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Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients

Clinical article

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Object. Decompression surgery followed by adjuvant radiotherapy is an effective therapy for preservation or recovery of neurological function and achieving durable local disease control in patients suffering from metastatic epidural spinal cord compression (ESCC). The authors examine the outcomes of postoperative image-guided intensity-modulated radiation therapy delivered as single-fraction or hypofractionated stereotactic radiosurgery (SRS) for achieving long-term local tumor control.

Methods. A retrospective chart review identified 186 patients with ESCC from spinal metastases who were treated with surgical decompression, instrumentation, and postoperative radiation delivered as either single-fraction SRS (24 Gy) in 40 patients (21.5%), high-dose hypofractionated SRS (24–30 Gy in 3 fractions) in 37 patients (19.9%), or low-dose hypofractionated SRS (18–36 Gy in 5 or 6 fractions) in 109 patients (58.6%). The relationships between postoperative adjuvant SRS dosing and fractionation, patient characteristics, tumor histology–specific radiosensitivity, grade of ESCC, extent of surgical decompression, response to preoperative radiotherapy, and local tumor control were evaluated by competing risks analysis.

Results. The total cumulative incidence of local progression was 16.4% 1 year after SRS. Multivariate Gray competing risks analysis revealed a significant improvement in local control with high-dose hypofractionated SRS (4.1% cumulative incidence of local progression at 1 year, HR 0.12, p = 0.04) as compared with low-dose hypofractionated SRS (22.6% local progression at 1 year, HR 1). Although univariate analysis demonstrated a trend toward greater risk of local progression for patients in whom preoperative conventional external beam radiation therapy failed (22.2% local progression at 1 year, HR 1.96, p = 0.07) compared with patients who did not receive any preoperative radiotherapy (11.2% local progression at 1 year, HR 1), this association was not confirmed with multivariate analysis. No other variable significantly correlated with progression-free survival, including radiation sensitivity of tumor histology, grade of ESCC, extent of surgical decompression, or patient sex.

Conclusions. Postoperative adjuvant SRS following epidural spinal cord decompression and instrumentation is a safe and effective strategy for establishing durable local tumor control regardless of tumor histology–specific radiosensitivity. Patients who received high-dose hypofractionated SRS demonstrated 1-year local progression rates of less than 5% (95% CI 0%–12.2%), which were superior to the results of low-dose hypofractionated SRS. The local progression rate after single-fraction SRS was less than 10% (95% CI 0%–19.0%).
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Key Words • **spinal metastases** • **radiotherapy** • **radiosurgery** • **spinal cord compression** • **surgery** • **oncology**

The aim of therapy in the treatment of metastatic spine tumors is palliative, with the goals of improving or maintaining neurological function, achieving spine stability, relieving pain, and providing durable tumor control. In our institution, the primary indications for surgery are relief of high-grade ESCC resulting from tumors radioresistant to cEBRT or gross spinal instability.[1,6] Multiple series have demonstrated that surgery is effective for addressing neurological, mechanical stability,

Abbreviations used in this paper: cEBRT = conventional external beam radiation therapy; ESCC epidural spinal cord compression; MSKCC = Memorial Sloan–Kettering Cancer Center; OS = overall survival; PFS = progression-free survival; RT = radiation therapy; SRS = stereotactic radiosurgery.

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This article contains some figures that are displayed in color online but in black-and-white in the print edition.

and pain issues, but very few have examined its ability to achieve durable control. With improvements in systemic therapy, patients are living longer, and this places a greater emphasis on the need to prevent local tumor recurrence and spinal cord compression. Conventional EBRT, such as 30 Gy delivered in 10 fractions, has traditionally been used in the postoperative setting, but high local recurrence rates have been observed in up to 70% of patients at 1 year.[18] Modern image-guided radiation methods allow precise delivery of high radiation doses administered as SRS, also known as stereotactic body radiation therapy (SBRT).Typically, SRS refers to high-dose, conformal radiation delivered in 1–5 fractions with daily image guidance. As definitive therapy in patients with minimal or no ESCC, it has demonstrated response rates of 85%–95%, even in tumors considered radioresistant to cEBRT, such as renal cell carcinoma, melanoma, and sarcoma.[9–12,29] Based on these improved response rates in the upfront setting, a number of centers have begun to explore the use of adjuvant SRS following surgical decompression of high-grade ESCC to achieve better tumor control than that seen with cEBRT and potentially to reduce the aggressiveness of tumor resection due to the expectation that residual tumor can be controlled with cytotoxic doses of radiation that spare the spinal cord.[23,25–27]

Moulding et al.[23] previously reported a pilot study from our institution involving 21 patients who underwent "separation surgery" in which the thecal sac was decompressed by limited posterolateral tumor resection and posterior segmental instrumentation. This limited tumor resection was followed by postoperative single-fraction SRS, with doses ranging from 18 to 24 Gy. The overall estimated 1-year local progression risk was 9.5%, and patients receiving high-dose single-fraction SRS (24 Gy) had a lower progression risk than those receiving low-dose single-fraction SRS (18–21 Gy)—6.3% and 20%, respectively. Given the improved outcomes of high-dose treatment, the present series examines only those single-fraction SRS patients treated with 24 Gy. Additionally, in our institution, re-irradiated or large-volume tumors are treated with hypofractionated SRS delivered in 3–5 fractions. Over the course of this study, hypofractionated SRS radiation schedules were escalated from low-dose (20–30 Gy in 5 fractions) prior to 2008 to high-dose (24–30 Gy in 3 fractions). This study reports the local tumor control and toxicity for patients who underwent "separation surgery" followed by 24-Gy single-fraction SRS, high-dose hypofractionated SRS, or low-dose hypofractionated SRS.

Methods

Study Design

A retrospective analysis was undertaken of all patients treated at MSKCC between 2002 and 2011 who harbored spinal metastases and underwent surgery followed by SRS. This study was approved by MSKCC's institutional review board. All cases were reviewed by the MSKCC spine tumor service during the weekly multidisciplinary clinic or tumor board. Exclusion criteria included patients with post-RT follow-up of less than 1 month (13 patients) or adjuvant low-dose single-fraction SRS (4 patients). The decision to operate was made using the NOMS decision framework, with the primary operative indications being high-grade ESCC from tumors radioresistant to cEBRT or gross spinal instability that was not amenable to percutaneous cement augmentation.[3] Patients with high-grade ESCC underwent surgical decompression to provide a separation between the tumor and the spinal cord, thereby enabling the safe delivery of a cytotoxic radiation dose to the tumor while avoiding spinal cord toxicity and radiation-induced myelopathy (Fig. 1).

Charts and imaging were reviewed to evaluate the association of PFS and OS with tumor histology–specific radiosensitivity, preoperative radiotherapy, postoperative radiation dose and fractionation, and degree of pre- and postoperative epidural tumor extension. The beginning of the OS and PFS time intervals was defined as the completion date of RT.

Surgery

All patients underwent "separation surgery" accomplished via a posterolateral laminectomy including a unilateral or bilateral facetectomy using a high-speed 3-mm matchstick bur, as previously described.[28] Epidural tumor was resected circumferentially starting from normal dural planes. The posterior longitudinal ligament was resected to achieve a margin on the anterior dura and to ensure spinal cord decompression. Typically, a partial vertebral body resection was accomplished, but there was no attempt at either aggressive or gross-total resection of the vertebral body or paraspinal tumor. Given the limited vertebral body resection, anterior reconstruction was rarely required. When more than 50% of the vertebral body was resected, the discs were removed and vertebral body replacement was accomplished from a posterior-only approach using either polymethylmethacrylate with Steinman pins or through placement of a titanium or polyetheretherketone carbon fiber cage.

Stereotactic Radiosurgery

Within 2–4 weeks of separation surgery either single-fraction (24 Gy) or hypofractionated SRS was administered. Hypofractionated SRS was further classified as low-dose (median total dose 30 Gy in 5 or 6 fractions, total dose range 18–36 Gy) or high-dose (median total dose 27 Gy in 3 fractions, total dose range 24–30 Gy). The preoperative MRI study was used to delineate the gross tumor volume, which included the intraosseous, epidural, and paraspinal components. The gross tumor volume coverage was contoured to the preoperative tumor volume rather than the postoperative residual tumor. A postoperatiive CT myelogram obtained after surgery was used as a guide to plan the treatment volume for the SRS that followed and to define the dural margin so that the CSF space and spinal cord could be clearly delineated in the setting of spinal instrumentation. The clinical tumor volume was an expansion of the gross tumor volume contoured to account for microscopic tumor. For example, the assumption is made that the entire vertebral body is at risk for tumor infiltration even though MRI shows a discrete lesion.[23] Thus, the clinical tumor volume includes

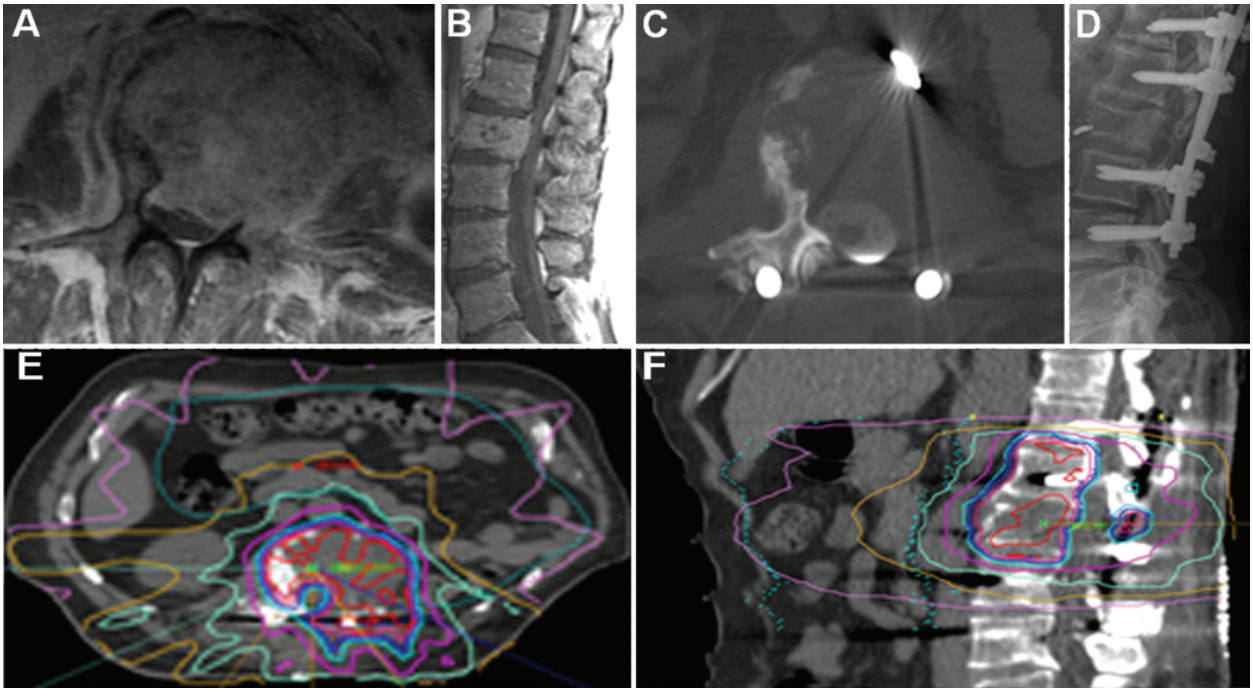

Fig. 1. Images obtained in a 66-year-old man with metastatic L-2 renal cell carcinoma. **A and B:** Initial axial (A) and sagittal (B) T1-weighted postcontrast MR images demonstrating Grade 3 ESCC. The patient was neurologically intact. **C and D:** Axial postoperative CT myelogram (C) and postoperative radiograph (D) obtained after "separation surgery" to decompress the spinal cord and CSF space and instrumentation placement. **E and F:** Axial (E) and sagittal (F) postoperative CT myelograms that were used for planning of the adjuvant high-dose hypofractionated SRS.

the entire volume of the vertebral body even in the setting of partial radiographic involvement. The planning target volume typically represents a 2-mm expansion of the clinical tumor volume, which accounts for uncertainties in radiation set-up and delivery. All of the treatment volumes were contoured so they did not transgress the dural margins, as defined on the postoperative CT myelogram.

Imaging

To monitor for tumor recurrence, patients underwent serial gadolinium-enhanced MRI at 4- to 6-month intervals following SRS or sooner if symptomatic recurrence was suspected. Tumor recurrence was determined with MRI or CT myelography, as indicated. Additional images reviewed include chest, abdomen, and PET CT studies. Actual imaging and reports for all patients were reviewed by a neuroradiologist (E.L.) and a neurosurgical member of the spine team, who were blinded to the treatment that the patients received. All measurements were made by consensus and with consultation of the original imaging reports, using the validated 6-point ESCC scale.[2]

Statistical Analysis

Univariate analysis of OS was performed using a proportional hazards model, while univariate and multivariate analyses of PFS were performed using the Gray competing risks method;[15] p values < 0.05 were considered statistically significant, and p values < 0.10 were considered to show a trend toward association. For the purpose of variable selection for multivariate analysis, $p < 0.10$ was used as a threshold due to the small number of local progression events. The statements regarding the difference in PFS are based on the statistical comparison of the entire Gray competing risks functions, rather than individual time points. With a median follow-up for survivors of 11 months (range 1.5–63.2 months), 1-year cumulative local progression rates were calculated for the entire study population. R package cmprsk version 2.9.2 and SAS version 9.2 software were used for statistical analysis.

Results

Patient and Tumor Characteristics

A total of 203 patients were identified who fit the inclusion criteria; 17 of these 203 were excluded for inadequate follow-up (13 patients) or low-dose single-fraction radiation (4 patients). Univariate analysis failed to reveal significant associations between OS and sex, tumor radiation sensitivity, preoperative radiation type, postoperative radiation fractionation or dose, degree of pre- or postoperative ESCC, or extent of tumor resection. Among the 186 evaluated patients, radiographic high-grade ESCC was present preoperatively in 136 (73.1%, Table 1). Tumors were categorized as either radiosensitive or resistant to cEBRT. The most prevalent primary radiosensitive tumors were breast and prostate, whereas radioresistant tumors included colorectal, non–small cell lung, renal cell carcinoma, and sarcoma (Table 2). Patients were followed up for an overall median of 7.6 months (range 1.0–66.4

TABLE 1: Tumor characteristics and local progression*

Characteristic	Total	Local Progression†	
		Yes	No
tumor location			
cervical	15	4 (26.7)	10 (66.7)
cervicothoracic	7	3 (42.9)	3 (42.9)
thoracic	107	18 (16.8)	78 (72.9)
thoracolumbar	10	1 (10.0)	6 (60.0)
lumbar	47	8 (17.0)	34 (72.3)
preop ESCC grade‡			
no compression (0, 1a)	6	1 (16.7)	4 (66.7)
dural compression (1b, 1c)	40	9 (22.5)	31 (77.5)
cord compression (2, 3)	136	23 (16.9)	95 (69.9)

* Values in data cells represent numbers of cases (%). The values in parentheses under preop ESCC represent ESCC grades.
† In 21 cases, the patients died without imaging follow-up sufficient to determine presence or absence of local progression.
‡ Preoperative imaging for analysis was unavailable in 4 cases.

months) after SRS. Among the patients who were alive at the conclusion of the analysis, the median follow-up time was 11.0 months (range 1.5–63.2 months, 54 patients). The median survival among patients who died was 6.1 months (range 1.0–66.4 months, 132 patients).

Surgery and SRS

A median of 2 spinal levels (range 1–8 levels) were decompressed and then treated with either low-dose hypofractionated SRS (109 cases, 58.6%), high-dose hypofractionated SRS (37 cases, 19.9%), or single-fraction SRS (40 cases, 21.5%) (Table 3). The RT regimen was completed within a median of 1.6 months from the date of surgery. There were no neurological complications due to radiotherapy; 4 patients underwent reoperation due to hardware failure, and 1 of these 4 had local progression.

TABLE 2: Tumor histology and local progression*

Histological Type	Total	Local Progression	
		Yes	No
radiation sensitive	42	9 (21.4)	26 (61.9)
breast	11	1 (9.1)	9 (81.8)
prostate	24	7 (29.2)	12 (50.0)
other	7	1 (16.7)	5 (83.3)
radiation resistant	144	25 (17.4)	103 (71.5)
colorectal	15	1 (6.7)	10 (66.7)
hepatocellular	6	1 (16.7)	4 (66.7)
lung, non–small cell	15	3 (20.0)	10 (66.7)
melanoma	9	0 (0)	9 (100)
renal cell	41	8 (19.5)	31 (75.6)
sarcoma	33	7 (21.2)	25 (75.8)
squamous cell	3	1 (33.3)	2 (66.7)
thyroid	5	2 (40.0)	3 (60.0)
other	17	2 (11.8)	11 (64.7)

* Values represent numbers of cases (%).

Local Tumor Control

Local progression was observed in 34 patients (18.3%) at a median of 4.8 months (range 0.2–38.3 months) following SRS, while 103 patients (55.4%) died without local progression (median survival 5.6 months, range 1.0–66.4 months) (Table 4). The remaining 49 patients (26.3%) were alive and free of local progression at last follow-up (median 7.1 months, range 1.3–55.6 months). The cumulative incidence of local progression was 16.4% at 1 year (95% CI 10.7%–22.2%). Univariate analysis by means of the Gray competing risks method revealed a significant association between PFS and postoperative radiation delivery scheme (low-dose hypofractionated SRS HR 1; high-dose hypofractionated SRS HR 0.12, p = 0.04; single-fraction SRS HR 0.45, p = 0.09) and a trend toward significant association between PFS and preoperative cEBRT (no preoperative radiation HR 1, failed preoperative cEBRT HR 1.96, p = 0.07, Table 5). Of the 91 patients who had local disease progression fol-

TABLE 3: Treatment characteristics and local progression*

Characteristic	Total	Local Progression	
		Yes	No
preop RT failure†	91	21 (23.1)	57 (62.6)
cEBRT	58	15 (25.9)	32 (55.2)
hypofractionated SRS	18	4 (22.2)	14 (77.8)
single-fraction SRS	7	1 (14.3)	6 (85.7)
surgical decompression			
age at surgery (yrs)			
median	58.9	61.5	57.9
range	14.8–81.4	16.2–79.4	14.8–81.4
no. of spinal levels			
median	2	3	2
range	1–8	1–8	1–6
time to RT (mos)			
median	1.6	1.5	1.8
range	0.4–46.1	0.6–20.3	0.4–46.1
postop ESCC			
no compression (0, 1a)	67	10 (14.9)	50 (74.6)
dural compression (1b, 1c)	98	19 (19.4)	71 (72.4)
cord compression (2, 3)	21	5 (23.8)	10 (47.6)
postop adjuvant SRS			
low-dose hypo	109	28 (23.5)	65 (54.6)
high-dose hypo	37	1 (2.7)	34 (91.9)
single-fraction	40	5 (12.5)	32 (80.0)
no. of spinal levels			
median	2	2	3
range	1–11	1–8	1–11

* Values in data cells represent numbers of cases (%) unless otherwise indicated. Abbreviation: hypo = hypofractionated.
† The fractionation scheme of preoperative radiation was unknown in 8 patients.

TABLE 4: Survival and local progression*

Characteristic	Total	Local Progression	
		Yes	No
total no. of pts (%)	186	34 (18.3)	131 (70.4)
FU (mos)			
median	7.6	12.4	6.8
range	1.0–66.4	1.8–63.2	1.0–66.4
no. of pts alive at last FU (%)	54	5 (9.3)	49 (90.7)

* FU = follow-up; pts = patients.

lowing attempted definitive RT that ultimately required separation surgery, 2 (2.2%) were treated with postoperative SRS, 14 (15.4%) with high-dose hypofractionated SRS, and 75 (82.4%) with low-dose hypofractionated SRS. In all 48 patients treated with postoperative low-dose hypofractionated SRS prior to 2008, preoperative RT had failed. The 95 patients without preoperative radiotherapy were treated with either postoperative SRS (38 patients, 40.0%), high-dose hypofractionated SRS (24 patients, 25.3%), or low-dose hypofractionated SRS (36 patients, 37.9%). When stratified according to the postoperative RT received, the 1-year cumulative local progression rates were 22.6% for low-dose hypofractionated SRS, 4.1% for high-dose hypofractionated SRS, and 9.0% for single-fraction SRS (95% CI 14.3%–30.8%, 0%–12.2%, and 0%–19.0%, respectively; Fig. 2). Stratification by preoperative fractionation scheme revealed a 1-year cumulative local progression rate of 22.2% for preoperative cBERT (95% CI 10.9%–33.6%), compared with 11.2% for patients who did not receive preoperative RT (95% CI 4.6%–17.9%, Fig. 3).

Multivariate Analysis

Preoperative and postoperative radiation variables met the selection criteria for multivariate analysis. Multivariate analysis that included the preoperative and postoperative radiation variables confirmed the significant improvement in local control after high-dose hypofractionated SRS compared with low-dose hypofractionated SRS (low-dose hypofractionated SRS HR 1, high-dose hypofractionated SRS HR 0.12, $p = 0.04$) but displayed no statistically significant difference between single-fraction SRS (HR 0.57, $p = 0.30$) and low-dose hypofractionated SRS. Controlling for postoperative SRS fractionation during multivariate analysis eliminated the trend toward a significant difference between PFS in patients who did not receive preoperative radiation and PFS in patients who received preoperative radiation.

Discussion

Treatment paradigms for metastatic spinal tumors must incorporate a wide range of radiation, surgical, and medical options currently available. Advances in systemic therapy have significantly extended the expected survival for patients with various tumor histological types. With improved survival comes an increasing emphasis on the maintenance of quality of life and durable local tumor control. Spinal cord decompression in the setting of high-grade ESCC and restoration of mechanical stability represent the main surgical indications.[1,5] In the absence of mechanical instability, tumor histology serves as a primary determinant in multimodality treatment decisions. The main distinction among tumor histological types lies in their sensitivity to cEBRT—for example, 30 Gy in 10 treatments.[11,13] Tumors such as lymphoma, myeloma, seminoma, and breast and prostate carcinomas are markedly radiosensitive to cEBRT.[14,21,22] The remaining solid tumor histological types fall within the spectrum of moderately to highly radioresistant. In the setting of radiosensitive metastases, durable local tumor control can be reliably obtained with cEBRT regardless of the degree of ESCC; however, radioresistant tumors demonstrate poor response rates on the order of 30%, with progression seen within 3 months of radiation.[21,22] Recently, a number of studies have demonstrated improved control of radioresistant tumors with the delivery of high radiation doses,

TABLE 5: Univariate competing risks analysis*

Factor	Univariate		Est Cumulative 1-Yr Incidence (%)	
	HR	p Value	Value	95% CI
postop adjuvant SRS				
low-dose hypo	reference		22.6	14.3–30.8
high-dose hypo	0.12	0.04	4.1	0–12.2
single-fraction	0.45	0.09	9.0	0–19.0
preop RT failure				
no preop RT	reference		11.2	4.6–17.9
cEBRT	1.96	0.07	22.2	10.9–33.6
hypo SRS	1.84	0.29	23.8	2.4–45.2
single-fraction SRS	0.98	0.99	17.1	0–51.2
radiation sensitivity	1.23	0.60	—	—
male sex	0.72	0.34	—	—
total incidence	NA	NA	16.4	10.7–22.2

* Est = Estimated; NA = not applicable.

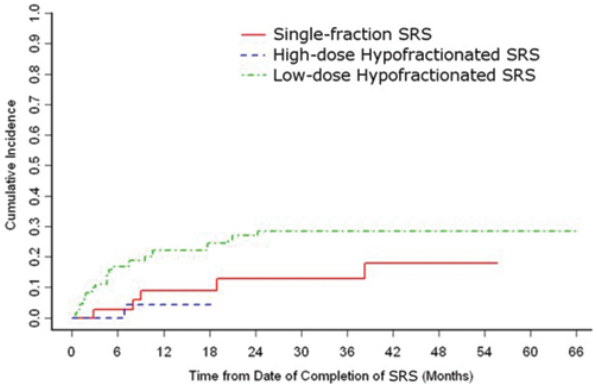

Fig. 2. The cumulative incidence of local progression by postoperative adjuvant SRS fractionation regimen.

administered as single-fraction or hypofractionated SRS using image-guided, intensity-modulated RT.[9,29,31] We have previously reported a 90% 1-year tumor control rate, regardless of tumor histology with higher single-fraction doses (24 Gy) providing control rates of 95%.[23,29]

The recommendation for surgical decompression as the initial treatment in the setting of high-grade ESCC and myelopathy caused by solid tumor metastases is based principally on a single prospective randomized trial and to a lesser extent on lower-quality evidence provided by retrospective reviews.[1,24] A systematic review of publications reporting outcomes after cEBRT in the setting of metastatic ESCC reported postradiation ambulation rates of 31%–76% and ambulation recovery rates of 16%–51%.[1] The rates of ambulation after surgical decompression and stabilization in patients with metastatic ESCC were significantly better, ranging between 74% and 100%, with ambulation recovery rates ranging between 57% and 82%. Patchell et al.[24] conducted a prospective randomized trial that, to date, provides the most convincing evidence for the superiority of surgical decompression over cEBRT in patients with high-grade ESCC and myelopathy secondary to metastatic solid tumors. They reported significantly superior rates of overall ambulation (84% vs 57%), maintenance of ambulation (94% vs 74%), recovery of ambulation (62% vs 19%), bowel and bladder continence, narcotic requirements, and survival in patients who underwent surgical decompression followed by cEBRT compared with cEBRT alone. Based on these data and expert opinion, the Spine Oncology Study Group published recommendations that patients with high-grade spinal cord compression resulting from solid tumor malignancies undergo surgical decompression followed by RT.[1]

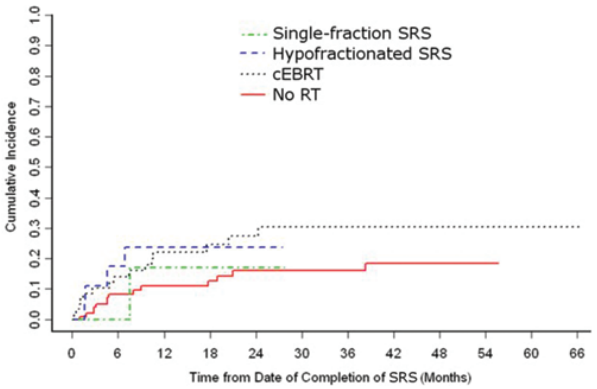

Fig. 3. The cumulative incidence of local progression by preoperative RT fractionation regimen.

The pain, functional, and neurological results of posterolateral decompression and stabilization were previously analyzed and reported by our institution; therefore, we did not repeat this analysis for the current patient series and concentrated instead on the analysis of local tumor control.[28] While multiple series have demonstrated that surgery for metastatic ESCC provides excellent rates of neurological recovery and stability, very few have examined the durability of tumor control. Klekamp and Samii[18] examined tumor control in 101 patients who underwent surgical decompression, of whom 60% were treated with cEBRT. The rates of overall recurrence were 57.9% at 6 months, 69.3% at 1 year, and 96% at 5 years, with tumor histological types favorable to cEBRT showing more durable control. It is a vexing proposition to subject a patient to a major spine operation for palliation only to have the tumor return within a few months. The deleterious effects of tumor recurrence have been adeptly documented previously.[8,16,20] The failure of surgery to control metastatic disease reflects the inability to achieve negative margins based on anatomical constraints and aggressive tumor biology. With the integration of effective spinal radiation methods even for radiation-resistant tumor types, "separation surgery" provides effective spinal cord decompression and stabilization, reducing the need for complex approaches and attempted gross-total resection of spinal metastases. To safely administer the tumoricidal radiation doses afforded by SRS, a small margin of 2–3 mm created by separation surgery between the tumor and the spinal cord allows a full radiation dose to the entire tumor volume while minimizing the radiation exposure to the spinal cord. Thus, in patients with radioresistant tumors causing high-grade ESCC, separation surgery is undertaken with the primary purpose of providing a small separation between the tumor and the spinal cord, but avoiding the risks associated with extensive or gross-total tumor resection.

The goals of the current analysis were to determine the long-term tumor control rates after "separation surgery" for metastatic spinal tumors and to delineate the oncological and surgical factors associated with tumor control. The overall local progression rate after radiation was 16% at 1 year. The only factor significantly associated with local tumor progression was the postoperative radiation dose, with high-dose hypofractionated SRS resulting in a 4% local progression rate after 1 year, compared with the significantly higher 22% 1-year local progression rate for low-dose hypofractionated SRS. The 1-year local progression rate for single-fraction SRS was 9%, which did not differ significantly from the rate for low-dose hypofractionated SRS. The lack of statistical significance may be due to the low number of local progression events in the SRS group, since the study is likely underpowered to adequately evaluate this difference. This finding echoes the results of previous publications where the radiation

dose was observed to be inversely proportionate to recurrence rate.[29]

There was no association between histology-specific sensitivity to radiation, previous radiation, and the degree of pre- or postoperative epidural spinal cord compression, confirming that tumor response to high-dose radiation is independent of these characteristics. The tumoricidal mechanisms activated by high-dose radiation require further elucidation; however, mounting evidence indicates that these mechanisms differ from those employed by conventional RT using multiple fractions of low-dose radiation. The linear-quadratic model describes the effect of conventionally fractionated radiation, but fails to accurately predict tumor response to radiosurgery.[17] Tumor xenograft experiments have shown that high radiation doses activate microvascular endothelial apoptosis, which is associated with tumor growth arrest, whereas low-dose radiation does not.[7] The difference in tumor arrest mechanisms may account for the finding that SRS provides improved local tumor control irrespective of tumor histological type and size, which differs from the results observed with conventional fractionation.[4,19,28,30] Because SRS provides local tumor control irrespective of the tumor volume, the extent of tumor resection loses importance as long as there is adequate separation of the tumor from vital structures to allow for optimal radiation dose delivery.

Several publications describe the results of postoperative SRS. Rock et al.[26] administered radiosurgical treatment to 18 patients who had undergone surgery for spinal metastatic tumors, with a median follow-up of 7 months. One patient suffered neurological deterioration secondary to rapid tumor progression, while 30% remained neurologically stable and 62% demonstrated neurological improvement. The MSKCC experience with postoperative SRS for radioresistant tumors was initially described in 21 patients, in whom the overall estimated incidence of local progression at 1 year was 9.5%, with patients who received 24-Gy doses having a 1-year recurrence risk of 6.3%.[23] Finally, Garg et al.[8] prospectively evaluated tumor control rates after spinal re-irradiation using hypofractionated SRS (6 Gy × 5 or 9 Gy × 3) for 59 patients with mostly radioresistant histological tumor types in whom cEBRT had failed, with more than one-half of the patients having undergone prior surgical intervention. They reported an actuarial 1-year local tumor control rate of 76% irrespective of tumor histology. An identical 1-year tumor control rate (76%) was reported by Damast et al.[5] for patients who underwent re-irradiation with the 6 Gy × 5 paradigm at MSKCC, which was independent of tumor histology. The results presented in the current analysis may demonstrate better tumor control; however, one limitation of this small sample size may be insufficient power to discern a statistical difference.

The retrospective nature of the analysis engenders several limitations. The study includes a heterogeneous population of patients with numerous tumor histological types undergoing a wide range of systemic therapies. Although the majority of chemotherapies have little effect on bone metastases, several agents may have contributed to the local control provided by SRS. However, due to the myriad of systemic treatments available, we could not effectively control for this factor. The study was not designed to objectively compare the efficacy of postoperative SRS to other available treatments such as cEBRT or more aggressive tumor excision. The results reported in this manuscript can only be compared with the results of previously published studies. Finally, our data indicate that imaging failed to confirm complete spinal cord decompression in 21 patients (11%). Whether this finding is due to the limitations of the postoperative imaging used or to true failure to achieve spinal cord decompression is difficult to determine. Although the degree of posterior and lateral epidural decompression was always confirmed intraoperatively using direct visualization, the ventral epidural space cannot be directly visualized using the posterior approach and instead we had to rely on probing of the ventral epidural space using surgical instruments or intraoperative ultrasonography. Postoperatively our patients routinely underwent CT myelography, rather than MRI, to evaluate the degree of epidural decompression. Magnetic resonance evaluation of the epidural space is generally limited due to instrumentation artifact, whereas myelography provides clear CSF definition. Nevertheless, CT myelography cannot reliably differentiate residual tumor in the epidural space from postoperative blood products, and this may account for a portion of the cases in which spinal cord decompression was not radiographically documented. It is interesting to note that the presence of spinal cord compression on the postoperative myelogram was not associated with local tumor progression. Further investigations are needed to address these limitations.

Conclusions

Spinal cord decompression, spinal stabilization, and durable tumor control represent the goals of treatment of spinal metastatic tumors. Although spinal cord compression due to radiosensitive tumors may be effectively treated with cEBRT, patients with radioresistant tumors causing high-grade spinal cord compression benefit from surgical decompression and postoperative single-fraction or hypofractionated SRS. The long-term tumor control provided by high dose per fraction postoperative SRS, which is irrespective of tumor histology-specific radiosensitivity, obviates the need for extensive tumor resection in favor of a limited spinal cord decompression and reconstitution of the CSF space around the spinal cord. Furthermore, SRS provides durable postoperative tumor control regardless of the previous radiation treatment or the degree of epidural tumor extension.

Disclosure

Dr. Laufer reports being a consultant for SpineWave.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bilsky, Laufer, Lis, Zhang, Yamada. Acquisition of data: Bilsky, Laufer, Iorgulescu, Chapman, Lis, Yamada. Analysis and interpretation of data: all authors. Drafting the article: Bilsky, Laufer, Iorgulescu, Yamada. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bilsky. Statistical analysis: Iorgulescu, Shi, Zhang. Administrative/technical/material support: Bilsky, Laufer, Iorgulescu, Lis, Yamada. Study supervision: Bilsky, Laufer, Yamada.

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