAS = Visual Analog Scale; VCF = vertebral compression fracture; WHO = World Health Organization.

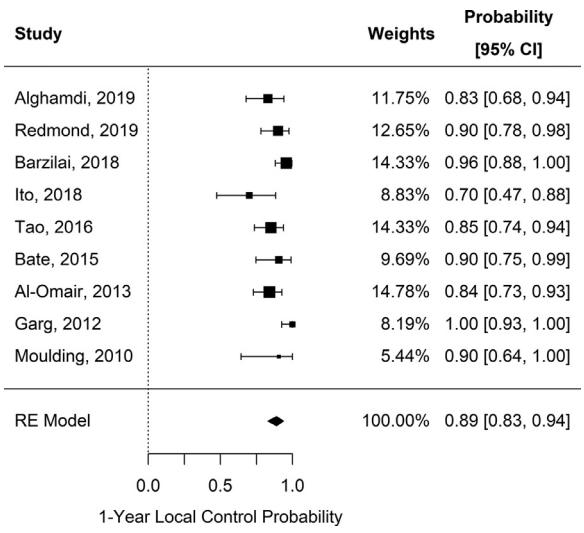

Figure 2 One-year local control probability forest plot.

was significant between-study heterogeneity (I^2 = 75.7%, P < .001) driven by Tao et al[25] and Barzilai et al.[16] There was no publication bias (P = .72).

Outcome predictors

Four studies reported a multivariate analysis (MVA) for LC (Table 3). Alghamdi et al[14] found that higher grade of postoperative epidural disease (P < .0001) and a shorter time between prior RT and postoperative SBRT (P = .004) predicted for greater rates of local failure (LF). Al-Omair et al[15] similarly showed that achieving a postoperative Bilsky grade 0 or 1 had a lower rate of LF versus grade 2 or 3 (P = .003, hazard ratio [HR] = 0.225). They also reported a higher rate of LC for high dose per fraction SBRT (18-26 Gy in 1-2 fx) versus lower dose per fraction SBRT [18-40 Gy in 3 to 5 fx, (P = .022, HR = 0.322)]. Tao et al[25] reported a lower rate of LC with both sarcoma histology (P = .04, subhazard ratio [SHR] = 2.38) and with a higher tumor volume before surgery (P = .006, SHR 1.01). A preoperative tumor volume cutoff of more than 50 cc was associated with diminished crude local control (P = .03). Garg et al[18] showed that failure to achieve durable pain control (<4 of 10 on brief pain inventory [BPI]) at 6 months strongly predicted for LF (P = .04, HR = 9.4).

Three of the included studies completed a MVA for OS. Tao et al[25] confirmed KPS as a prognostic factor with longer survival in those patients with a KPS of 90 to 100 versus 60 to 80 (P = .02, HR = 2.22). Systemic therapy post-SBRT significantly improved survival in the analysis by Al-Omair et al[15] (P = .025, HR = 2.34). Lack of pain control (>3 of 10 on BPI) at both 3 months (P = .04, HR = 3.28) and 6 months (P = .03, HR = 5.28) post-SBRT was a significant predictor for inferior survival in the study by Garg et al.[18]

Adverse events

Eleven studies specifically described the toxicity outcomes of patients treated with postoperative spine SBRT. Of a total of 445 patients, one event of myelopathy developed 30 months after SBRT. The patient who developed myelopathy was previously treated with carbon-ion beam of 70.4 GyE (photon gray equivalent) and 7 years later underwent decompression surgery and SBRT at the same spinal levels. Tao et al[25] reported 5 patients experiencing a grade 1 neurologic toxicity (numbness, tingling, or both) and 3 patients experiencing grade 2 neurologic toxicity (radiculitis, numbness, and tingling). Alghamdi et al[14] reported on 1 patient experiencing radiculopathy.

Other reported toxicities included 26 cases (5.6%) of VCF and 25 events (5.4%) of pain flare. Meta-analysis for crude VCF probability was 2.4% (95% CI, 0.3%-6.7%). Heterogeneity was high (I^2 = 79.2%, P < .001), with no single study that was overly influential. There was no publication bias (P = .82). One patient developed grade 4 esophageal toxicity with a fistula requiring surgical repair. Barzilai et al[16] reported on 2 patients who required revision surgery: one for wound revision, and the other for removal of a postoperative hematoma. One instance of hardware failure in a previously irradiated patient was observed by Al-Omair et al.[15] Two cases of durotomy were noted by Bate et al,[17] both of which were closed primarily with no further consequence. Other toxicities cited in the literature included grade 1 to 2 gastrointestinal toxicity, skin reaction, and alopecia.

Discussion

The purpose of this investigation was to focus on the postoperative spine SBRT population and to our knowledge there are no randomized trials planned and the literature is limited and evolving. Twelve studies were identified reporting outcomes for a total of 461 patients based on our strict inclusion and exclusion criteria. The 1-year local control rate ranged from 70% to 100%. Serious toxicities included myelopathy in a single patient, which was specific to a previously heavily irradiated segment. Postoperative spine SBRT VCF was reported in 26 patients (5.6%), and one patient developed an esophageal fistula requiring surgical repair. Based on this systematic review, ISRS summary recommendations are presented in Table 4.

Surgery for spinal metastases can be associated with significant morbidity, with complication rates ranging from 5% to 76%.[26] As such, patient selection for surgery is critical. One group of patients, in addition to the post-

Table 3 Uni- and Multivariable analyses for local control and overall survival after postoperative SBRT

Study, y	Risk factors on UVA for LC	Risk factors on MVA for LC	Risk factors on UVA for OS	Risk factors on MVA for OS
Alghamdi et al (2019)[14]	Grade of postoperative epidural disease ($P < .0001$) Time interval between prior RT and start of pSBRT ($P = .002$)	Grade of postoperative epidural disease ($P < .0001$) Time interval between prior RT and start of pSBRT ($P = .004$)	Presence of lung or liver disease ($P = .012$)	Not reported
Ito et al (2018)[21]	Rades score, favorable vs intermediate/ poor survival prognosis ($P < .01$)	Not reported	Not reported	Not reported
Tao et al (2016)[25]	Sarcoma histology ($P = .014$, SHR = 2.90) Tumor volume before surgery ($P < .001$, SHR = 1.01)	Sarcoma histology ($P = .04$, SHR = 2.38) Tumor volume before surgery ($P = .006$, SHR 1.01)	KPS 90-100 vs 60-80 ($P = .009$, HR = 2.35) BPI baseline pain ($P = .04$, HR = 1.16)	KPS 90-100 vs 60-80 ($P = .02$, HR = 2.22)
Bate et al (2015)[17]	Nonsignificant	Not reported	Not reported	Not reported
Al-Omair et al (2013)[15]	18-26 Gy/1-2 fx vs 18-40 Gy/3-5 fx ($P = .029$) Postoperative Bilsky grade 0/1 vs 2/3 ($P = .009$)	18-26 Gy/1-2 fx vs 18-40 Gy/3-5 fx ($P = .022$, HR = 0.322) Postoperative Bilsky grade 0/1 vs 2/3 ($P = .003$, HR = 0.225)	Systemic therapy post-SBRT ($P = .021$)	Systemic therapy post-SBRT ($P = .025$, HR = 2.34)
Garg et al (2012)[18]	No statistically significant predictors of recurrence	Lack of durable pain control (score <4 of 10 on BPI) at 6 mo ($P = .04$, HR = 9.4)	Neurologic function preservation, yes or no ($P < .01$) Durable pain control (score <4 of 10 on BPI) at 3mo ($P = .01$)	Lack of durable pain control (score >3 of 10 on BPI) at 3mo ($P = .04$, HR = 3.28) Lack of durable pain control (score >3 of 10 on BPI) at 6 mo ($P = .03$, HR = 5.28)

Abbreviations: BPI = Brief Pain Inventory; ED = epidural disease; fx = Fractions; HR = hazard ratio; KPS = Karnofsky Performance Status; LC = local control; MVA = multivariable analysis; OS = overall survival; SHR = subhazard ratio; UVA = univariable analysis.

MESCC surgical patients, that is likely to benefit from a combined approach are those undergoing surgery for mechanical instability. After surgery, the intent of postoperative SBRT is to achieve durable long-term local control and potentially optimize pain control. The degree to which surgical stabilization mitigates the risk of SBRT induced VCF remains an unanswered question. VCF after postoperative SBRT in this analysis was noted in 5.6% of patients, suggesting that stabilization of fractures with surgery is maintained despite postoperative SBRT. A prior literature review focusing on VCF after denovo spine SBRT, in which the majority of patients did not have a history of surgery, reported a crude VCF rate of 13.9% for comparison.[27]

Although the aforementioned Patchell trial and North American AOSpine study affirmed benefit for surgery for symptomatic MESCC, the role of surgical decompression for asymptomatic high-grade epidural disease (Bilsky 2-3) is controversial. Among the included studies reporting postoperative spine SBRT patterns of failure, epidural space remains the most common site of tumor recurrence. The multivariable analyses by both Al-Omair et al and Alghamdi et al noted an increased risk of local recurrence with higher postoperative epidural disease grade.[14,15] A potential therapeutic benefit from downgrading epidural disease with respect to local control was observed; hence, indirectly supporting surgery as an indication to optimize postoperative SBRT outcomes. Jakubovic et al also showed that even a small reduction in epidural tumor volume can result in significantly improved dose received by the tumor.[1] These observations also highlight the importance of new surgical directions for these patients such as separation surgery where the intent is to stabilize with instrumentation and circumferentially decompress the epidural disease without aggressive vertebral body tumor debulking.[28] Minimally invasive spine surgery (MIS) and laser interstitial thermotherapy are innovations that potentially avoid the invasiveness of traditional separation

Table 4 ISRS recommendations for the use of postoperative spine SBRT

Key recommendations
Patient selection
- Patients with oligometastatic disease. - Patients with radioresistant histologies and/or those with mass-type tumors with paraspinal extension. - If prior cEBRT or SBRT has been given to the affected spinal segment then salvage postoperative SBRT can be considered.
Treatment planning
- All patients should undergo an axial high-resolution 1.5 Tesla T1/T2 MRI of the affected spinal segment including at least one vertebral segment above and below the target volume for both target and OAR delineation. This MRI is fused to the planning CT scan. Use of gadolinium or CT contrast can assist in delineation of soft tissue tumor extension. A CT-myelogram can be considered, especially for cases where hardware artifact obscures canal on the MRI scan. In this scenario it is best to perform a simulation CT myelogram as opposed to a diagnostic CT myelogram that is then fused to the radiation planning CT. - A 1.5-2 mm PRV should be applied to the spinal cord. The thecal sac does not need a PRV. Spinal cord and thecal sac dose limits vary based on fractionation. Published guidelines for dose constraints can be consulted as indicated.[34-36] - The preoperative extent of epidural/paraspinal disease should be included in the postoperative CTV. This often requires the use of a "donut" type CTV.[38] A 5 mm superior/inferior CTV expansion including the spinal canal beyond visible epidural disease should also be considered, in addition to a 5 mm margin surrounding any paraspinal soft tissue disease extension while respecting anatomic boundaries. The surgical scar does not need to be included in the CTV. Contouring recommendations have been published by Chan et al and Redmond et al.[38,39] - A minimum time interval of 1-week from the time of a minimally invasive spinal surgery, and 8-14 days for more invasive surgeries, should be maintained before simulation for SBRT. Delays longer than 4 weeks postoperatively to the initiation of radiation may result in worse tumor control.
Follow-up
- In addition to history and physical examination, a spine MRI should be considered every 2-3 months post-SBRT for the first year and then every 3-6 months thereafter.

Abbreviations: CT = computed tomography; CTV = clinical target volume; cEBRT = conventional external beam radiation therapy; ISRS = International Stereotactic Radiosurgery Society; MRI = magnetic resonance imaging; OAR = organ at risk; PRV = planning organ-at-risk volume; SBRT = stereotactic body radiation therapy.

surgery. This can reduce the time from surgery to radiation planning which is critical in minimizing delays in systemic therapy administration.

With respect to patient selection for postoperative SBRT the literature is evolving. Patients with longer-term survival, such as those with spinal oligometastases, should be considered for this treatment given the high rates of local control observed.[10] Barzilai et al reported a significant survival advantage for those with spinal oligometastatic disease compared with a more diffuse pattern of metastases supporting this patient group as an indication.[12] A second group of patients who may benefit from dose escalation are those with complex "mass" type tumors given the more limited local control observed after cEBRT. Mizumoto et al reported a 1 year LC rate of <50% within this population after cEBRT, and the presence of "mass" was a stratification factor in the SC.24 randomized trial for this reason.[29] Additionally, patients with radioresistant histology (renal cell carcinoma, gastrointestinal, thyroid, melanoma, and sarcoma) have historically poor tumor control rates with cEBRT.[11] As such it is reasonable to offer these patients postoperative spine SBRT given the high rates of local control specifically for these histologies.[30-33]

The last group of patients for whom this review advises consideration for postoperative spine SBRT are those with prior history of radiation therapy to the affected spinal segment. When retreatment is completed with conventional fractionation and technique, a lower dose of radiation is typically used than the first time due to the feared complication of myelopathy. This puts the patient at risk for further local failure at the treated site. Retreatment with SBRT has been extensively investigated and a literature review by Myrehaug et al reported high rates of local control at >75% and a risk of myelopathy of 1.2%.[34] A recent analysis by Detsky et al also found a 1-year LC rate of 86% in 83 spinal segments that underwent retreatment with SBRT.[35] Adverse events included a 4% VCF rate and no radiation myelopathy was observed. Although survival may be more limited in patients with brain metastases, neurologic deficits, poor performance status, and unfavorable histologies, it is reasonable to recommend postoperative spine SBRT in patients with previous cEBRT operated on for salvage of progression with a time interval of at least 5 months from prior cEBRT.[36-38]

Treatment planning

The median doses used for SBRT in the included studies ranged from 15 to 30 Gy delivered in 1 to 5 fx. Of the included studies, only one demonstrated a relationship between dose and local-control. Al-Omair et al found in

their multivariate analysis that patients treated with a higher dose per fraction of SBRT, 18 to 26 Gy in 1 to 2 fx, had a statistically significant improvement in local control compared with those that received 18 to 40 Gy in 3 to 5 fx.[15] Laufer et al also reached a similar conclusion in their analysis of 186 patients who underwent separation surgery followed by SBRT.[39] Patients who received low-dose hypofractionated SBRT (median 30 Gy in 5-6 fx; range, 18-36 Gy) had a higher 1-year local failure rate of 22% compared with 4% for those that received high-dose hypofractionated SBRT (median 27 Gy in 3 fx; range, 24-30 Gy). Both authors credit these results to the different mechanisms thought to be at play with high-dose per fraction RT, including its ability to activate microvascular endothelial apoptosis and the ceramide pathway. Given the lack of prospective data comparing different fractionation regimens, a firm conclusion about the optimal dose for postoperative SBRT is not possible at this time. Doses used for patients with intact previously untreated spinal metastases on randomized clinical trials include 16 to 18 Gy in 1 fx and 24 Gy in 2 fx, both of which have a high-dose per fraction and can be considered in the postoperative setting as well.[40,41]

Of the 4 studies that reported patterns of failure after postoperative SBRT, progression within the epidural space was observed in 65% to 100% of those local failures.[14,15,18,25] This observation signifies the importance of covering the epidural space adequately in the CTV. The International Spine Radiosurgery Consortium (ISRC) helpfully created an anatomic classification system subdividing the spinal segment into 6 sectors (Fig. 3).[42] Chan et al investigated the pattern of epidural progression for 24 cases, and determined that for patients with preoperative epidural disease involving both the anterior (ISRC sectors 1, 2, and 6 and posterior compartments ISRC sectors 3, 4, and 5), progression at the time of failure was observed in all sectors.[43] Therefore, for these patients a donut CTV encompassing the entire epidural space may be safest, and there is data reported on this approach that do not suggest any added toxicities.[14,15] For the subset of patients with epidural disease confined to the anterior compartment, the rate of failure in the posterior most compartment (ISRC sector 4) was significantly lower than if disease involved both the anterior and posterior compartments. A horseshoe type CTV sparing sector 4 may be appropriate for patients with anterior confined epidural involvement alone on both pre- and postoperative MRI. The lack of posterior epidural disease alone limited the analyses with respect to sparing the anterior epidural space, and our recommendation is that for limited epidural disease the diametrically opposed sector can be spared as indicated. Redmond et al have also published a consensus guideline for postoperative spine SBRT treatment planning.[44] It is recommended that the postoperative CTV include the entire extent of pre- and postoperative tumor and the anatomic compartment involved. Other areas that can also be included per physician discretion are the circumferential epidural space, up to a 5 mm expansion on paraspinal disease and up to a 5 mm superior/inferior (SI) margin consisting of the appropriate canal based sectors beyond known epidural disease based on both pre- and postoperative imaging. Surgical tract, instrumentation, and incision do not need to be included in the CTV unless they are considered to be involved with disease. A margin of up to 2 mm for planning target volume (PTV) and PRV are advised as expansions on the CTV and spinal cord respectively. Guidelines have been published by the HYTEC group providing recent modeling data to maintain a risk of radiation myelopathy of less than 5%.[36] The higher end of the tolerance thresholds may be applicable to patients with high-grade epidural disease to balance the low risk of radiation myelopathy with the goal of local control in patients with epidural disease.

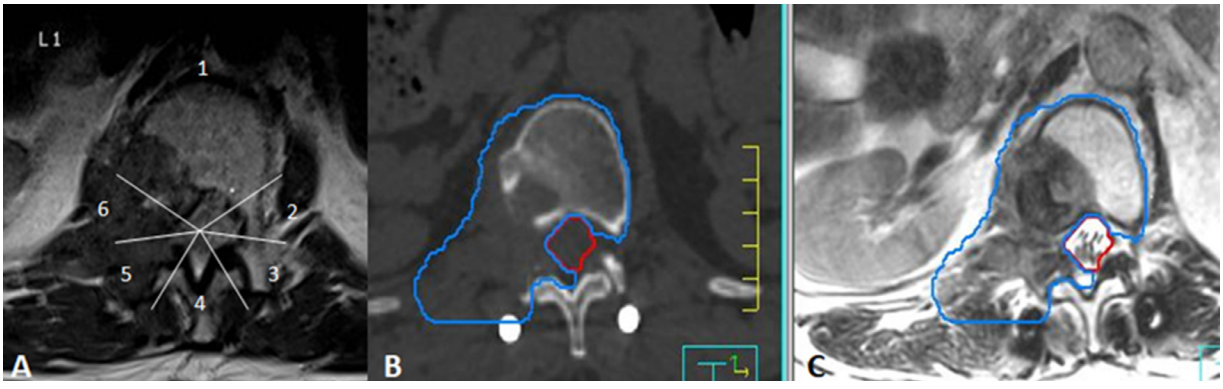

Figure 3 (A) Preoperative magnetic resonance imaging of a patient with an L1 metastasis centered around the right pedicle, transverse process, lamina and vertebral body. The International Spine Radiosurgery Consortium sectors have been superimposed on this image and reveal epidural disease involvement in sectors 1, 6, and 5. Postoperative computed tomography (B) and magnetic resonance imaging (C) show the clinical target volume applied to this target. Given the preoperative involvement, almost the entire epidural space is covered with sparing of the diametrically opposed International Spine Radiosurgery Consortium segment 3.

A CT-myelogram can aid in the delineation of the spinal cord or thecal sac post-spinal instrumentation insertion. Of the included studies, only 2 used a CT-myelogram on all patients. Other authors cited hardware artifact or high-grade epidural disease as factors that led to the use of CT-myelogram in selected patients. A postoperative MRI fusion with the treatment planning CT scan is still essential for accurate cord/thecal sac and, moreover, tumor delineation. The PRV expansion used by the included studies was 1.5 to 2 mm for the spinal cord. The thecal sac does not require a PRV margin. The PTV margin varied between institutions from 0 to 3 mm.

Influence of spinal instrumentation on treatment planning

At the time of planning, it is important to account for the titanium hardware in the treatment planning system. In a multi-institutional analysis, Furuya et al evaluated the dosimetric effect of spine SBRT with an in-house spine phantom assessed with and without metal hardware in place.[45] Dose differences introduced by the presence of metal was within 3% in both the target and spinal cord between the 2 phantoms as measured by radiophotoluminescent glass dosimeters, thus implying that the effect of titanium hardware on dose delivery is clinically acceptable. Additionally, dose calculation with the metal hardware density assigned effected the calculated maximum point dose (Dmax) of the spinal cord especially in the area close to the screws, affirming the importance of delineating the metal hardware before dose calculation. Due to potential for increased instrumentation artifact with 3 Tesla (T) MRI, a 1.5T MRI is recommended for the purposes of treatment planning.[46] Carbon fiber constructs are also increasingly used for spine surgery and these can reduce the instrumentation artifact compared with titanium, making them suitable for further study in patients planned for postoperative spine SBRT.[47]

Effect on wound healing and time interval between surgery and SBRT

The median time interval between surgery and SBRT was reported by 5 of the included studies and ranged from 14 days to 45 days.[14-16,21,22] Two studies reported the mean time as 14 days and 44 days, and a additional 2 investigators treated patients within 2 months and 4 months, respectively.[19,20,23,24] The 2 studies that reported a median and mean time of 14 days were investigations of MIS and percutaneous treatment of vertebral body tumors, respectively.[19,22]

Of the included studies, only one patient was noted by Barzilai et al in their sample of 111 that required revision surgery for wound complication post SBRT.[16] In a review of the literature specifically addressing the risk of wound complication in postoperative SBRT, Itshayek et al reported on wound healing complications in 8 of 82 patients (9.8%).[48] However, 7 patients had received prior cEBRT before surgery, which is known risk factor for perioperative wound complications.

Based on limited evidence, the risk of wound complication with postoperative SBRT in patients with no prior history of palliative radiation therapy remains low and acceptable. The ideal timing of SBRT postsurgery will depend on a number of factors including the type of procedure that was performed. A minimum interval of 1-week from the time of a MIS, and 8 to 14 days for more invasive surgeries, should be maintained before undergoing simulation for SBRT.[22] Although no maximum interval before initiating radiation therapy exists, a recent analysis of 89 postoperative patients treated with radiation therapy by Gong et al showed that patients with tumor progression before radiation therapy (TPBR) had increased LF and reduced OS compared with patients without TPBR. Progression of disease occurred in only 1.2% of patients postoperatively at 1 month and increased to 24% and 45% at 3 and 6 months, respectively.[49] As such, delays longer than 4 weeks postoperatively may lead to worse tumor control in proportion to the duration of the delay.

The limitations of this systematic review include the heterogenous patient population, variable surgical technique and radiation dose delivered in the included studies. Additionally, 2 of these studies were published by authors of the same institution 6 years apart and overlap in the patient populations within these studies is possible.

Conclusion

Spine SBRT offers patients a high degree of local control postoperatively. Patients who may benefit from this modality include those with oligometastatic disease, radioresistant histology, paraspinal masses, or those with a history of prior radiation therapy to the affected spinal segment. An interval before simulation of 1 week for minimally invasive procedures and 2 weeks for open surgeries should be maintained, with treatment delivered within 4 weeks of the surgery. The ISRS summary recommendations are presented in Table 4.

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods of care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on the characteristics and circumstances of individual patients.

Adherence to these guidelines will not ensure successful treatment in every situation. The authors of these guidelines and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusion, and recommendations contained in this report.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2021.10.004.

References

1. Jakubovic R, Ruschin M, Tseng C-L, Pejovic-Milic A, Sahgal A, Yang VXD. Surgical resection with radiation treatment planning of spinal tumors. *Neurosurgery*. 2019;84:1242-1250.
2. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomised trial. *Lancet*. 2005;366:643-648.
3. Fehlings MG, Nater A, Tetreault L, et al. Survival and clinical outcomes in surgically treated patients with metastatic epidural spinal cord compression: Results of the prospective multicenter AOSpine study. *J Clin Oncol*. 2016;34:268-276.
4. Bond MR, Versteeg AL, Sahgal A, et al. Surgical or radiation therapy for the treatment of cervical spine metastases: Results from the Epidemiology, Process, and Outcomes of Spine Oncology (EPOSO) cohort. *Glob Spine J*. 2020;10:21-29.
5. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: An analysis of reliability and validity from the spine Oncology Study Group. *J Clin Oncol*. 2011;29:3072-3077.
6. Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: An evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)*. 2010;35:E1221-E1229.
7. Versteeg AL, Sahgal A, Rhines LD, et al. Health related quality of life outcomes following surgery and/or radiation for patients with potentially unstable spinal metastases. *Spine J*. 2020:1-8.
8. Redmond KJ, Lo SS, Fisher C, Sahgal A. postoperative stereotactic body radiation therapy (SBRT) for spine metastases: A critical review to guide practice. *Int J Radiat Oncol Biol Phys*. 2016;95:1414-1428.
9. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet*. 2019;6736:1-8.
10. Poon I, Erler D, Dagan R, et al. Evaluation of definitive stereotactic body radiotherapy and outcomes in adults with extracranial oligometastasis. *JAMA Netw Open*. 2020;3: e2026312.
11. Zeng KL, Tseng C-L, Soliman H, Weiss Y, Sahgal A, Myrehaug S. Stereotactic body radiotherapy (SBRT) for oligometastatic spine metastases: An overview. *Front Oncol*. 2019;9:337.
12. Barzilai O, Versteeg AL, Sahgal A, et al. Survival, local control, and health-related quality of life in patients with oligometastatic and polymetastatic spinal tumors: A multicenter, international study. *Cancer*. 2019;125:770-778.
13. Sahgal A, Myrehaug SD, Siva S, et al. CCTG SC.24/TROG 17.06: A randomized phase II/III study comparing 24 Gy in 2 stereotactic body radiotherapy (SBRT) fractions versus 20 Gy in 5 conventional palliative radiotherapy (CRT) fractions for patients with painful spinal metastases. *Int J Radiat Oncol*. 2020;108:1397-1398.
14. Alghamdi M, Sahgal A, Soliman H, et al. Postoperative stereotactic body radiotherapy for spinal metastases and the impact of epidural disease grade. *Clin Neurosurg*. 2019;85:E1111-E1118.
15. Al-Omair A, Masucci L, Masson-Cote L, et al. Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy. *Neuro Oncol*. 2013;15:1413-1419.
16. Barzilai O, Amato MK, McLaughlin L, et al. Hybrid surgery-radiosurgery therapy for metastatic epidural spinal cord compression: A prospective evaluation using patient-reported outcomes. *Neuro-Oncology Pract*. 2018;5:104-113.
17. Bate BG, Khan NR, Kimball brent Y, Gabrick K, Weaver J. Stereotactic radiosurgery for spinal metastases with or without separation surgery. *J Neurosurg Spine*. 2015;22:409-415.
18. Garg AK, Shiu AS, Yang J, et al. Phase 1/2 trial of single-session stereotactic body radiotherapy for previously unirradiated spinal metastases. *Cancer*. 2012;118:5069-5077.
19. Gerszten PC, Monaco 3rd EA. Complete percutaneous treatment of vertebral body tumors causing spinal canal compromise using a transpedicular cavitation, cement augmentation, and radiosurgical technique. *Neurosurg Focus*. 2009;27:E9.
20. Harel R, Emch T, Chao S, et al. Quantitative evaluation of local control and wound healing following surgery and stereotactic spine radiosurgery for spine tumors. *World Neurosurg*. 2016;87:48-54.
21. Ito K, Nihei K, Shimizuguchi T, et al. Postoperative re-irradiation using stereotactic body radiotherapy for metastatic epidural spinal cord compression. *J Neurosurg Spine*. 2018:1-7.
22. Massicotte E, Foote M, Reddy R, Sahgal A. Minimal access spine surgery (MASS) for decompression and stabilization performed as an out-patient procedure for metastatic spinal tumours followed by spine stereotactic body radiotherapy (SBRT): First report of technique and preliminary outcomes. *Technol Cancer Res Treat*. 2012;11:15-25.
23. Moulding HD, Elder JB, Lis E, et al. Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. *J Neurosurg Spine*. 2010;13:87-93.
24. Redmond KJ, Sciubba D, Khan M, et al. A phase 2 study of postoperative stereotactic body radiation therapy (SBRT) for solid tumor spine metastases. *Int J Radiat Oncol Biol Phys*. 2020;106:261-268.
25. Tao R, Bishop AJ, Brownlee Z, et al. Stereotactic body radiation therapy for spinal metastases in the postoperative setting: A secondary analysis of mature phase 1-2 trials. *Int J Radiat Oncol Biol Phys*. 2016;95(5):1405-1413.
26. Luksanapruksa P, Buchowski JM, Zebala LP, Kepler CK, Singhatanadgige W, Bumpass DB. Perioperative complications of spinal metastases surgery. *Clin Spine Surg*. 2017;30:4-13.
27. Faruqi S, Tseng C-L, Whyne C, et al. Vertebral compression fracture after spine stereotactic body radiation therapy: A review of the pathophysiology and risk factors. *Neurosurgery*. 2017:1-9.
28. B O, A MK, M L, et al. Hybrid surgery-radiosurgery therapy for metastatic epidural spinal cord compression (MESCC): A prospective evaluation using patient-reported outcomes. *Clin Neurosurg*. 2017;64(Suppl 1):246-247.
29. Mizumoto M, Harada H, Asakura H, et al. Radiotherapy for patients with metastases to the spinal column: A review of 603 patients at shizuoka cancer center hospital. *Int J Radiat Oncol Biol Phys*. 2011;79:208-213.
30. Nguyen Q-N, Shiu AS, Rhines LD, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. *Int J Radiat Oncol*. 2010;76:1185-1192.
31. Folkert MR, Bilsky MH, Tom AK, et al. Outcomes and toxicity for hypofractionated and single-fraction image-guided stereotactic radiosurgery for sarcomas metastasizing to the spine. *Int J Radiat Oncol Biol Phys*. 2014;88:1085-1091.
32. Thibault I, Al-Omair A, Masucci GL, et al. Spine stereotactic body radiotherapy for renal cell cancer spinal metastases: Analysis of

outcomes and risk of vertebral compression fracture. *J Neurosurg Spine*. 2014;21:711-718.
33. Zeng KL, Sahgal A, Husain ZA, et al. Local control and patterns of failure for "radioresistant" spinal metastases following stereotactic body radiotherapy compared to a "radiosensitive" reference. *J Neurooncol*. 2021:1-10.
34. Myrehaug S, Sahgal A, Hayashi M, et al. Reirradiation spine stereotactic body radiation therapy for spinal metastases: Systematic review. *J Neurosurg Spine*. 2017:1-8.
35. Detsky JS, Nguyen TK, Lee Y, et al. Mature imaging-based outcomes supporting local control for complex reirradiation salvage spine stereotactic body radiotherapy. *Neurosurgery*. 2020;87:816-822.
36. Sahgal A, Chang JH, Ma L, et al. Spinal cord dose tolerance to stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 2021;110:124-136.
37. Sahgal A, Ma L, Weinberg V, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;82:107-116.
38. Sahgal A, Weinberg V, Ma L, et al. Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. *Int J Radiat Oncol Biol Phys*. 2013;85:341-347.
39. Laufer I, Iorgulescu JB, Chapman T, et al. Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: Outcome analysis in 186 patients. *J Neurosurg Spine*. 2013;18:207-214.
40. Sahgal A, Myrehaug SD, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: An open-label, multicentre, randomised, controlled, phase 2/3 trial. *Lancet Oncol*. 2021;2045:1-11.
41. Ryu S, Deshmukh S, Timmerman RD, et al. Radiosurgery compared to external beam radiotherapy for localized spine metastasis: Phase III results of NRG oncology/RTOG 0631. *Int J Radiat Oncol*. 2019;105:S2-S3.
42. Cox BW, Spratt DE, Lovelock M, et al. International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012:83.
43. Chan MW, Thibault I, Atenafu EG, et al. Patterns of epidural progression following postoperative spine stereotactic body radiotherapy: Implications for clinical target volume delineation. *J Neurosurg Spine*. 2016:652-659.
44. Redmond KR, Roberston S, Lo SS, et al. Consensus contouring guidelines for postoperative stereotactic body radiation therapy for metastatic solid tumor malignancies to the spine. *Int J Radiat Oncol Biol Phys*. 2017;97:64-74.
45. Furuya T, Lee YK, Archibald-Heeren BR, et al. Evaluation of multiinstitutional end-to-end testing for post-operative spine stereotactic body radiation therapy. *Phys Imaging Radiat Oncol*. 2020;16:61-68.
46. Radzi S, Cowin G, Robinson M, et al. Metal artifacts from titanium and steel screws in CT, 1.5T and 3T MR images of the tibial Pilon: A quantitative assessment in 3D. *Quant Imaging Med Surg*. 2014;4:163-172.
47. Fleege C, Makowski M, Rauschmann M, et al. Carbon fiber-reinforced pedicle screws reduce artifacts in magnetic resonance imaging of patients with lumbar spondylodesis. *Sci Rep*. 2020;10:1-6.
48. Itshayek E, Cohen JE, Yamada Y, et al. Timing of stereotactic radiosurgery and surgery and wound healing in patients with spinal tumors: A systematic review and expert opinions. *Neurol Res*. 2014;36:510-523.
49. Gong Y, Zhuang H, Chong S, et al. Delayed postoperative radiotherapy increases the incidence of radiographic local tumor progression before radiotherapy and leads to poor prognosis in spinal metastases. *Radiat Oncol*. 2021;16:1-8.