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Stereotactic body radiotherapy for treatment of spinal metastasis: A systematic review of the literature

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Abstract

Background. Advances in local and systemic therapies continue to improve overall survival for patients with cancer, increasing the incidence of spine metastases. Up to 15% of patients with solid tumors develop spinal metastases. Spinal metastases can be particularly devastating for quality of life given the potential pain, neurological deficits from spinal cord compression or cauda equina syndrome, spinal instability, and pathological fractures that may result. Stereotactic body radiotherapy (SBRT) with or without adding less invasive surgical techniques for stabilization or separation has gained favor. SBRT uses smaller, more precise treatment volumes, allowing for higher doses per fracture, thus increasing ablative abilities.

Methods. We conducted a systematic review using MEDLINE, Embase (Elsevier), and Web of Science to identify all articles investigating the effectiveness of SBRT in providing local disease control, pain control, and relief of spinal cord compression for patients with metastatic disease of the spine.

Results. The review yielded 84 articles that met inclusion criteria. The evidence indicates SBRT provides excellent local control and pain control for patients with spine metastesis, and this remains true for patients with spinal cord compression managed with surgical separation followed by postoperative spine SBRT.

Conclusion. While not all patients are appropriate candidates for SBRT, carefully considering appropriate frameworks that consider the patient's overall prognosis can guide a multidisciplinary team toward the patients who will benefit the most from this treatment modality.

Keywords

radiation myelopathy | radiotherapy | spinal cord compression | spinal metastases | stereotactic body | vertebral compression fractures

Advances in local and systemic therapies continue to improve overall survival for patients with cancer. This increase in expected survival for many patients with metastatic cancer has led to an increase in the incidence of spine metastases.[1] Metastases to the spine are the most common bony metastasis, with some studies approximating that nearly 60% of osseous metastases are to the spine.[2] Some studies estimate that up to 15% of patients with solid tumors develop spinal metastases.[3,4] Spinal metastases can be particularly devastating for a patient's quality of life given the potential pain, neurological deficits from spinal cord compression or cauda equina syndrome, spinal instability, and pathological fractures that may result.[5,6]

Multidisciplinary teams including oncologists, radiation oncologists, and neurosurgeons are becoming increasingly necessary as treatment paradigms switch from palliative-based care to a focus on delivering durable symptom management and prevention given improved systemic control and extended survival for patients with metastatic cancer.[6,7] Historically, spinal metastases were treated with either morbid, en-bloc resections, low-dose palliative conventional external-beam radiotherapy (EBRT), or a combination of both modalities.

Invasive surgeries often result in extensive patient morbidity and suboptimal local control, whereas the emphasis of EBRT is on short-term (median duration < 4 months) pain reduction.[8–12] In a landmark trial, Patchell et al.[13] performed a randomized, multiinstitutional, nonblinded trial in which patients with spinal cord compression from the metastatic disease were randomized to either surgery followed by radiotherapy compared to radiotherapy alone with a primary endpoint of ability to walk. In this trial, they found that patients who underwent surgery followed by radiotherapy were significantly more likely to be able to walk compared to the radiotherapy-only group (odds ratio 6.2 [95% CI 2.0–19.8] $P = .001$).[13] Additionally, more rapid relief and reduced time to neurologic recovery with surgery vs. radiotherapy alone have helped guide contemporary management of spine metastasis. In the years since the Patchell et al.[13] trial, palliative stereotactic body radiotherapy (SBRT) with or without the addition of less invasive surgical techniques for stabilization or separation has gained favor by providing higher rates of pain control and local tumor control.[14]The primary advantage of SBRT is the ability to provide more precise treatment with very high doses per fraction, but this technique does come with potential risk from the higher dose per fraction on the normal tissues. Therefore, there is a need for high-quality immobilization and accurate delivery systems including image-guided radiation therapy.

While SBRT is an effective and safe treatment option for spinal metastatic disease, there are an insufficient number of high-quality, prospective, randomized trials to adequately guide the preferred treatment of spinal metastatic lesions. Several frameworks and algorithms have been created to assist oncologists, radiation oncologists, and neurosurgeons in their decision making. These frameworks utilize multiple important aspects of the patient's presentation and oncologic disease (eg, the neurological, oncological, mechanical, and systemic framework [NOMS], and the location of disease in the spine, mechanical instability, neurology, oncology, and patient fitness, prognosis, and response to prior therapy framework [MNOP]) to guide further treatment decisions.[15,16] Spratt et al.[7] provides a comprehensive overview of both of these frameworks, synthesizing the available research to help guide when different treatment modalities such as SBRT will potentially provide the most benefit to patients. In this article, we perform a systematic review of the evidence behind the use and efficacy of SBRT in treating metastatic disease to the spine and discuss its implications.

Methods

This systematic review was conducted by the most recent PRISMA guidelines.[17]

Outcome Measures

The primary outcome measures of interest were local control, pain control, and relief of spinal cord compression. Additional outcomes were vertebral fractures and radiation myelopathy.

Study Types

Randomized control trials, Prospective cohort studies, and retrospective cohort studies were eligible for inclusion. Narrative and systematic reviews that did not report new cases or data were excluded.

Eligibility Criteria

Eligibility criteria, established using the PICO (Population Intervention Comparison Outcome) format, were a patient population of adults clinically diagnosed with spinal metastases from any type of primary neoplasm and an intervention of SBRT of any dose or timing. Comparators were patients treated with EBRT or cRT for 2-arm studies and no comparators were acceptable for single-arm studies evaluating SBRT. Outcomes were local disease control, pain control, and relief of spinal cord compression as well as complications, specifically vertebral fracture, and radiation myelopathy.

Information Sources

Information sources were MEDLINE (OVID), Embase (Elsevier), and Web of Science dating from 1944 to November 2023. The primary search term was the MeSH of "Radiosurgery" OR "Stereotactic Body Radiation Therapy" and secondary terms included the following: AND Spinal Neoplasms AND "external beam radiotherapy" AND Metastases OR Neoplasm Metastasis. Additionally, the reference lists from prior review articles were searched to identify any additional articles.

Eligibility Assessment

Assessment for eligibility was performed by 2 independent reviewers (L.G.M. and E.D.) in a standardized manner. Any disagreements between reviewer assessments were resolved by consensus or by consulting a senior reviewer (N.S.).

Results

Literature Search

Our systematic search of OVID ($n = 376$), Web of Science ($n = 374$), and Embase ($n = 568$), 1318 records (PRISMA flow diagram, Figure 1)—985 records remained after removal of duplicates. Titles and abstracts were screened by 2 independent reviewers to produce 214 remaining articles for full-text review. Full-text assessment yielded 84 total articles that fully met the criteria for inclusion. Articles included 5 randomized controlled trials with a primary indication of local control or pain control (Table 1),[18–22] 15 prospective cohort studies with a primary indication of local control or pain control (Table 2),[23–37] 54 retrospective cohort studies with a primary indication of local control or pain control (Table 3),[38–91] and 10 articles with a primary indication of spinal cord compression (Table 4).[92–101]

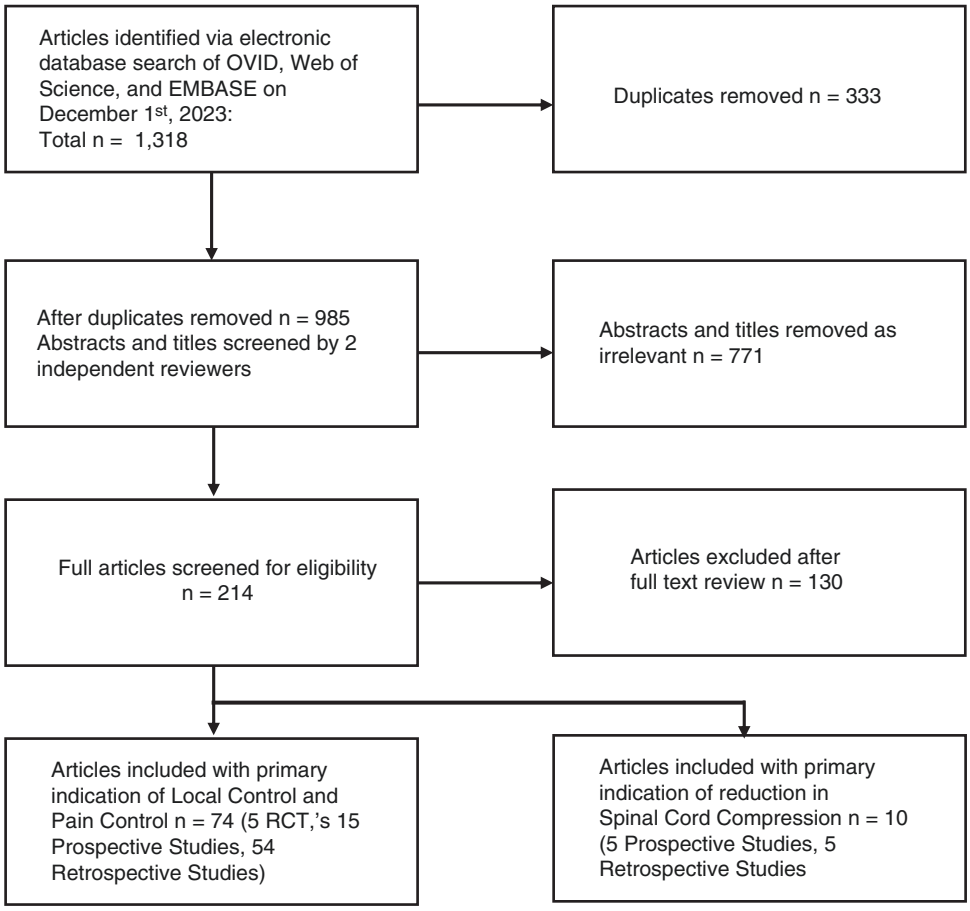

Figure 1. PRISMA flow diagram.

Discussion

Indications for SBRT to Treat Spinal Metastases

Local control—.

Randomized Controlled Trials

To the best of our knowledge, there are no published randomized trials with a primary endpoint of local control comparing SBRT to EBRT in the management of spine metastases. However, a retrospective review of patients treated on the randomized Canadian Cancer Trials Group Symptom Control 24 phase II/III randomized trial (SC.24), suggests improved local control rates with SBRT compared to conventional EBRT. The SC.24 trial randomized 229 patients to receive either SBRT with 24 Gy in 2 fractions or 20 Gy in 5 fractions with conventional EBRT. The primary outcome was the proportion of patients with a complete pain response 3 months after treatment. During the randomization process, the 2 cohorts were balanced for radioresistant histology. The trial was limited in its ability to assess durable local control between arms as follow-up was limited to 6 months. The authors however performed a retrospective review of the subset of patients followed long-term with MRI surveillance who typically had follow-up every 2–3 months. In the 137 patients included in this analysis of MRI-defined local control, the authors found that the risk of local failure after SBRT vs. conventional EBRT was 2.8% (95% CI, 0.8–7.4%) vs 11.2% (95% CI, 6.9–16.6%) at 6 months, 6.1% (95% CI, 2.5–12.1%) vs. 28.4% (95% CI, 21.3–35.9%) at 12 months, and 14.8% (95% CI, 8.2–23.1%) vs. 35.6% (95% CI, 27.8–43.6%) at 24 months ($P < .001$).[87]

Nonrandomized Controlled Trials

Chang et al.[23] performed a phase I/II trial in 63 patients with spinal metastases who underwent CT-guided SBRT to assess overall efficacy. They reported a 1-year tumor progression-free incidence of 84% with progression-free defined as abscess of MR imaging-documented progression of the treated spinal tumor. Amdur et al.[26] also performed a prospective, phase II study assessing single-fraction SBRT/ SRS in 25 patients with spine metastases and found excellent local control (95%) at the last follow-up (average of 11 months) with local control defined as no evidence of progression of tumor at the site of SBRT based on MR, PET, or CT imaging. Garg et al.[28] led a phase I/II trial at the M.D. Anderson Cancer Center which demonstrated excellent outcomes with a local control rate of 88% at 18

Table 1. Randomized Controlled Trials Included with Primary Indications of Local Control and/or Pain Control

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean follow-up	Local Control Results	Pain Control Results
Sprave et al. (2018)[18]	Germany	Randomized controlled trial, phase II	55	Lung, breast, renal, other	No	SBRT group: 24 Gy in 1 fraction; EBRT group: 30 Gy in 10 fractions	8.1 months	N/A	3-month incidence of new pathological fractures was 8.7% in the SBRT arm vs. 4.3% in the 3DCRT arm
Sprave et al. (2018)[19]	Germany	Randomized controlled trial, phase II	55	Lung, breast, renal, other	No	SBRT group: 24 Gy in 1 fraction; EBRT group: 30 Gy in 10 fractions	8.1 months	N/A	There was a trend toward improved pain response in the SBRT arm at 3 months. ($P = .057$), but significantly so after 6 months. ($P = .003$)
Sprave et al. (2018)[20]	Germany	Randomized controlled trial, phase II	55	Lung, breast, renal, other	No	SBRT group: 24 Gy in 1 fraction; EBRT group: 30 Gy in 10 fractions	8.1 months	N/A	No significant QOL differences between cohorts, including painful sites, pain characteristics, functional impairment, or psychosocial aspects ($P > .05$ for all)
Sahgal et al. (2021)[21]	Canada, Australia	Randomized controlled trial	229	Breast, GU, renal, prostate, lung, GI, skin, head and neck, other	No	SBRT group: 24 Gy in 2 daily fractions; EBRT group: 20 Gy in 5 daily fractions	6.7 months	N/A	At 3 months, 40 (35%) of 114 patients in the stereotactic body radiotherapy group, and 16 (14%) of 115 patients in the conventional external-beam radiotherapy group had a complete response for pain (risk ratio 1·33, 95% CI 1·14–1·55; $P = ·0002$).
Ryu et al. (2023)[22]	U.S.A.	Randomized controlled trial	339	N/A, radiosensitive and radioresistant types included	No	SBRT group: a single dose of 16 Gy or 18 Gy; EBRT group: a single dose of 8 Gy	24 months	N/A	Pain response at 3 months favored cEBRT (41.3% for SRS vs. 60.5% for cEBRT)

Table 2. Prospective Nonrandomized Studies Included with Primary Indications of Local Control and/or Pain Control

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Chang et al. (2007)[23]	United States	Prospective phase 1–2 trial	63	Renal, breast, lung, skin, colon, unknown	Yes	27 Gy in 3 fractions	21.3 months	84% at 1-year follow-up	N/A
Gerszten et al. (2007)[24]	United States	Prospective, nonrandomized cohort	500	Renal cell, breast, lung, melanoma, colon, sarcoma, prostate, multiple myeloma, unknown primary, squamous cell (laryngeal), thyroid, other	Yes	Mean 20 Gy in 1 fraction	21 months	88% at last follow-up	86% improvement at last follow-up
Levine et al. (2009)[25]	United States	Prospective, single arm	10	Sarcoma	Yes	Mean 30 Gy in 3 fractions	11.1 months	90% at last follow-up	90% pain relief at last follow-up
Amdur et al. (2009)[26]	United States	Prospective, single arm, phase 2 clinical trial	21	Tonsil, renal, GI lung, ependymoma, liposarcoma, skin, breast, Hodgkin's lymphoma	Yes	15 Gy for patients with no prior spine radiotherapy and 5 Gy for patients with prior spine radiotherapy, single fraction	11 months	95% local control at last follow-up	43% pain relief at 3-month follow-up
Garg et al. (2011)[27]	United States	Prospective, single arm	59	Renal, lung, sarcoma, breast, colon, other	Yes, 100%	27 grays (Gy) in 3 total fractions or 30 Gy in 5 total fractions.	17.6 months	76% at 1-year follow-up	N/A
Garg et al. (2012)[28]	United States	Prospective phase 1–2 trial	61	Renal, thyroid, sarcoma, breast, lung, other	No	16–24 Gy in 1 fraction	20 months	88% at 18-month follow-up	N/A
Ahmed et al. (2012)[29]	United States	Prospective, single arm	66	Renal, lung, sarcoma, melanoma, uterine, colon, prostate, thyroid, liver, breast, parotid gland, other	Yes	Median 24 Gy (range, 10–40 Gy) in a median 3 fractions (range, 1–5)	8.2 months	83.3% in patients with prior RT and 91.2% in those without prior RT at 1-year follow-up	N/A
Ho et al. (2016)[30]	United States	Prospective phase 1–2 trial	38	N/A	Yes	18–30 Gy in 1–5 fractions	75.7 months	85% at 1 year, 82% at 2 years, and 78% at 5-year follow-up	N/A
Bernstein et al. (2016)[31]	United States	Prospective phase 1–2 trial	23	Thyroid	Yes	Range from 16–18 Gy in single fraction to 27–30 Gy in 3–5 fractions	28.9 months	88% at 2 years, 79% at 3 years follow-up	N/A
Guckenberger et al. (2018)[32]	United States	Prospective, single arm, phase 2 clinical trial	54	Breast, lung, prostate, colorectal, renal, skin, other	No	48.5 Gy in 10 fractions or 35 Gy in 5 fractions	12 months	85.9% at last follow-up	87% had pain reduction at 12-month follow-up
Ning et al. (2019)[33]	United States	Prospective phase 1–2 trial	52	N/A, radiosensitive and radioresistant types included	Yes	16-24 Gy in 1 fraction or 30 Gy in 5 fractions	80.4 months	91% at 5-year follow-up	N/A
Ito et al. (2019)[34]	Japan	Prospective, single arm	20	Lung, breast, thyroid, colorectal, other	No	24 Gy in 2 fractions	24.5 months	100% at 6-month follow-up	83% pain response at 6-month follow-up

Table 2. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Mantel et al. (2019)[35]	Germany	Prospective, single arm, phase 2 clinical trial	56	Breast, lung, colon, renal, skin, prostate, other	No	Patients with intermediate life expectancy treated with 35 Gy in 5 fractions. Patients with long life expectancy were treated with 48.5 Gy in 10 fractions.	16.2 months	82% at last follow-up (median 7.8 months)	N/A
Guckenberger et al. (2021)[36]	U.K.	Prospective, single arm, multicenter phase 2 clinical trial	57	Breast, nonsmall cell lung cancer, prostate, colorectal, kidney, melanoma, other	Yes	48.5 Gy in 10 SBRT fractions or 35 Gy in 5 SBRT fractions	60 months	82% at last follow-up	82% at last follow-up
Hussain et al. (2022)[37]	U.S.A.	Prospective, single arm	90	Renal cell carcinoma	Yes	24 Gy in single fraction, 9–10 Gy in 3 fractions, 18 Gy in a single fraction, 18 Gy in 3 fractions or 6–7 Gy in 5 fractions	14.2 months	95.4% at 1-year follow-up	N/A

months with single-fraction SBRT for noncervical spine metastases. Local failure was defined by MR-documented progression of the treated spinal tumor as determined by the expert opinion of a dedicated radiologist. Bernstein et al.[31] performed a secondary analysis of a phase I/II trial examining the efficacy of SBRT on patients with metastatic thyroid cancer and found that patients who underwent SBRT as primary treatment achieved a local control rate of 88% at 2 years and 79% at 3 years. Local control was determined by MR imaging scans showing no evidence of progressive disease. In patients who had initially undergone conventional radiation therapy (RT) with progressive disease and then underwent SBRT for salvage therapy, local control remained at 88% at 3 years.[31] Of note, there is potential for heterogeneity in the timing of imaging follow-up for local control and inter-reader variability of analyzing imaging which can interpret local control between studies difficult to compare.

Local control rates appear to be excellent with spine SBRT, though there is some variation based on the radiosensitivity of the tumor histology. Bernard et al.[71] studied the outcomes of SBRT stratified by different histologies utilizing 24 Gy in 1 fraction for radioresistant tumors and either 27 Gy in 3 fractions or 18 Gy in 1 fraction for radiosensitive tumors. Their study confirmed that while local control rates were high for the total population (82.6% at 1 year and 75.8% at 2 years), radioresistant tumors such as nonsmall cell lung cancer or colorectal cancers had significantly higher failure rates and lower overall survival compared to radiosensitive histologies (failure rate of 30.4% vs. 8.0% at 1 year and 38.7% vs. 14.1% at 2 years; $P = .0008$), suggesting the need for continued study into optimal dosing for radioresistant tumor histologies.[71]

Pain control—. Randomized Controlled Trials

Multiple randomized controlled trials have demonstrated a significant degree of pain improvement in patients with spinal metastases after SBRT compared to their preoperative pain. Three trials have specifically compared pain improvement in patients treated with SBRT vs. conventional EBRT, which have provided mixed results with regard to which technique is superior. Sahgal et al.[21] reported the results of the SC.24 multicenter, randomized controlled trial comparing SBRT to conventional EBRT in patients with painful spinal metastases. The primary outcome was the proportion of patients with a complete pain response at 3 months posttreatment. At 3 months posttreatment, 35% of the patients who underwent SBRT compared to 14% of the patients who underwent EBRT had complete resolution of pain (risk ratio 1.33, 95% CI 1.14–1.55; $P = .0002$), thus meeting the primary endpoint. This significant difference was maintained in multivariable-adjusted analyses (odds ratio [OR] 3.47, 95% CI 1.77–6.80; $P = .0003$).[21]

Sprave et al.[19] performed a randomized phase II trial comparing the pain response between SBRT and three-dimensional conformal RT by using pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months following radiotherapy completion. There was no statistically significant

Table 3. Retrospective NonRandomized Studies Included with Primary Indications of Local Control and/or Pain Control

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Milker-Zabel et al. (2003)[38]	Germany	Retrospective cohort	19	Breast, lung, renal, other	Yes, 100%	Median total dose 39.6 Gy (range 24–45, median dose 2 Gy/ fraction).	12.3 months	94.7% at last follow-up	N/A
Gerszten et al. (2005)[39]	United States	Retrospective cohort	48	Renal cell carcinoma	Yes	Mean 20 Gy (range 17.5–25 Gy) in single fraction	37 months	N/A	89% pain improvement at last follow-up
Gagnon et al. (2007)[40]	United States	Retrospective cohort, matched pair	36 (18 SBRT, 18 EBRT)	Breast	Yes	24 Gy in 3 fractions for intial SBRT, 21 Gy in 3 fractions for reirradiation SBRT	24 months	N/A	Overall pain decreased significantly from levels before metastases to those 1 month postmetastases, and decreased somewhat thereafter, but there was no evidence of statistically significant differences between treatment groups.
Ryu et al. (2008)[41]	United States	Retrospective cohort	49	Lung, breast, prostate, kidney, other	No	Mean 13 Gy (range, 10–16 Gy) in single fraction	6.4 months	N/A	84% overall pain control rate at 1 y
Sheehan et al. (2009)[42]	United States	Retrospective cohort	40	Lung, prostate, renal cell carcinoma	No	Mean 17.3 Gy	12.7. months	N/A	85% improvement at last follow-up
Sahgal et al. (2009)[43]	United States	Retrospective cohort	39	N/A, radiosensitive and radioresistant types included	Yes	Median 24 Gy in 3 fractions	8 months	96% at 1-y follow-up	N/A
Molding et al. (2010)[44]	United States	Retrospective cohort	21	Melanoma, renal cell, sarcoma, angiosarcoma, leiomyosarcomas, colorectal carcinoma, thyroid, teratoma, hemangiopericytoma, cholangiocarcinoma, adenoid cystic carcinoma, hemangioma (epithelioid), prostate	No	Median 24 Gy, range 18–24 Gy, single fraction	11 months	81% at last follow-up	N/A
Nguyen et al. (2010)[45]	United States	Retrospective cohort	48	Renal cell carcinoma	Yes	24 Gy in 1 fraction, 27 Gy in 3 fractions, or 30 Gy in 5 fractions	13.1 months	82.1 % at 1-y follow-up	52% pain free at 1-y follow-up
Hunter et al. (2012)[46]	United States	Retrospective cohort	100 (34 EBRT, 76 SBRT)	Renal cell carcinoma	Yes	14 Gy maximum point dose and V10 Gy < 10% for the spinal cord, and 16 Gy maximum point dose and V12 Gy < 10% for the cauda equina.	4.3 months	N/A	68% for EBRT, 62% for SBRT ($P = .01$) improvement
Mahadevan et al. (2011)[47]	United States	Retrospective cohort	60	Lung, breast, renal, melanoma, GI, other	Yes, 100%	Median 30 Gy in 10 fractions	12 months	93% at last follow-up	65% improvement at 1 month

Table 3. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Haley et al. (2011)[48]	United States	Retrospective cohort	44 (22 EBRT, 22 SBRT)	Lung, breast, renal, unknown	No	EBRT group treated with either 20 Gy in 5 fractions or 30 Gy in 10 fractions; SBRT patients received doses ranging from 14 Gy to 20 Gy in1 fraction.	10 months	N/A	At the 1-month follow-up, no statistically significant difference in pain relief between the 2 groups ($P = .11$)
Nikolajek et al. (2011)[49]	Germany	Retrospective cohort	54	Renal, lung, breast, prostate, colorectal, gynaecological, skin, other	Yes, 100%	Median 18 Gy (range, 10–28 Gy) in single fraction	14.5 months	93% at 6 months, 88% at 12 months, and 85% at 18 months follow-up	Significant decreased in VAS score at 3 months, median score decreased from 6 to 4 posttreatment
Martin et al. (2012)[50]	UK	Retrospective cohort	29	Breast, kidney, thyroid, sacroma, prostate, lung, colorectal, skin, unknown primary	Yes	8–30 Gy in 1–3 fractions	11.1 months	91% at last follow-up	65% at last follow-up
Chang et al. (2012)[51]	Korea	Retrospective cohort	185 (54 reirradiated, 131 initial)	Breast, prostate, renal, GI	Yes	Dose was calculated to 2-Gy equivalent normalized BED	21.8 months	81% for retreatment and 89% for initial treatment at 12 months	Pain control rate was 86% for retreatment and 93% for initial at 6 months, 81% for retreatment and 89% for initial at 12 months, and 86% for treatment and 90% for initial at 2-y follow-up.
Lee & Chun (2012)[52]	Korea	Retrospective cohort	57	Breast, liver, lung, GI, cervix, prostate, other	Yes	15–35 Gy in 1–5 fractions	6.8 months	N/A	88% pain relief for a median 3.2 months
Laufer et al. (2013)[53]	U.S.A.	Retrospective cohort	186	Breast, prostate, colorectal, liver, lung, melanoma, renal, sarcoma, squamous cell, thyroid, other	No	single-fraction SRS (24 Gy) in 21.5%, high-dose hypofractionated SRS (24–30 Gy in 3 fraction) in 19.9%, or low-dose hypofractionated SRS (18–36 Gy in 5 or 6 fractions) in 58.6%.	7.6 months	83.6% at 1-y follow-up	N/A
Kim et al. (2013)[54]	Korea	Retrospective cohort	22	Thyroid, lung, breast, stomach, hepatobiliary, colorectum, prostate, soft tissue	Yes	24 Gy in 3 fractions, 30 Gy in 5 fractions, or 16 Gy in a single fraction	10 months	81.3% at 6 months follow-up	96.8% pain response rate and 93.5% pain progression-free survival rate at 3 months
Guckenberger et al. (2014)[55]	United States, Canada, Germany	Retrospective cohort	301	Breast, renal, lung, other	No	Median total 24 Gy (range 8–60 Gy) in 3 fractions (range 1–20)	11.8 months	83.9% at 2 ys follow-up	Patients suffering from mild/moderate and severe pain prior to SBRT were pain-free at the time of the last follow-up in 76.8%, 56.3% and 43.8%, respectively.

Table 3. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Folkert et al. (2014)[56]	U.S.A.	Retrospective cohort	88	Angiosarcoma, chondrosarcoma, fibrosarcoma, hemangiopericytoma/solitary fibrous tumor, leiomyosarcoma, liposarcoma (myxoid), other/unspecified spindle-cell	Yes	Hypofractionated median dose, 28.5 Gy in 3–6 fractions or single fraction median dose, 24 Gy	12.3 months	87.9% at 1-y follow-up, 77.4% at 2-y follow-up	N/A
Wang et al. (2014)[57]	China	Retrospective cohort	62	Lung, breast, renal, H&N, liver, GI	Yes	20–48 Gy in 1-5 fractions for unirradiated patients, 21–38 Gy in 1–5 fractions for the previously irradiatied patients	9.4 months	97.3% at 1-y follow-up	93.3% complete or partial reduction of pain at 1-month follow-up
Sohn et al. (2014)[58]	Korea	Retrospective cohort	26 (SBRT 13, EBRT 13)	Renal cell carcinoma	No	Mean total 38.0 and 29.4 Gy in the SRS and RT group, respectively ($P = .04$). Median number of fractions was 4 and 11 in the SRS and RT groups, respectively.	N/A	SBRT rates of 100%, 100%, 100%, 100%, and 85.7% at 1, 2, 3, 6, and 12 months after SRS, respectively. EBRT rates of 100%, 91.7%, 83.3%, 58.3%, and 29.2% at 1, 2, 3, 6, and 12 months after RT, respectively.	Perioperative VAS score decrease was larger in the SRS group than that in the RT group ($P = .04$). More SRS patients had complete or partial pain relief although the difference was not significant.
Finnigan et al. (2015)[59]	Australia	Retrospective cohort	34	Melanoma, prostate adenocarcinoma, breast adenocarcinoma, other	Yes	20 Gy in a single fraction or 24–28 Gy in 2–3 fractions	7.4 months	86% at last follow-up	N/A
Puvanesarajah et al. (2015)[60]	United States	Retrospective cohort	99	RCC, breast, prostate, NSCLC, sarcoma, colon, melanoma, nasopharyngeal, pancreas, urothelial, atypical pulmonary carcinoid, other	Yes	21 Gy (range 6–54.9 Gy) in a median of 3 fractions	6 months	79% at last follow-up	59% improvement at last follow-up
Bishop et al. (2015)[61]	United States	Retrospective cohort	285	Renal, lung, thyroid, sarcoma, breast, other	No	18 Gy in 1 fraction, 24 Gy in 1 fraction, or 27 Gy in 3 fractions	19 months	88% at 1-y follow-up	N/A
Moussazadeh et al. (2015)[62]	United States	Retrospective cohort	31	Prostate, breast, sarcoma, renal, thyroid, skin, solitary fibrous tumor	No	24 Gy in single fractions	73 months	90% at last follow-up	N/A

Table 3. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Park et al. (2015)[63]	Korea	Retrospective cohort	39	Breast, liver, stomach, lung, bile duct, colon and rectum, parotid gland, pancreas, endometrium, prostate, others	Yes	Median 27 Gy (range, 18–35 Gy) in median of 3 fractions (range, 1–5)	7.4 months	93% at 1-y follow-up	At 1–3 months after completion of SBRT, VAS score was reduced to a median post-SBRT score of 1 (range, 0–8). The median pre-SBRT VAS score was 4 (range, 0–10)
Anand et al. (2015)[64]	India	Retrospective cohort	52	Breast, lung, prostate, soft tissue sarcoma, renal, head and neck, multiple myeloma, thyroid, other	No	Median 24 Gy (range 24–27 Gy) in a median of 3 fractions (range 1–3)	8.5 months	94% at 1-y follow-up	Complete pain relief was seen in 90% of patients with epidural extension and 93.75% without epidural extension
Leeman et al. (2016)[65]	United States	Retrospective cohort	88	Angiosarcoma, chondrosarcoma, fibrosarcoma, solitary fibrous tumor, leiomyosarcoma, liposarcoma, unspecified spindle cell	Yes	Most lesions treated with 24 Gy (range 18–36 Gy) with single-fraction. The remaining lesions treated with hypofractionated SBRT (median 3 fractions, range 2–6).	14.4 months	85.9% at 1-y follow-up	N/A
Hashmi et al. (2016)[66]	United States	Retrospective cohort	215	N/A	Yes, 100%	Median 18 Gy for patients treated with 1 fraction, median 24 Gy in 3 fractions for patients treated with multiple fractions	8.1 months	83% at 1-y follow-up	N/A
Sohn et al. (2016)[67]	Korea	Retrospective cohort	56 (28 SBRT, 28 EBRT)	Hepatocellular carcinoma	No	Mean total dose 35.4 Gy and 31.5 Gy in the SRS and RT groups, respectively ($P = .10$). Mean number of fractions was 4.0 in the SRS group and 10.2 in the RT group	11.3 months	SRS rates of 92%, 92%, 80%, 59%, and 25% at 1, 2, 3, 6, and 12 months, respectively. EBRT rates of 92%, 87%, 78%, 64%, and 32% at 1, 2, 3, 6, and 12 months after RT, respectively. No statistically significant difference.	Perioperative visual analog scale (VAS) decrease was larger in SRS group than in RT group, but the difference was not significant (3.7 vs. 2.8, $P = .13$). Number of patients with complete ($n = 6$ vs. 3) or partial ($n = 12$ vs. 13) relief was larger in SRS group than in RT group; however, the difference was not significant ($P = .83$).
Chang et al. (2017)[68]	Australia	Retrospective cohort	60	Prostate, breast, skin, sarcoma, renal, lung, gastroesophageal, head and neck, unknown primary	No	20 Gy in 1 fraction, 24 Gy in 2 fractions, or 24 Gy in 3 fractions	21 months	92% at 1-y and 86% at 2-y follow-up	N/A

Table 3. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Gestaut et al. (2017)[69]	United States	Retrospective cohort	73	Lung, breast, renal, prostate, skin, rectal, colon, esophageal, head and neck, thyroid, sarcoma, hepatocellular carcinoma	No	20 Gy in single fraction	12.7 months	97% at last follow-up	69% complete resolution at last follow-up
Yoo et al. (2017)[70]	Korea	Retrospective cohort	29	Hepatocellular carcinoma	No	6-20 Gy in 1 fraction, or 18–45 Gy in 3 fractions	7 months	68.3% at 1-y follow-up	73.3% at a mean of 7 months follow-up
Bernard et al. (2017)[71]	United States	Retrospective cohort	127	All radiosensitive (thyroid, breast, lung, colon)	Yes	27 Gy in 3 fractions or 18 Gy in 1 fraction	22.6 months	82.6% at 1-y and 75.8% at 2-y follow-up	N/A
Ito et al. (2018)[72]	Japan	Retrospective cohort	131	Lung colorectal, thyroid, renal, breast, prostate, sarcoma, other	Yes	24 Gy in 2 fractions	9 months	72.3% at 1-y follow-up	61.7% pain relief at 1-y follow-up
Silva et al. (2019)[73]	United States	Retrospective cohort	61	Adenocarcinoma, renal, breast, squamous cell, other	Yes	3-fraction (median dose, 27 Gy; range, 24-30 Gy) or 5-fraction (median dose, 35 Gy; range, 25–40 Gy)	13.6 months	83% at 1-y follow-up	N/A
Kelley et al. (2019)[74]	United States	Retrospective cohort	127	Renal, lung, breast, GI, thyroid, prostate, ovarian, uterine, head and neck, skin	Yes	16 Gy (range, 16–20 Gy) for single-fraction and 24 Gy (range, 16–40 Gy) for hypofractionated	5.9 months	84.7% at 6 months, 74.7% at 1-y follow-up	53.8% improvement at last follow-up
Ozdemir et al. (2019)[75]	Turkey	Retrospective cohort	78	Breast, prostate, lung, other	No	16–18 Gy in single fraction	13 months	88% at last follow-up	N/A
Ito et al. (2020)[76]	Japan	Retrospective cohort	34	Colorectal cancer	Yes	24 Gy in 2 fractions	12 months	56% at 1-y follow-up	84% at 1 month, 86% at 3 months, 52% at 6 months, 60% at 9 months and 50% at 12 months
Detsky et al. (2020)[77]	Canada	Retrospective cohort	43	Lung, renal, other	Yes, 100%	24–30 Gy using 2–5 fractions	12.4 months	93% at 6 months, 86% at 1 y, and 81% at 2 y follow-up	N/A
Sasamura et al. (2020)[78]	Japan	Retrospective cohort	40	Renal, lung, liver, colon, thyroid, others	Yes, 100%	25 Gy in 5 fractions	9.7 months	67% at 1-y and 51% at 2-y follow-up	60% pain relief at last follow-up
Rothrock et al. (2020)[79]	United States	Retrospective cohort	29	Adrenal, chordoma, GI, solitary fibrous tumor, liver, lung, germ cell, renal, salivary, sarcoma, skin, thyroid, uterine	Yes	Median 27 Gy in 3 fractions	Surviving patients median follow-up 25 months	89.6% at 1-y and 78% at 2-y follow-up	N/A

Table 3. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Sogono et al. (2021)[80]	Australia	Retrospective cohort	371	Bone and soft tissue, breast, gastrointestinal, genitourinary, prostate, lung, skin, other clear cell carcinoma (11%), sarcoma (7%), squamous cell carcinoma (5%), other (12%)	Yes	16–28 Gy and the most common 20 Gy (58%)	37 months	96% at 1 y, 92% at 3 y, 92% at 5 y	N/A
Blakaj et al. (2021)[81]	United States	Retrospective cohort	63	Renal, lung breast, GI, thyroid, prostate, head and neck, skin	No	Median 27 Gy in 3 fractions	12.5 months	81% at 1-y follow-up	N/A
Ehret et al. (2021)[82]	Germany	Retrospective cohort	53	Renal, lung, colon, prostate, head and neck, breast, other	Yes, 100%	18 Gy in 1 fraction	22.2 months	77% at last follow-up	N/A
Perez-Montero et al. (2022)[83]	Spain	Retrospective cohort	60	Breast, prostate, endometrium, head and neck, lung, vipoma, pancreas, lung, rectum, renal, thyroid, unknown	Yes	16 Gy in 1 fraction	26.1 months	76.3% at 1-y and 70.6% at 2-y follow-up	N/A
Dibs et al. (2022)[84]	United States	Retrospective cohort	58	Renal, sarcoma, lung, breast, thyroid, prostate, GI, skin, head and neck, neruosendocrine, pituitary, paraganglioma, bladder	Yes	14–27.5 Gy in 1–5 fractions	15 months	85% at 1-y follow-up	N/A
Dibs et al. (2022)[85]	United States	Retrospective cohort	165	Breast, renal, sarcoma, thyroid, GI, lung, neuroendocrine, prostate, melanoma, head and neck, pituitary, bladder, paraganglioma	No	14–35 Gy in 1–5 fractions	15 months	88% at 1-y follow-up (89% for 1–2 levels vs. 84% for ≥ 3 levels, $P = .747$)	N/A
Wang et al. (2022)[86]	China	Retrospective cohort	71	Lung, liver, thyroid, breast, esophagus, rectum, kidney, sarcoma, ovarian	No	Standard-risk patients 30 Gy (range 21–36) with median fractions of 3 (range 1–3) and high-risk patients 35 Gy (range 24–50) with median fractions of 5 (range 4–5)	17 months	93.1% at 1-y, 90% at 2-y follow-up	95.7% pain response and 83.6% complete pain relief at 12 weeks follow-up
Zeng et al. (2022)[87]	Canada	Retrospective cohort	137 (66 SBRT, 71 EBRT)	Breast, GI, skin, lung, prostate, renal, thyroid, other, no significant difference between groups	No	SBRT Group: 24 Gy in 2 fractions EBRT Group: 20 Gy in 5 fractions	11.3 months	SBRT 97.2% vs. EBRT 88.8% at 6 months, SBRT 93.9% vs. EBRT 71.6% at 1 y, SBRT 85.2% vs. EBRT 64.4% at 2 y ($P < .001$)	N/A

Table 3. Continued

Study	Country	Study Design	Patient No.	Primary Cancer Location/Histology	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control Results	Pain Control Results
Ito et al. (2022)[88]	Japan	Retrospective cohort	17	Renal, thyroid, breast, sarcoma, other	Yes, 100%	Initial dose 24 Gy in 2 fractions, second dose 30 or 35 Gy in 5 fractions	19 months	100% at 12 months, 92% at 18 months follow-up	N/A
Lee et al. (2023)[89]	United States	Retrospective cohort	60	Renal	Yes	27 Gy delivered in 3 fractions, 40 Gy delivered in 5 fractions, or 18 Gy delivered in 1 fraction	8.6 months	87.8% at 1-y and 83.2% at last follow-up	N/A
Cuccia et al. (2023)[90]	Italy	Retrospective cohort	177	Prosate, breast, lung, renal, other	No	Median 21 Gy (14–35 Gy) in 3 fractions (1–5 fractions)	18 months	90.3% at 1 y, 84.3% at 2 y and 84.3% at 3 y follow-up	N/A
Deodato et al. (2023)[91]	Italy	Retrospective cohort	40	Prostate, breast, ovarian, head and neck, thyroid, lung	No	25 Gy in 10 daily fractions. Sequentially, the dose to spinal metastases was progressively increased (8 Gy, 10 Gy, 12 Gy) in the patient cohorts.	70 months	88.5% at 2-y follow-up	N/A

Table 4. Studies Included with Primary Indications of Spinal Cord Compression

Study	Country	Study Design	Patient No.	Primary Cancer Location/ Histology	Patients with Prior Surgery?	Patients with Prior Radiation?	Radiation Doses	Mean Follow-up	Local Control/Cord Compression Results
Ryu et al. (2010)[92]	United States	Prospective, single-arm, cohort	62	Breast, prostate, lung, renal, liver, thyroid, gynecological, skin, chordoma, bladder, GI, liposarcoma, neuroendocrine, paraganglioma, osteosarcoma, unknown	No	No	Median 16 Gy (range 12–20 Gy) in single fraction	11.5 months	Mean epidural tumor volume reduction was 65% at 2 months after radiosurgery ($p < .001$). Thecal sac patency improved from 55% to 76% ($P < .001$). Overall, neurological function improved in 81%.
Al-Omair et al. (2013)[93]	Canada	Retrospective cohort	80	Breast, lung, thyroid, renal, liver, other	Yes	Yes	18–26 Gy in 1-2 fractions, or 18–40 Gy in 3–5 fractions	8.3 months	86% local control at 1-y follow-up
Lee et al. (2014)[94]	United States	Retrospective cohort	33	Breast, prostate, Merkel cell, myeloma, lung, renal, GI, Ewing's sarcoma, skin, thyroid	No	No	16–18 Gy	14.5 months	Significant epidural tumor response rate of 74%. 67% of patients ambulatory pretreatment were ambulatory at last follow-up. Ultimately, 27% of patients eventually required surgery for neurologic compromise or mechanical instability.
Tao et al. (2016)[95]	United States	Prospective phase 1–2 trial	66	Renal, sarcomas, breast, thyroid, colon, lung, unknown primary, other	Yes	Yes	16–18 Gy in 1 fraction, 27 Gy in 3 fractions, or 30 Gy in 5 fractions	30 months	85% local control at 1-y follow-up
Ito et al. (2018)[96]	Japan	Retrospective cohort	28	Thyroid, lung, renal, colorectal, other	Yes	Yes	24 Gy in 2 fractions	13 months	70% local control at 1-y
Meleis et al. (2019)[97]	United States	Retrospective cohort	20	Renal, skin, sarcoma, thyroid, prostate, lung, breast, lymphoma, hepatocellular	No	Yes	16 Gy in single fraction, 18 Gy in 3 fractions, 24 Gy in 3 fractions, 24 Gy in 4 fractions, or 30 Gy in 5 fractions	8.4 months	55% local control at median 6 months
Versteeg et al. (2019)[98]	Netherlands	Prospective cohort	13	Renal, breast, lung, prostate, skin	Yes	No	Median doses for SBRT plans with and without dose sparing were 17.9 Gy and 17.5 Gy, respectively.	N/A	Median dose in the surgical area 2.6 Gy (1.6–5.3 Gy) in the SBRT plan with active sparing of the surgical area, 3.7 Gy (1.6–6.3 Gy) in the SBRT plan without sparing, and 6.5 Gy (3.5–9.1 Gy) in the EBRT plans ($P < .001$).
Redmond et al. (2020)[99]	United States	Prospective, single-arm, phase 2 clinical trial	35	Lung, renal, breast, skin, pancreas, prostate, other	Yes	No	30 Gy in 5 fractions	10.5 months	Radiographic and symptomatic local control at 1 y were 90% (95% confidence interval, 76%-98%)
Ito et al. (2022)[100]	Japan	Prospective, single-arm, phase 2 clinical trial	33	Renal, sarcoma, thyroid, breast, hepatocellular, colorectal, lung, other	Yes	Yes	24 Gy in 2 fractions	15 months	88% local control at 1 y; pain response rates at 1, 3, 6, 9, and 12 months were 82%, 92%, 80%, 74%, and 83%, respectively.
Chakravarthy et al. (2023)[101]	United States	Retrospective cohort	50	Colorectal	Yes	Yes	Median 27 Gy over a median of 3 fractions.	N/A	86.7% local control at 2 yfollow-up. Progression of disease occurred in 14% patients at the index level, requiring reoperation and/or reirradiation at a mean of 400 days after surgery.

difference between the 2 groups at 3 months; however, pain values decreased faster within this period in the SBRT group ($P = .01$) and there were significantly lower VAS scores at 6 months posttreatment in the SBRT group ($P = .002$).[19]

Conversely, in recently published results of NRG/RTOG 0631, a randomized trial comparing stereotactic radiosurgery to conventional radiotherapy for localized vertebral spine metastases, the superiority of SRS compared with conventional EBRT regarding pain control was not demonstrated.[22] In this trial, patients with 1–3 vertebral metastases were randomized 2:1 to the SRS or conventional EBRT groups with the primary endpoint being patient-reported pain response defined by at least a 3-point improvement on the Numerical Rating Pain Scale without worsening in pain at the secondary site(s) or the use of pain medication. The primary endpoint of pain response at 3 months favored conventional EBRT (41.3% for SRS vs. 60.5% for conventional EBRT; $P = .01$), thus not supporting the superiority of SRS.[22] However, the trial did not utilize the Spinal Instability Neoplastic Score,[102] as the protocol was developed the use of this tool. As such, patients may have been enrolled who had primarily mechanical spine pain that would not be expected to improve with radiation therapy. Furthermore, there was an imbalance between arms, with patients in the SRS arm having worse baseline performance status, and having a higher baseline performance status was associated with improved pain response.

Lee et al.[103] performed a meta-analysis of 6 randomly controlled trials[19,21,104–107] comparing SBRT vs. conventional EBRT for the management of painful bone metastases. This analysis included the 3 spine specific trials discussed above, and 3 additional nonspine specific trials. Overall, their analysis demonstrated that SBRT improved complete pain response rates at 3 months (OR, 3.38; 95% CI, 1.88–6.07, $P < .01$), reduced local progression rates (OR, 0.19; 95% CI, 0.06–0.62, $P < .01$), and increased pain flare rates.[103]

Nonrandomized Controlled Trials

Multiple, single institutional studies report significant improvement in pain following SBRT. Ryu et al.[41] examined 49 patients with 61 solitary spinal metastases treated with SBRT and demonstrated that medial time to pain relief was 14 days, with 46% of patients achieving complete pain relief, 18.9% achieving partial relief, and 16.2% having stable symptoms. About 7% of patients had a relapse of pain at the treated spinal segment; however, the overall pain control rate for 1 year was 84%.[41] Levine et al.[25] analyzed a small cohort of patients with primary sarcomas and metastatic sarcomas to the spine and found that in the patients who underwent SRS, complete pain relief was achieved in 8 patients, partial relief in 7 patients, and no relief in 1 patient.

On the other hand, Sprave et al.[20] performed a secondary analysis of an exploratory phase II randomized trial comparing patients who underwent SBRT compared to conventional 3D conformal RT and found that there were no significant quality of life differences between the 2 groups, including painful sites, pain characteristics, functional impairment, or psychosocial aspects ($P > .05$ for all).

Spinal cord compression—.
Randomized Controlled Trials

No randomized controlled trials evaluated the role of SBRT in treating metastatic spine disease with spinal cord compression.

Nonrandomized Controlled Trials

Approximately 10% of patients with spinal metastatic disease develop spinal cord compression, which can cause permanently disabling neurological symptoms.[4] There are some small, retrospective studies that demonstrate decompression of metastatic epidural compression with SBRT alone. Ryu et al.[92] demonstrated epidural tumor volume reduction 2 months after radiosurgery. The epidural tumor area at the level of the most severe spinal cord compression was 0.82 ± 0.08 cm^2 before radiosurgery compared to 0.41 ± 0.06 cm^2 after ($P < .001$). Neurological function also improved in 81% of the patients.[92] Similarly, Lee et al.[94] used SRS to treat 33 patients with 35 treatment centers with severe epidural compression with 74% of patients experiencing significant epidural tumor response.

However, given the acuity of patients presenting with spinal cord compression and the desire to maximize SBRT dose delivered to gross disease, it has become common for patients to undergo separation surgery, where the tumor is separated from the spinal cord and stabilization is provided, before SBRT. Once the spinal cord is free from severe epidural compression with reconstitution of the thecal sac, SBRT can be delivered safely with improved coverage of the gross disease, simultaneously allowing for appropriate sparing of the spinal cord. Versteeg et al.[98] studied the radiation plans for patients with symptomatic spinal cord compression status post-decompression surgery who received EBRT, SBRT, or SBRT with active sparing of the posterior surgical area. They found that the median total dose given to the surgical area was 2.6 Gy (1.6–5.3 Gy) in the SBRT plan with active sparing of the surgical area compared to a median total dose of 3.7 Gy (1.6–6.3 Gy) in the SBRT plan without sparing and 6.5 Gy (3.5–9.1 Gy) in the EBRT plans ($P < .001$).[98] SBRT was able to significantly decrease the radiation exposure to the surgical area, which lowers the risk of wound complications when surgery and radiotherapy are combined for the treatment of spinal metastases.

Redmond et al.[99] performed a single-arm, phase II study of postoperative SBRT for solid tumor spine metastases, which demonstrated both radiographic and symptomatic local control of 90% at 1-year post-SBRT. Among the patients who did experience a recurrence, the median time to local recurrence was 3.5 months. Importantly, the median time to return of systemic therapy in this study was 0.5 months (range, 0–9.4 months). None of these patients experienced any wound dehiscence, hardware failure, or new symptoms of myelopathy. The results from this study demonstrated superior rates of local control compared to conventional RT at that time (ie, 69.3% local control at 1 year) without significant toxicity, though there was no specific comparative group.[99,108]

Tao et al.[95] performed a secondary analysis of phase I/II trials of patients who underwent SBRT after spine surgery, including laminectomy, vertebrectomy, or a combination

of these techniques. While this study did not have a comparative arm, the actuarial 1-year rate of tumor control was 85%, adjacent vertebral body control was 85%, and overall survival was 74% (median 29 months). There were no grade 3 or higher neurological toxicities.[95] Similarly, Ito et al.[100] performed a phase II clinical trial of separation surgery followed by SBRT in the setting of metastatic, compressive epidural disease. After 3 months of treatment, 90% of the patients had disease of Bilsky grade ≤ 1 (impingement or deformation of the dural sac, without spinal cord compression), and the 12-month local failure rate was 13%. Al-Omair et al.[93] found that postoperative SBRT was able to provide significantly greater local control in the subset of patients where their severe epidural disease was surgically decompressed to a Bilsky grade 0 or 1 (Bone only disease or impingement or deformation of the dural sac, without spinal cord compression) ($P = .0009$).

Oligometastatic cancer—.
Randomized Controlled Trials

There were no randomized controlled trials evaluating the role of SBRT in treating spine metastases in which they clarified that spine metastases are the only site of oligometastatic disease for all patients included.

Nonrandomized Controlled Rials

Oligometastatic disease of the spine can also be treated with SBRT with high efficacy. Ho et al.[30] performed a secondary analysis of a subset of patients from a phase I/II trial who had oligometastatic disease and were treated with SBRT. Of that population, 45% had prior conventional EBRT and those patients generally had worse overall survival. However, 1-, 2-, and 5-year local progression-free survival rates were 85%, 82%, and 78%, respectively, in the patients who underwent SBRT, with only 2 patients experiencing late grade 3–4 toxicity.[30]

Deodato et al.[91] performed a dose-escalation study with 52 treatment centers in 40 consecutive patients with oligometastatic spinal disease. For their treatment plan, 25 Gy was delivered in 10 daily fractions (2 weeks) of 3D conformal radiation therapy to the metastatic lesion, affected vertebrae, and adjacent ones (one cranial and one caudal vertebra). Sequentially, the SBRT dose to spinal metastases was progressively increased to either 8 Gy, 10 Gy, or 12 Gy. At all of the different boost levels, there were no acute toxicities greater than grade 2 and no late toxicities greater than grade 1, and the 24-month actuarial local control rate was 88.5%, suggesting that a 12-Gy spine metastasis SBRT boost following 25 Gy was safe and provided excellent local control.[91]

Re-irradiation—.
Randomized Controlled Trials

No randomized controlled trials evaluated the role of SBRT in treating metastatic spine disease in which they clarified that all patients had previously undergone radiation therapy.

Nonrandomized Controlled Trials

As patients with metastatic cancer continue to have improved overall survival, the role of re-irradiation to spine metastases is increasing. However, re-irradiation of the spine is complicated by the radiosensitivity of the spinal cord and cauda equina and the potential for increased risk of radiation-induced myelopathy. Ito et al.[88] assessed 19 lesions in 17 patients who had previously undergone radiation. The initial radiation dosing for patients was 24 Gy in 2 fractions and reirradiation dosing was 30–35 Gy in 5 fractions at the same target site. Their 12- and 18-month local failure rates were 0% and 8%, respectively; however, while radiation-induced myelopathy was not found in any of their patients, 4 (21%) developed radiculopathy, and 2 (11%) developed vertebral compression fractures. Of the 4 patients who developed radiculopathy, 3 (75%) had almost complete upper/lower limb paralysis. While re-irradiation via SBRT provided good local control and did not increase myelopathy, there was high-grade radiculopathy toxicity in this cohort.[88]

Gerszten et al.[39] analyzed a cohort of 60 renal cell carcinoma radiation sites, 42 of which had previously been treated with EBRT to a level precluding further conventional EBRT. The maximum tumor dose was maintained at 17.5–25 Gy with a mean of 20 Gy. SBRT was utilized for these patients without any immediate, new neurological deficits or radiation-induced myelopathy or radiculopathy in the follow-up period.

While SBRT does appear to provide excellent local control in patients who had previously undergone conventional RT, the degree of radiation-induced myelopathy or radiculopathy that may result from re-irradiation is unclear.

Complications of SBRT

The following sections will discuss some of the most common complications that can result from the treatment of spinal metastases with SBRT.

Vertebral Compression Fractures

The most common complications following SBRT are vertebral compression fractures at the treated levels or levels adjacent to the treatment site. Sprave et al.[18] performed a randomized, controlled trial comparing the bone density of vertebral bodies post-SBRT vs. 3D conformal RT at presentation, 1 month, and 3 months along with rates of pathological fractures following treatment. They found that compared to baseline, bone density significantly increased post-SBRT and post-3D conformal RT at 3 and 6 months ($P < .01$). While there was no significant difference between SBRT and 3D conformal RT in terms of the increased bone density, there was a trend towards more pathological fractures in the SBRT arm compared to the 3D conformal RT arm (8.7% vs. 4.3%, $P = .06$).[18]

Another study by Mantel et al.[35] found that 34.4% of the post-SBRT lesions in their population had a vertebral compression fracture; however, only 5% were symptomatic as defined by an increase in VAS by > 2 or the need for surgical stabilization. In their multivariate analysis, relative vertebral body involvement, osteolytic volume, and pre-SBRT vertebral compression fractures were predictive for

post-SBRT compression fractures with an area under the curve (AUC) = 0.930.[35]

Many studies report vertebral compression fractures following SBRT. Ferini et al.[109] performed a meta-analysis of patients who underwent RT for the treatment of spine metastases from primary hepatocellular carcinoma, and the post-SBRT rate of vertebral compression fractures was 16% (95% CI 10–23%), with fracture rates significantly higher after SBRT compared to other types of RT ($P = .033$). Zeng et al.[110] studied dose escalation to 28 Gy in 2 daily fractions compared to 24 Gy in 2 daily fractions, which improved local control rates, but the higher radiation dose did not increase the rate of vertebral compression fractures.

While the rate of vertebral compression fractures can be as high as 30% in the literature, less than 5% of vertebral compression fractures require any percutaneous intervention or surgical stabilization.[87,111–113]

Radiation Myelopathy

Radiation myelopathy is a rare, but devastating complication of spine SBRT. In a review of nearly 1400 patients who underwent SBRT by Hall et al.[114] the reported incidence of radiation-induced myelopathy was less than 1%. While additional research needs to be performed to determine risk factors for radiation myelopathy and specific guidelines regarding re-irradiation, a recent modeling analysis in the Hypofractionation Treatment Effects in the Clinic (HyTEC) report provides some recommendations.[115] For de novo spine SBRT, the recommended maximum point dose exposure to the spinal cord is 12.4–14 Gy in 1 fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions. Estimates describe the risk of radiation myelopathy of 1-5% if these guidelines are followed.[115] Per the HyTEC report, for re-irradiation SBRT, "reported factors associated with a lower risk of radiation myelopathy include cumulative thecal sac equivalent dose in 2 Gy fractions with an alpha/beta of 2 ($EQD2_2$) Dmax ≤ 70 Gy; SBRT thecal sac $EQD2_2$ Dmax ≤ 25 Gy, thecal sac SBRT $EQD2_2$ Dmax to cumulative $EQD2_2$ Dmax ratio ≤0.5, and a minimum time interval to reirradiation of ≥5 months."[115,116]

Conclusions

SBRT provides excellent local control and pain control for patients with metastatic disease to the spine, and this remains true for patients with spinal cord compression managed with surgical separation followed by postoperative spine SBRT. SBRT is an advantageous technique as it allows for precise treatment with very high doses per fraction when compared to EBRT. However, the technique does not come without its limitations as there is a potential risk to normal tissues from the very high dose per fraction if it is not delivered with great accuracy. This high level of precision requires high-quality immobilization and accurate delivery systems. Additionally, SBRT is primarily suitable for small, well-defined tumors that can be identified with CT or MR imaging. Patients who do not fit these criteria may be better treated with other modalities such as systemic treatment of EBRT. While not all patients are appropriate candidates for SBRT, careful consideration of appropriate frameworks that take into account the patient's overall prognosis can guide a multidisciplinary team toward the patients who will benefit the most from this treatment modality.

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Conflict of interest statement

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