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REVIEW

Radiation therapy, radiosurgery, chemotherapy and targeted therapies for metastatic spine tumors: WFNS Spine committee recommendations

Vashisht Sekar[1] · Jamie Walsh[2] · Luke H. Pearson[1] · Ori Barzilai[3] · Salman Sharif[4] · Mehmet Zileli[5]

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Abstract

Objective This review aims to formulate the most current, evidence-based recommendations regarding radiation therapy, radiosurgery, and chemotherapy for patients with metastatic spine tumors.

Methods A systematic literature using PRISMA methodology was performed from 2010–2023 using the search terms “radiosurgery,” "radiation therapy," "external beam radiation therapy," or "stereotactic body radiation therapy” in conjunction with “spinal,” “spine,” “metastasis,” “metastases,” or “metastatic.”

Results Spinal metastases should be managed in a multidisciplinary team consisting of spine surgeons, radiation oncologists, radiologists and oncologists. Patients identified as potential candidates for SRS/EBRT using internationally recognized frameworks and criteria should be assessed by surgeons to see if surgical cyto-reduction/ separation surgery can be achieved. Choices for treatment of recurrence include re-irradiation with SBRT vs EBRT, surgical debulking, additional chemotherapy or palliative care. There is a lack of current clinical evidence to support the routine use of targeted therapies in the management of metastatic spinal tumors.

Conclusions Improving the management of spinal metastasis will lead to increased quality of life and improved survival. This review provides current, evidence-based guidelines on radiation therapy, radiosurgery, and chemotherapy for patients with metastatic spine tumors.

Keywords Radiosurgery · Radiation · Metastatic spine tumor · Targeted chemotherapy

Abbreviations

CTV	Clinical tumors volume
EBRT	External beam radiotherapy
ESCC	Epidural spinal cord compression
GTV	Gross tumors volume
LC	Local control
NOMS	Neurologic, Oncologic, Mechanical and System scale
NSCLC	Non-small cell lung cancer
OS	Overall survival
SBRT	Stereotactic body radiotherapy
SINS	Spinal Instability Neoplastic Score

Introduction

The increasing incidence of cancer and improved life expectancy has led to a greater proportion of patients being diagnosed with spinal metastatic tumors, impacting approximately 40% of cancer patients during their disease [1, 2].

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✉ Vashisht Sekar
vashisht.sekar@jax.ufl.edu

[1] Department of Neurological Surgery, University of Florida Jacksonville, Jacksonville, FL, USA

[2] Department of Neurological Surgery, Queens University Belfast, Belfast, Northern Ireland

[3] Department of Neurosurgery, Memorial Sloan Kettering Hospital, New York, USA

[4] Department of Neurosurgery, Liaquat National Hospital and Medical College, Karachi, Pakistan

[5] Department of Neurosurgery, Sanko University, Gaziantep, Türkiye

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The estimated incidence of spinal metastases varies across different histologies, with rates reported at 65–90% for prostate cancer, 65–75% for breast cancer, and 16–74% for lung cancer [3]. Some post-mortem studies have suggested the rate of microscopic metastases to the spine is in the region of 90% [1, 4, 5]. Current management options include a combination of surgery, targeted therapy and radiotherapy. Spinal metastases, primarily localized to the bone, may be effectively treated with radiotherapy alone, nevertheless, specific scenarios may necessitate surgical intervention [6]. Common indications for surgery include significant morbidities such as spinal instability, vertebral compression fracture (VCF), and oncological emergencies like epidural spinal cord compression (ESCC) [2]. Patchell et al. propose that surgical decompression followed by radiotherapy represents first line management, particularly for patients with symptomatic single-level ESCC which is supported by level one evidence [7]. Rothrock et al. demonstrated an increase in overall survival among patients who underwent surgery for spinal metastatic disease, which indicates there will be a greater role for adjuvant therapy to enhance survival and quality of life [8]. Stereotactic body radiotherapy (SBRT) allows the delivery of highly ablative biologically equivalent doses (BEDS) in a condensed timeframe. This shift in approach has transformed the management of spinal metastases, with a focus on achieving local control (LC) rather than solely providing palliation [9]. Furthermore, advances in genomic medicine have facilitated the identification of numerous molecular markers that can serve as therapeutic targets in spinal metastases, leading to improvements in LC and overall survival (OS) [10].

Material and methods

Literature review

We performed a systematic literature review in PubMed, Scopus, and Embase from 2010–2023 using the following keywords: “radiosurgery,” "radiation therapy," "external beam radiation therapy," or "stereotactic body radiation therapy" in conjunction with “spinal,” “spine,” “metastasis,” “metastases,” or “metastatic.” This initial search yielded 1626 results. Duplicate articles and those without full text available, not in the English language, clinically non-relevant studies, non-human studies, and case reports were excluded. Two separate reviewers performed the screening process, resulting in 75 articles that were used in the final analysis. The screening methodology is shown in Fig. 1 and adhered to PRISMA guidelines. The final selected articles represent Level I through IV evidence and cover the following topics: (1) Radiation therapy for spine metastatic tumors; (2) Radiosurgery for spine metastatic tumors; (3) Chemotherapy for spine metastatic tumors; (4) Targeted therapies for spine metastatic tumors.

Results and discussion

Radiation classification

The mode of action of radiotherapy can be explained by the 5 Rs which are repair, redistribution, reoxygenation, repopulation and radiosensitivity [11]. There are two distinct approaches used in the treatment of metastatic spinal tumors: external beam radiotherapy (EBRT) and Stereotactic body radiotherapy (SBRT). EBRT, involves the delivery of high energy radiation to the tumors cells in multiple fractions without high precision or conformal techniques [12]. This is administered over several weeks allowing for the accumulation of radiation doses to target the tumors while minimizing damage to healthy tissues as the spinal cord is intolerant to high levels of irradiation [13]. On the other hand, SBRT delivers higher dose radiation with precise, conformal techniques to the tumors in fewer fractions which spares surrounding healthy tissue [14]. SBRT has been established as the standard treatment for patients with early non-small cell lung cancer which has metastasized to the spine but who are not candidates for surgery [15]. In contrast, ERBT is used for patients with spinal metastatic tumors that benefit from more gradual accumulation of radiation over multiple treatment sessions, which minimizes the risk of damage to the spinal cord [16].

Scoring systems

The management of spinal metastases involves the utilization of various scoring systems to assess prognosis, spinal instability, mechanical complications and neurological deficits, which aids treatment planning. The Tokuhashi scale was constructed in 1990 and used 6 components: Karnofsky performance status (KPS), number of non-spinal bone metastases, number of spinal metastases, type of the primary lesion, presence or absence of metastases to major organs, and state of paralysis [17, 18]. The score was revised in 2004 and the staging of the primary lesion was modified from 3 levels (0–2) to 6 levels (0–5), with the projected survival anticipated to be less than 6 months for a score between 0–8, over 6 months for a total score of 9–11 and over 1 year for a total greater 12 [19]. Tokuhashi et al. prospectively evaluated 183 patients using the revised score and found 87.9% concurrence with actual survival. The Spinal Instability Neoplastic Score (SINS) was devised in 2010 by the Spinal Oncology Study Group (SOSG) and it assesses and scores 6 variables; lesion location, the degree of pain, the type of bony lesion,

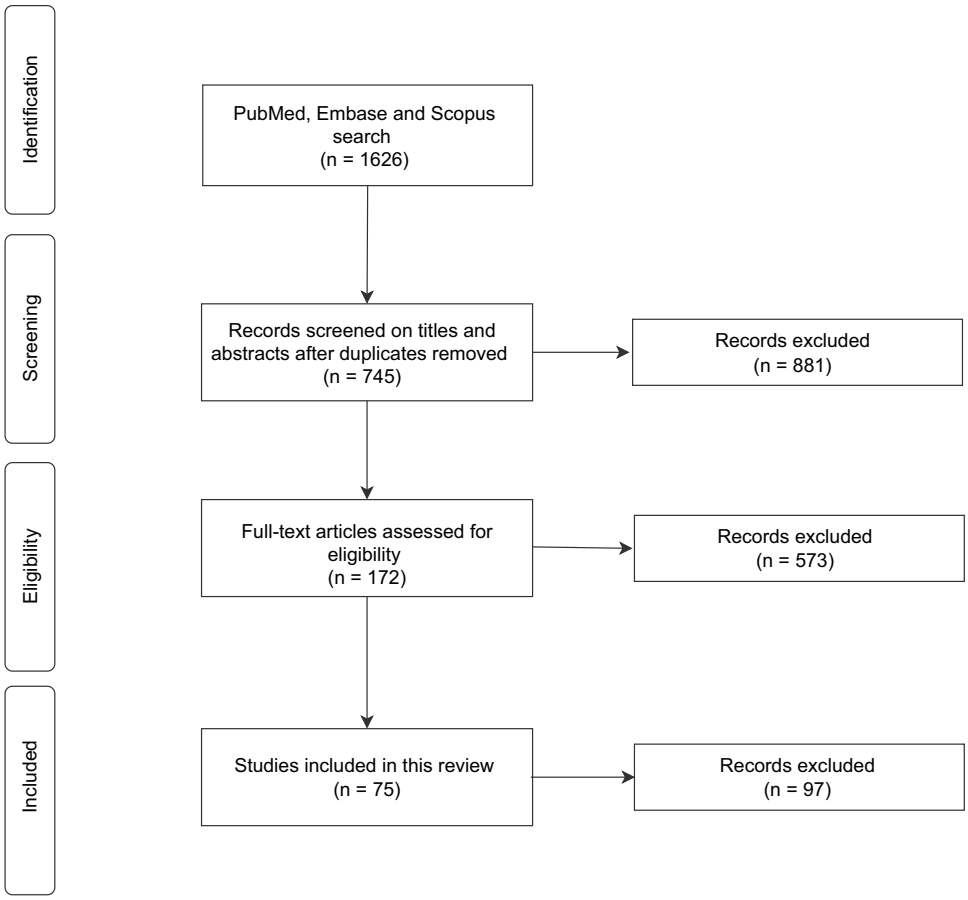

Fig. 1 Flowchart used for searching the literature

spinal radiographic alignment, degree of vertebral body destruction and the involvement of posterolateral spinal elements [20]. The score for each variable is added and a final score is obtained with a higher score denoting a greater degree of instability (Table 1).

Additionally, the Neurologic, Oncologic, Mechanical and System (NOMS) scale provides a decision-making framework, incorporating 4 subgroups. Neurologic considerations such as the degree of focal neurology and ESCC, oncologic considerations predicting the degree of response and durability of response to available treatment such as EBRT, SBRT and targeted therapies, mechanical considerations relating to spinal stability and the final consideration relates to the extent of the patient's systemic disease and their survival based on tumor histology and metastatic spread [9]. Furthermore, the Bilsky Scale utilizes MRI to assess the severity of ESCC due to metastatic disease aiding in the selection of optimal treatment to alleviate tumor burden [9]. These scores play an important role in the multidisciplinary management of patients with metastatic spinal disease and provide guidance to plan treatment and optimize patient outcomes.

Post surgery External Beam Radiotherapy (EBRT)

In 2016 Redmond et al. [6] completed a systematic review on post-operative SBRT for spinal metastases. The authors also reviewed the literature on conventional post-surgery EBRT. Conventional RT schedules include 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 40 Gy in 20 fractions [6]. They reviewed 6 studies with 386 total patients [7, 21–25]. Conventional EBRT trials showed LC rates of between 0–79%, however, Epstein et al. who showed the highest LC rate did not report if radioresistant pathology was included in their cohort [22]. Only three studies used imaging to compare pre-treatment disease extent and post-treatment LC [22–24], instead neurological function and pain [21, 25] or ambulation [7] are used as surrogate markers of LC. These surrogate markers are non-specific and do not definitively localize disease to specific spinal segments [6], it also means disease progression may not be noted until canal compromise causes neurological deficits.

Patchell et al. used ambulation as a marker of LC, reporting ambulatory rates of 84% after surgical decompression

Table 1 Summary of conventional postoperative radiation therapy studies— Adapted from Redmond et al. [3]

Series	N	Surgical technique	Dose	Fx	Local control definition	Long term pain control	Crude LC/1 year LC rate	Ambulatory rate	N radio-resistant primaries	Local control radio-resistant primaries
Klekamp Retrospective [21]	106 lesions, 60% received RT	Decompression & reconstruction with polymethyl-methacralate (PMMA) ± instrumentation	NR	NR	Pain & neurologic function	NR	4%/31.70%	80%	9 thyroid 12 RCC 2 melanoma	0% at 2 years
Epstein-Peterson Retrospective [22]	30 lesions	Decompression with reconstruction & stabilization	Median 30 Gy (range 20–37.5 Gy)	Median 10 (range 5–15)	Imaging	NR	79%/NR	NR	NR	NR
Sellin Prospective database [23]	6 patients	Decompression with reconstruction & stabilization	Median 30 Gy (range 30–40 Gy)	Median 10 (range 10–15)	Clinical &/or imaging	NR	50%/NR	NR	6 thyroid	50%
Sellin Prospective database [24]	25 patients	Decompression with reconstruction & stabilization	Median 30 Gy	Median 10	Clinical &/or imaging	NR	72%/NR	NR	25 melanoma	72%
Patchell Randomized controlled phase II clinical trial [7]	50 patients	Decompression with reconstruction & stabilization	30 Gy	10	Ambulation	NR	NR/NR	84%	3 melanoma	NR
Fehlings Prospective observational cohort study [25]	121 patients	Decompression with reconstruction & stabilization	NR	NR	Pain & neurologic function	Significantly improved ($p=0.012$)	NR/100% of 10 reported patients ambulatory at 12 months	87%	22 RCC 3 HCC	NR

Abbreviations: *N* number, *fx* fraction, *LC* local control, *NR* not reported, *NA* not applicable, *CR* complete response, *PR* partial response, *RCC* renal cell carcinoma, *HCC* hepatocellular carcinoma Unless otherwise noted, data reported in this table included only patients receiving adjuvant conventional RT

Crude LC is LC at last follow-up. Reported results include all patients and are not limited to those receiving adjuvant conventional RT

and conventional EBRT and 57% for EBRT used alone [7]. However, Redmond et al. notes there was no imaging-based LC endpoint and ambulatory function alone is not an adequate surrogate for LC as progression without neurological compromise may not impact ambulation [6]. In summary these studies show that EBRT is a widely used treatment in patients with spinal metastatic tumors and can offer good pain relief and works well for radiosensitive pathology. However, LC is variable, and treatment is delivered in multiple fractions with a higher risk of complications such as pseudoarthrosis, however for these studies interpretation of the data is difficult as many of the studies did not use imaging as a marker of LC for follow up.

Stereotactic Body Radiotherapy (SBRT)

Pre-SBRT imaging requirements

The planning of SBRT for spinal metastatic tumors involves the use of various imaging modalities to assess gross tumors volume (GTV) and clinical tumors volume (CTV). The Spine Response Assessment in Neuro-Oncology (SPINO) group is a committee comprising a panel of international experts in spine SBRT. They recommended that prior to SBRT, patients should undergo simulation CT with external immobilization with slice thickness of < 2 mm with 1 mm being preferred to ensure precision when delineating target volumes [11]. Additionally thin section volumetric MRI is recommended for pre-SBRT planning by both the SPINO group and the International Spine Radiosurgery Consortium. The use of specific MRI sequences such as sagittal T1, sagittal T2, sagittal STIR, sagittal T1 with contrast, axial T1 with contrast (STIR) and axial T2 has been advocated to enhance the visualization of spinal metastatic tumors [26, 27]. CT myelogram and PET scanning were used in circumstances in which MRI was contraindicated such as in the case of surgical hardware which would lead to artifact preventing MRI-based spinal cord delineation [28].

Consensus criteria for SBRT target delineation in spinal metastatic tumors

Consensus criteria for the target delineation in spinal SBRT came from the International Spine Radiosurgery Consortium (ISRC) in 2012 [29] and these are noted in Table 1. A modified anatomical model was used based on the Weinstein-Boriani-Biagini system for spinal tumors staging [23]. However, unlike the traditional 12 sector Weinstein-Boriani-Biagini system, which was felt to be cumbersome, they adopted a modified 6 sector model (Fig. 2). The consensus recommendations suggest that the CTV should include abnormal bone marrow signal as this can indicate potential microscopic progression, along with an additional margin of adjacent normal bone to accommodate potential subclinical tumors invasion in the marrow space [22]. They advised not to delineate the CTV into the epidural space without evidence of epidural disease. Furthermore, circumferential CTVs which encircle the spinal cord should only be employed when there is involvement of the vertebral body, bilateral pedicles or lamina, and spinous process or in the case of extensive metastatic disease along the circumferential epidural space [22]. This consensus paper showed sensitivity and specificity of the consensus contours, which showed substantial agreement between panel members and significant P values for the CTV and GTV agreement levels show this agreement is not random. They also overcame common limitations associated with human analysis by using expectation maximization STAPLE analysis to identify the consensus contour recommendations using automated medical image segmentation performance analysis [29]. There were limitations noted with this study as there were limited cases of epidural disease extension and these cases would need to be individualized with respect to the degree of epidural space included in the CTV, they also focused on scenarios where SBRT was used as an upfront treatment and cannot be easily applied to scenarios where a patient is re-irradiated or in post-surgical SBRT [29].

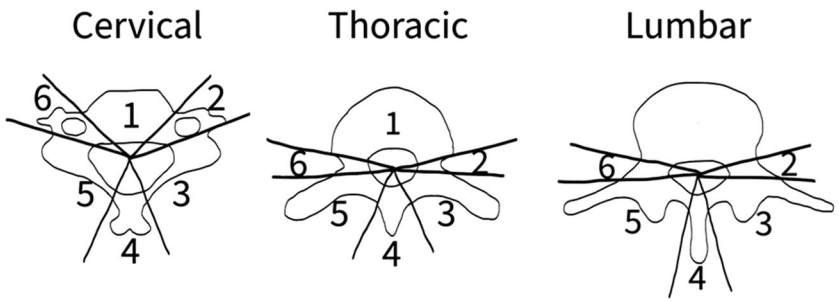

Fig. 2 International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery. Sector 1 represents the vertebral body, sector 2 represents the left pedicle, sector 3 represents the left transverse process and lamina, sector 4 represents the spinous process, sector 5 represents the right transverse process and lamina, and sector 6 represents the right pedicle. Adapted from Cox et al. [29]

Upfront SBRT

Upfront SBRT refers to the use of SBRT as the primary treatment for patients who have not undergone previous surgery or irradiation to the effected spinal segments. Systematic reviews have shown that treatment with upfront SBRT demonstrate high tumors control rates and favorable local control outcomes [30, 31]. Hussein et al. completed as systematic review of 14 published reports which included 1024 spinal lesions treated in single or multiple fractions and found a LC rate of approximately 90% at 1 year [23]. These findings were supported by Hall et al. who reviewed 15 published reports of 1388 patients with 1775 lesions and found that at median follow up of 15 months the combined LC rate was 90% [7]. A single institution randomized phase 2 trial compared SBRT and EBRT and used a primary end point of pain relief at three months [32]. Using a visual analogue scale, they found better pain relief at three months, significantly faster pain relief and better pain relief at six months with SBRT compared to EBRT [25]. Moussazadeh et al. completed a study of 278 patient's examining long term survival over 5 years. They found 11.2% patients survived at 5 years with a LC rate of 90.3% despite 58% patient's having radioresistant primaries [33]. These patients had been treated with 24-Gy single fraction SBRT, and they found a vertebral compression fracture (VCF) rate of 36% at median follow up of 25.7 months and only 14% requiring intervention [24].

Upfront SBRT can be offered in single or multiple fractions with single fraction 24-Gy SBRT associated with increased rates of VCF but high rates of long-term local control [34]. Tseng et al. found SBRT in multiple fractions can be used to reduce the risk of VCF [27]. The cohort consisted of 279 spinal metastases treated with 24-Gy in 2 fractions and they found lower comparative rates of VCF of 8.6% at 1 year and 17.6% at 2 years [35]. They found local failure rates at 1 and 2 years were 9.7% and 17.6% respectively [35]. In a retrospective series of 712 spinal metastases by Yamada et al. it was found that high dose single fraction SBRT at 24-Gy produced durable local control regardless of histology or tumors size [36].

The only statistically significant factors were related to radiation dose, and they found that those radiated with a median 24-Gy had a higher rate of local control than those radiated at a median of 22-Gy [36]. These findings were supported by a phase I/II trial examining the effects of single vs multi-fraction spinal SBRT in the treatment of renal cell carcinoma metastases. This study compared single fraction treatment with 24-Gy to multi-fraction SBRT of 25–30-Gy in 3–5 fractions and found greater local control rates at years 1 and 2 with single fraction SBRT at 95% and 71% respectively compared to 86% and 55% respectively with multi-fraction [37]. This may be due to the higher BED utilized with single fraction regimes.

Dose and constraints

There is currently no randomized data comparing different fractionation schemes for spine SBRT. Retrospective studies suggest that delivering a higher dose per fraction produces greater rates of local control than lower dose per fraction regimes [16, 38]. In 4 retrospective series examining post operative SBRT in a single fraction with doses ranging from 14–24-Gy they found LC rates of 81–100% [39–42]. Comparatively, 8 studies examining post-operative SBRT in multiple fractions showed a LC rate of 70–100% [38, 24, 16, 43–47]. This data may contribute to the hypothesis that single fraction SBRT produces greater LC than multiple fractions. Fuks et al. suggests this works by activation if alternative cell death pathways such as the sphingomyelinase pathway [48], this pathway overcomes the hypoxia induced resistance which occurs when tissues are devascularized in the post-operative setting. However, advocates of hypo-fractionated doses criticize the retrospective data suggesting the patient populations are unbalanced and higher risk patients are treated more frequently with multiple fractions to respect normal tissue constraints while covering the larger at-risk target volume than patients with lower risk disease [49]. Therefore, the greater LC rates in single fraction studies may suggest better outcomes in patients with less severe disease [50, 51]. Based on level IV evidence, Redmond et al. suggests prescription doses of 18–24 Gy in 1 fraction, 24 Gy in 2 fractions, 27–30 Gy in 3 fractions, and 30–40 Gy in 4 to 5 fractions [6]. However, Glickman et al. suggests regimes including 24 Gy in 1–2 fractions, 16–18 Gy in 1 fraction and 27 Gy in 3 fractions are being prospectively assessed in clinical trials and should provide evidence on the most appropriate schedule [34]. Regardless, all of these schema deliver substantially higher BEDs compared with conventional EBRT such as 20 Gy in in 5 fractions or 30 Gy in 10 fractions. There is a lack of sufficient evidence regarding the ideal target coverage and prescription isodose line and in many cases the prescription dose covers approximately 85–95% of the planning target volume (PTV) at a range of 90–100% [6]. However, this coverage varies depending on the prescription dose. Nevertheless, meeting normal tissue constraints should be prioritized over target coverage and in cases where tumors coverage or organ at risk (OAR) constraints are not met in 1–2 fractions then a multiple fraction regime should be considered [6].

SBRT vs EBRT for Pain

In a recent systematic review Wong et al. compared 3 randomized control trials comparing SBRT and conventional EBRT in the management of painful spinal metastatic lesions [52]. A total of 642 patients were included in this review and there was variation in dose fractionation with Sahgal et al.

using 2 fractions [53] and Sprave et al. and Rhu et al. using single fraction SBRT between 16–24 Gy [54, 55]. The dose fractionations used for conventional EBRT were 30-Gy in 10 fractions, 20 Gy in 5 fractions, and 8 Gy in a single fraction [52]. This review showed that in patients with unirradiated spinal metastatic tumors without cord compression there was no significant difference in overall pain response, quality of life, local progression and overall survival between SBRT and EBRT [52], however, there is a significant difference in complete pain response between SBRT and CBRT ranging from 33.3–35.1% and 13.1–13.9% respectively at 3 months [52]. Although, the largest study of 353 patients by Rhu et al. did not include complete pain relief as an outcome [55]. The findings in Wong et al.'s review are supported by previous systematic reviews comparing SBRT and EBRT in the management of painful bone metastatic tumors in all locations [56–58].

Post-operative SBRT

Surgical management of spinal metastases is preferred for symptomatic VCF, mechanical instability and ESCC [34], however, SBRT can be used as an adjunct to optimize LC and minimize disease recurrence. Previously conventional EBRT had been used as an adjunct to surgery with good effect, a randomized controlled trial by Patchell et al. [7] demonstrated superior neurological outcomes, ambulation and survival with post-operative conventional EBRT compared to EBRT alone. However, local failure rates were high at 69.3% and 96% at 1 and 4 years respectively [7]. This suggested that the use of SBRT may be useful post-operatively in selected patients [21, 28]. Redmond et al. [6] completed a review of 12 series examining post-operative SBRT with a cohort of 426 patients [16, 23, 24, 38–42, 44–47] (Table 2). Although there is no level 1 evidence or prospective level 2 studies, this review found a crude LC rate of 88.6% with a range of 70–100% [6]. The largest study in the series with 186 patients was carried out by Laufer et al. [16] and found a high cumulative 1-year LC rate of 83.6%. They also noted significantly higher LC rates with fewer fractions with 24–40 Gy in 3 fractions showing a 96% LC rate competed to 18–36 Gy in 5–6 fractions [16]. These results were supported by a smaller review of 66 patient's enrolled in prospective phase 1 and 2 trials, which found the actuarial 1-year LC rate was 85% and overall survival was 74% [59].

There were high rates of pain control ranging from 92–100%, however, this was only reported in 4 of the 12 series [39, 41, 45, 47]. Despite the lack of data directly comparing post-operative SBRT to post-operative EBRT Redmond et al. suggests LC between the modalities is equivalent, if not greater with SBRT [6]. They also suggest detection of local progression is more sensitive in the SBRT studies as they use radiographic control rates [6]. However, as previously suggested, Glicksman et al. suggests these results may be related to patient selection bias favoring SBRT [34]. More prospective randomized trials are needed (Tables 3, 4 and 5).

Consensus criteria for post-operative SBRT

As with the consensus criteria for upfront SBRT suggested by Cox et al. [29], new consensus criteria were suggested for post-operative SBRT in a study by Redmond et al. and are noted in Tables 2 and 4 [49]. They suggested post-operative spine SBRT is appropriate in cases with limited disease, radioresistant tumors or as salvage following the failure of conventional EBRT [49].

Table 2 Summary of GTV, CTV, and PTV contouring guidelines for postoperative spine SBRT for spinal metastases- Adapted from Cox et al. [26]. (CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume; SBRT = stereotactic body radiation therapy.)

Target volume	Guidelines
GTV	* Gross tumor based on postoperative CT and 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, can be considered for near-circumferential epidural disease involvement * Modified at reconstructed dural space and to account for changes in anatomy after surgery at discretion of treating physician * Consider additional anatomic expansions of up to 5 mm beyond paraspinal extension and cranio-caudally for epidural disease
PTV	* Uniform CTV to PTV expansion of up to 2.5 mm * Treating physician may modify expansion at the interface with critical organs at risk * May subtract cord avoidance structure from PTV as a modified PTV for planning and dose reporting purposes * Include entire GTV and CTV

Table 3 Summary of postoperative spine SBRT studies- Adapted from Redmond et al. [6]

Series	N post-op	Surgical technique	Dose	Fx	CTV description	Pre-op Bilsky grade	Local control definition	Long term pain control	Crude LC/ 1 year LC rate	Ambulatory rate	N radio-resistant primaries	Local control radio-resistant primaries
Gerszten Prospective database [39]	26	Kyphoplasty	16–20 Gy	1	Entire vertebral body and any adjacent area where tumor extended based on pre-procedure CT and MRI	100% grade 0,1a	Pain	92%	92%/NR	100%	4 RCC 1 melanoma	NR
Rock Retrospective [40]	18	Heterogenous	Mean 11.4 Gy (range 6–16 Gy)	1	NR	NR	Neuro fin	NR	92%/NR	NR	3 sarcoma	NR
Gerszten Prospective database [41]	11	Percutaneous transpedicular coblation corpectomy with closed fracture reduction	Mean dose 19 Gy	1	Entire vertebral body and any adjacent area where tumor extended based on pre-procedure CT and MRI including extra-vertebral extension	100% grade 1b, 1c	Imaging and pain	100%	100%/NR	100%	2 RCC 1 HCC	NR

Table 3 (continued)

Series	N post-op	Surgical technique	Dose	Fx	CTV description	Pre-op Bilsky grade	Local control definition	Long term pain control	Crude LC/1 year LC rate	Ambulatory rate	N radio-resistant primaries	Local control radio-resistant primaries
Massicotte Prospective database [45]	10	Minimal access spine surgery	Median 24 Gy (range 18–35 Gy)	Median 3 (range 1–5)	Visible tumor based on post-operative MRI and CT plus margin to account for regions at microscopic risk as well as the ipsilateral surgical tube trajectory	50% grade 1b, 1c 50% grade 2, 3	Imaging	100%	70%/NR	NR	1 thyroid	NR
Laufer Retrospective [16]	186	Decompression with instrumentation	18–36 Gy	Range 1–6	GTV based on pre-operative MRI plus regions believed to be at risk microscopically	3.2% grade 0, 1a 21.5% grade 1b, 1c 73.1% grade 2, 3	Imaging	NR	81%/83.6%	NR	6 HCC 9 melanoma 41 RCC 33 sarcoma 5 thyroid	83.3% HCC 100% melanoma 80.5% RCC 78.8% sarcoma 60% thyroid
Al-Omair Prospective database [38]	80	Heterogenous	18–40 Gy	Range 1–5	Circumferential donut: 72 (90%)	8.7% grade 0, 1a 31.2% grade 1b, 1c 60% grade 2, 3	Imaging	NR	74%/84%	NR	10 thyroid 7 RCC 4 HCC	NR
Tatsui Retrospective [44]	11	Laser interstitial thermotherapy ± stabilization	A) 24 Gy B) 24–27 Gy	A) 1 B) 3	NR	27.3% grade 1b, 1c 72% grade 2, 3	Imaging	NR	NR/NR	100%	6 RCC 1 melanoma 1 sarcoma 1 HCC	NR
Sellin Retrospective [24]	5	Decompression with stabilization ± instrumentation	NR	NR	NR	NR	Imaging	NR	100%/100%	NR	5 thyroid	100%

Table 3 (continued)

Series	N post-op	Surgical technique	Dose	Fx	CTV description	Pre-op Bilsky grade	Local control definition	Long term pain control	Crude LC/ 1 year LC rate	Ambulatory rate	N radio-resistant primaries	Local control radio-resistant primaries
Sellin Retrospective [23]	4	Decompression with stabilization ± instrumentation	A) 27 Gy B) 24 Gy	A) 3 B) 1	NR	NR	Clinical &/ or imaging	NR	100%/NR	NR	4 melanoma	100%
Puvanesarajah Retrospective [46]	32	Decompression with stabilization ± instrumentation	Median 21 Gy (range 12–30 Gy)	Median 3 (range 1–5)	GTV based on pre-operative MRI plus regions believed to be at risk microscopically	NR	Imaging and pain	Decreased proportion of patients reporting pain at 12 mos compared to baseline	92%/100%	100%	7 RCC 3 sarcoma 4 chordoma 1 melanoma	90%
Bate Retrospective [47]	21	Posterolateral decompression with stabilization	Median 16 Gy (range 16–22 Gy)	Median 1 (range 1–5)	GTV based on pre-operative imaging including contiguous elements of involved vertebral body as well as post-operative residual based on CT myelogram	100% grade 2, 3 or pathologic fraction	Imaging	100%	85.7%/90.5%	NR	NR	NR
Harel Prospective database [42]	22	Decompression plus stabilization	Mean 14.58 Gy (range 12–16 Gy)	1	NR	NR	Imaging (in 17) and clinical	NR	88.3%/NR	NR	2 RCC 2 melanoma	NR

(Abbreviations: number (N), fraction (fx), local control (LC), function (fxn), not reported (NR), not applicable (NA), months (mos), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC).)

*Crude LC represents LC at last follow-up. All studies are either retrospective or prospective databases representing level III evidence

Table 4 Consensus indications and contraindications for postoperative spine SBRT-Adapted from Redmond et al. [43]

Indications	Contraindications
Radio-resistant primary	Involvement of more than 3 contiguous vertebral bodies
1–2 levels of adjacent disease	ASIA Grade A status (complete spinal cord injury without preservation of motor or sensory function)
Prior overlapping radiation therapy	Postoperative Bilsky Grade 3 residual (spinal cord compression without any CSF around the spinal cord)

Table 5 Consensus and predominant practices for GTV, CTV, PTV, spinal cord, and spinal cord PRV delineation for postoperative spine SBRT-Adapted from Redmond et al. [43]

Volume	Include
Gross tumor volume (GTV)	Postoperative residual based on MRI
Clinical tumor volume (CTV)	Entire extent of preoperative tumor, anatomic compartment involved, & any postoperative residual Surgical instrumentation & incision not included unless involved Prophylactic circumferential treatment of epidural space controversial Additional expansion up to 5 mm for paraspinal extension controversial Consider an additional expansion of up to 5 mm cranio-caudally beyond known epidural disease extent based on pre- & postoperative imaging
Planning target volume (PTV)	0- to 2-mm expansion from CTV
Spinal cord	True spinal cord based on postoperative T2-weighted MRI or CT pyelogram in cases of significant hardware artifact
Spinal cord planning risk volume (PRV)	0- to 2-mm expansion of spinal cord volume

It was proposed that the target volume should include the pre-operative tumors, the anatomical compartment and the post-operative residual tumors, like the consensus guidelines for upfront SBRT [29]. This is supported by a study from Chan et al. examining patterns of failure that found the location of pre-operative epidural disease had greater predictive value for failure than post-operative residual disease [60].

Accurate spinal cord delineation is essential in spinal SBRT, this is complication in post-operative patient's where operative hardware may lead to artifact [49]. The consensus panel suggest using T2 weighted MRI with the addition of CT myelogram and suggest spinal cord tolerances for post-operative SBRT patients based on the number of fractions, spinal cord compromise and prior radiation [49]. However, it remains unclear whether these dose constraints should be applied to the true spinal cord or a spinal cord PRV which includes 1.5–2 mm expansion (49). The consensus committee suggested that those who use the true spinal cord encompass more of the epidural space which is the highest risk for recurrence [38], however, those who apply the same constraints as the spinal cord PRV believe this conservative approach allows for errors in CT myelogram and MRI fusion and physiological cord motion [49]. Finally, the consensus committee suggest the use of techniques to calculate dose within a heterogenous medium and provide algorithms to do this [49], as the surgical hardware can lead to significant electron backscatter which may not be included in standard treatment planning algorithms [61–64].

Factors associated with recurrence

Despite the high rates of LC, some patients progress or recur leading to a decrease in performance status, declining quality of life and significant pain [12, 65]. The proximity of the spinal cord means that tumors progression or recurrence can lead to ESCC which is an oncological emergency associated with poor prognosis [7, 66]. Despite this, there is limited data examining patterns of failure. One prospective study of 74 spinal tumors showed that the epidural space is the most common site of recurrence [67]. A larger study by Bishop et al. of 332 spinal tumors found that there were no statistically significant differences in recurrence between age, sex, gender, race, or fractionation schemes, but found the main predictor of local recurrence were the GTV dosimetric characteristics including DMin, D98 and D95, which were higher in the non-recurrence group [68]. These findings were corroborated by Lovelock et al. who observed no local failure in patients with a DMin greater than 14-Gy [69]. However, Bishop et al. only included patient's undergoing upfront SBRT, therefore we may not be able to apply these findings to the post-operative cohort.

Complications of SBRT

SBRT has several clinically important toxic effects. The acute toxic effects are often related to proximity to anatomical structures in the radiation field for example oesophagitis in cervicothoracic SBRT, Nausea in lumbar SBRT and in cases of sacral SBRT patients can experience loose stools. Acute pain is also a common early side effect of SBRT regardless of location [34]. This usually occurs in the first 24–48 h after SBRT and occurs in approximately 25% of cases [34], with some series noting pain flare frequency between 23–68% [70, 71]. These flares can be managed with dexamethasone, with recent evidence suggesting a benefit to prophylactic use [70]. Prophylactic dexamethasone reduces the incidence of pain flare to 19.2% at a dose of 4 mg daily for 5 days, commencing on the day of the first fraction [72]. VCF can occur as an acute or late side effect of SBRT [34]. Sahgal et al. examined the predictive factors for VCF with an emphasis on radiation dose and found the risk of VCF was 10–40% depending on the dose and fractionation schedule [73]. They found the greatest predictor of VCF was radiation dose, with the risk greatest in fractions greater than 20-Gy [73]. They also found an association with three of the SINS components, lytic lesions, spinal deformity and baseline VCF, which suggests caution should be exercised when treating these patients with fractures greater than 20-Gy [73]. These findings were supported by a systematic review of 11 studies examining the risk factors for VCF which identified a crude VCF rate of 13.9% over a median time point of 1.6–3.3 months [74]. They also corroborated the risk factors identified by Sahgal et al. with the addition of age over 55 years and more than 40% of the vertebral body consumed by tumors [74]. VCF can result in significant morbidity and may require surgical stabilization [74], however, no data exists to support prophylactic stabilization in patients with VCF [34], as preliminary data from Sahgal et al. 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 [73]. One of the more severe complications of SBRT is radiation myelopathy. However, with adherence to existing guidelines and safe dose schedules this risk is less than 1% in low-risk patient's [34, 75]. With regards to post-operative complications one series of patient's managed with surgery plus or minus convention EBRT or SBRT noted complication rates of 35% with an 11.6% rate of wound dehiscence [24], and this was comparable to a series where all patients underwent post-operative EBRT or SBRT with complication rates of 30% and wound infection rate of 10% [25]. Similarly, Harel et al. noted postoperative wound infections in 9% of their cohort but no new infections in patient's undergoing post-operative SBRT [42]. Redmond et al. speculated that SBRT may reduce radiation related post-operative complications due to the conformal dose distribution, which allows for selective wound sparing [6]. It has been hypothesized, that SBRT may reduce the need for reoperation through a reduction in hardware failure as not all the hardware is exposed to radiation [6]. Redmond's systematic review only included 3 studies that reported this data and found 2.1% of patient's required revision for hardware failure [6]. This is comparable to a series of patient's receiving post-operative EBRT with a crude hardware failure rate of 1.4% [25]. Therefore, it is plausible that, despite SBRT's hardware sparing potential, the increased incidence of radionecrosis of the bone from the higher doses per fraction may lead to a comparable failure rate in the more limited regions that are irradiated [6].

Histological classification of radiosensitivity

Histology has important implications for prognosis with a prospective study by Maranzano et al. showing that dose-fractionation schedule was insignificant, but tumors histology was significant [76]. In a systematic review of 6 studies utilizing EBRT Gerszten et al. noted that radiosensitive histologies included breast cancer, prostate cancer, myeloma, lymphoma, and leukemia while radioresistant histologies included lung cancer, kidney cancer, gastrointestinal cancer, head and neck cancer, melanoma, and sarcoma [12]. A randomized, multicenter trial by Maranzano et al. found that there was a significant difference in survival and motor control duration for favorable histologies compared to radioresistant tumors (6 months vs 3 months) [77]. However, a large prospective series showed local control of 88% with SBRT with no significant difference in response from radiosensitive or radioresistant histologies [78]. This was supported by Greco et al. who reported renal cell histology to be highly dose responsive with 81% LC in renal cell tumors receiving 23–20-Gy compared to 30% LC in patient's receiving less than 22-Gy [79]. Another study by moulding et al. showed LC rates of 91% at 1 year following post-operative SBRT to highly radioresistant histologies [80]. This suggests that high dose single fraction SBRT can overcome radioresistance to conventional EBRT. A study by Moore et al. identified that BRCA2 and the APC/BRCA2 gene pair mutations were associated with local failure following EBRT however, there were no genes associated with local failure in high BED SBRT which supports the concept that SBRT may overcome radioresistance [81].

Re-irradiation with SBRT

Re-irradiation of spinal metastatic tumors, which can involve irradiating the circumference of the spinal cord, can pose challenges due to the cumulative radiation dose to the spinal cord and care must be taken to avoid toxicity [82].

Re-irradiation with conventional EBRT includes fractionation schedules such as 8 Gy in 8 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, 20 Gy in 8 fractions and 25 Gy in 10 fractions [2, 83]. A systematic review by Huisman et al. of 527 patients undergoing repeat EBRT across 7 series showed an overall pain response of 58% and complete pain response between 16–28% [84]. SBRT allows a conformal high dose of radiation to the spinal cord, allowing higher dose delivery to the lesion with a reduced risk of radiation myelopathy [85, 86]. A systematic review of 9 studies examining re-irradiation with SBRT found a median 1-year LC rate of 76%, ranging 66–90% [87]. They also found pain scores improved following re-irradiation and delivery was deemed safe with crude rate of VCF at 12% and radiation myelopathy at 1.2% [87]. However, the quality of evidence was poor with heterogenous study populations and variation in methodology and reporting endpoints [88]. Detsky et al. found that in the re-irradiation population epidural progression is the most common pattern of failure [5], which was supported by Garg et al. who found that progression was within 5 mm of the spinal cord in 13/16 tumors in their cohort with 6 developing ESCC [65].

Chemotherapy and Targeted Therapy

As discussed previously, various frameworks exist for decision-making and prognostication of patients with metastatic spinal tumors. However, the oncological management and outcomes of patients with various tumors histologies have been transformed with the introduction of genomic analysis leading to the identification of targetable mutations in a large proportion of patients. Fomchenko et al. [89] demonstrated a significant number of targetable molecules in common metastatic spinal tumors with non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (ALK) rearrangements are found in 4–5% of patients whilst epidermal growth factor receptor (EGFR) mutations are present in 10–15% of cases, Breast cancer samples exhibit ERBB2, CD340 and human epidermal growth factor receptor 2 (her2)/Neu alterations with 18–25% of patient's exhibiting an overexpression of HER2. They also state BRAF V600E mutations are noted in 33–55% of patients with metastatic melanoma [89]. These mutations play a significant role in prognostication and have implications for targeted therapeutic interventions. Abugharib et al. reported outcomes of LC following SBRT based on hormone sensitivity in patients with prostate cancer spinal metastases [90]. The study included 183 spine segments and revealed that LC rates at 1 and 2 years were 99% and 95% respective in hormone sensitive prostate cancer compared to 94% and 78% respectively in hormone insensitive cases [90]. This greater response to SBRT in hormone sensitive lesions may suggest a prognostic benefit to tumors profiling. NSCLC is linked to poor prognosis with an overall survival of 8–11 months, primarily attributed to rapid lung and distant metastasis [89]. Skeletal metastases are prevalent in NSCLC, affecting approximately 30% of patients with nearly half of these occurring in the spine [91]. Due to the poor prognosis, these patients are often not candidates for spinal decompression surgery [19]. The presence of EGFR in patients with lung adenocarcinoma serves as a predictor of treatment efficacy [92–94]. A systematic review by Batista et al. that included 27 studies showed improved survival in patients with adenocarcinoma with EGFR mutations that were treated with tyrosine kinase inhibitors, with overall survival up to 18% [95]. One included study of 118 patient's identified 7 patients who had lived for over 2 years, the common factors were mutations in EGFR treated with tyrosine kinase inhibitors [96]. Advancing lung cancer genomics have identified further molecular targets such as oncogenic fusion genes like EML4 and ALK, which have shown responsiveness to targeted therapy, as evidenced in the broader lung cancer literature [97–99]. The effect of targeted therapy has prognostic implications in other spinal metastatic histologies. Based on a small retrospective series of 18 patients with metastatic melanoma to the spine, univariate analysis indicated a significant association between prior immunotherapy treatment and reduced survival following surgery [100]. Specifically, the median survival was 98 days for patient's previously treated with immunotherapy compared to 315 days for those who were not [100]. Chakavarthy et al. completed a retrospective analysis of patients with NSCLC metastases presenting with ESCC, the patients underwent separation surgery and post-operative SBRT and found 95% LC at 2 years [101]. They found that patients with NSCLC found a two-fold increase in progression free survival from the date of surgery, they also found that patients with EGFR treatment naïve spinal metastasis who initiated EGFR targeted therapy exhibited a significantly longer overall survival, even after adjusting for smoking status [101]. Conversely, this survival benefit was not observed in patients who had received EGFR targeted therapy before surgery and SBRT. Therefore, targeted therapy will need to be considered in future prognostication models. A retrospective analysis of 50 patients with colorectal cancer who underwent hybrid therapy showed 2-year LC of 86.7% [102]. During follow-up 40% of patients experienced progression of spinal disease outside the index treatment field [102]. They also identified APC mutations in 15 of 17 patients and in 3 of 7 local failures, this suggests APC mutations are commonly present in colorectal cancer patients with spinal metastases and may indicate poor prognosis [102]. Barzilai et al. used next generation sequencing to compare genomic profiles between spinal metastasis and the corresponding primary tumors [103]. They found genetic alterations in spinal metastasis samples show high concordance with the primary tumors and other visceral metastases in the same patient,

particularly for driver mutations. It is noteworthy that over 25% of patients carried at least one genetic variant among samples tested, although this was not specifically for known driver mutations [103]. The author suggests spinal metastasis samples can be utilized for genomic based decision making and prognostication, especially in NSCLC, prostate cancer, and breast cancer.

A recent systematic review investigated the effectiveness of radiofrequency ablation (RFA) for treating pain from spinal metastases [104]. Analyzing 15 studies, the review found that RFA significantly reduced pain levels in the short-term (3–6 months), and also improved disability and quality of life. However, longer-term effectiveness remains unclear, with limited data on tumor control and a high mortality rate (23.6%) within a year. While RFA appears safe and effective for managing refractory pain or radiotherapy-resistant tumors, the authors recommend further research through controlled trials to compare its efficacy with current front-line treatments.

Recommendations

1. Spinal metastases should be managed in a multidisciplinary team consisting of Spine surgeons, Radiation Oncologists, Radiologists and Oncologists. Patients identified as potential candidates for SRS/EBRT using internationally recognized frameworks and criteria should be assessed by surgeons to see if surgical cytoreduction/ separation surgery can be achieved. (SRS: Stereotactic Radiosurgery, EBRT: External Beam Radiotherapy)
2. Choices for treatment of recurrence include re-irradiation with SBRT vs EBRT, surgical debulking, additional chemotherapy or palliative care.
3. There is a lack of current clinical evidence to support the routine use of targeted therapies in the management of metastatic spinal tumors.

Conclusion

Advances in systemic therapy and prolonged survival will continue to lead to increased incidence of spinal metastatic disease. Improving the management of spinal metastasis will lead to increased quality of life and improved survival. Studies have shown the SBRT is useful for LC in patients with spinal metastasis and can be employed upfront or in the post-operative setting with consensus criteria to guide treatment. However, given the paucity of data there should be further prospective studies to optimize treatment. The development of personalized, targeted therapies has relied on the discovery of new mutations in many cancers. However, there is a lack of agents that can specifically target cancer within bony metastases. Select cases have demonstrated robust responses but overall, the existing literature lacks data on safety, efficacy, and overall response rates of many new treatment agents when administered to patients with spinal metastatic disease. The identification of prognostic indicators of responsiveness to target inhibition, chemotherapy or immunotherapy for spinal metastasis represents the next mountain to scale in this field.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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