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These data were presented in part as a virtual poster at the American Society of Radiation Oncology (ASTRO) October 24-28, 2020 (virtual meeting due to COVID-19).

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Received, May 20, 2020.
Accepted, November 15, 2020.
Published Online, February 11, 2021.

Postoperative Stereotactic Body Radiotherapy for Spinal Metastasis and Predictors of Local Control

BACKGROUND: Spine surgery is indicated for select patients with mechanical instability, pain, and/or malignant epidural spinal cord compression, with or without neurological compromise. Stereotactic body radiotherapy (SBRT) is an option for durable local control (LC) for metastatic spine disease.

OBJECTIVE: To determine factors associated with LC and progression-free survival (PFS) for patients receiving postoperative stereotactic spine radiosurgery.

METHODS: We analyzed consecutive patients from 2013 to 2019 treated with surgical intervention followed by SBRT. Surgical interventions included laminectomy and vertebrectomy. SBRT included patients treated with 1 to 5 fractions of radiosurgery. We analyzed LC, PFS, overall survival (OS), and toxicity. Univariate and multivariate analyses were performed.

RESULTS: A total of 63 patients were treated with a median follow-up of 12.5 mo. Approximately 75% of patients underwent vertebrectomy and 25% underwent laminectomy. One-year cumulative incidence of local failure was 19%. LC was significantly improved for patients receiving radiosurgery $\leq$40 d from surgery compared to that for patients receiving radiosurgery $\geq$40 d from surgery, 94% vs 75%, respectively, at 1 yr ($P = .03$). Patients who received preoperative embolization had improved LC with 1-yr LC of 88% vs 76% for those who did not receive preoperative embolization ($P = .037$). Significant predictors for LC on multivariate analysis were time from surgery to radiosurgery, higher radiotherapy dose, and preoperative embolization. The 1-yr PFS and OS was 56% and 60%, respectively.

CONCLUSION: Postoperative radiosurgery has excellent and durable LC for spine metastasis. An important consideration when planning postoperative radiosurgery is minimizing delay from surgery to radiosurgery. Preoperative embolization and higher radiotherapy dose were associated with improved LC warranting further study.

KEY WORDS: Postoperative, Surgery, Radiosurgery, SBRT, Spine metastasis, Embolization

Neurosurgery 88:1021–1027, 2021 DOI:10.1093/neuros/nyaa587 www.neurosurgery-online.com

Improvements in systemic therapy have led to improvements in survival for patients with metastatic spine disease.[1,2] Spine surgery is indicated for select patients, typically those with mechanical instability, pain, and/or malignant epidural spinal cord compression with or without neurological compromise.[3,4] Although postoperative conventional palliative external beam radiation therapy has been the standard of care,[3] technical improvements in radiation planning and image-guided radiotherapy have allowed for the application of stereotactic body radiotherapy (SBRT) to the spine for patients with radioresistant tumor histologies.[5-8] The SBRT dose distribution allows for an increase in therapeutic index by allowing dose escalation to the tumor while maintaining lower doses to nearby critical organs such as spinal cord, bowel, and esophagus.[2,9]

ABBREVIATIONS: CTCAE, Common Terminology Criteria for Adverse Events; **CTV,** clinical target volume; **HR,** hazard ratio; **KPS,** Karnofsky performance status; **LC,** local control; **NOMS,** Neurologic; **Oncologic,** Mechanical stability and Systemic disease; **PRV,** planning risk volume; **PTV,** planning target volume; **SBRT,** stereotactic body radiotherapy; **STROBE,** STrengthening the Reporting of OBservational studies in Epidemiology; **VB,** vertebral body

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Commonly, SBRT is delivered in 1 to 5 fractions for patients with radioresistant histologies or oligometastatic disease.[6,10-14] Frequently, the Neurologic, Oncologic, Mechanical stability and Systemic disease (NOMS) criteria are used to determine the use of SBRT.[15-17] Previous studies have shown improvements in local control (LC) using radiosurgery for spine metastasis compared to conventional palliative treatment.[18] This study aimed to determine factors associated with LC and progression-free survival for patients receiving postoperative stereotactic spine radiosurgery.

METHODS

Study Design

In this Institutional Review Board (IRB)-approved retrospective study, we evaluated patient records including treatment details and outcomes of consecutive patients with metastatic spine tumors from 2013 to 2019 treated with surgical intervention followed by SBRT. Patient consent was not sought nor required by our IRB for this retrospective chart review study. Guidelines from the STROBE (STrengthening the Reporting of Observational studies in Epidemiology) statement were followed.

Treatment

Surgical interventions included laminectomy and vertebrectomy. Surgical technique was chosen by the treating neurosurgeon taking into account the patient comorbidities and tumor extent. Select patients underwent preoperative embolization at the discretion of the treating neurosurgeon.

SBRT included patients treated with 1 to 5 fractions of radiosurgery. Radiosurgery volumes were based on the gross disease and involved boney anatomy using the accepted postoperative contouring guidelines and no additional clinical target volume (CTV) to planning target volume (PTV) margin was used.[19] All patients received image-guided stereotactic radiosurgery (SRS) or fractionated stereotactic radiosurgery (SBRT). Treatments were delivered with Varian Truebeam STX and Edge (Varian Medical Systems), using an Aquaplast frameless mask for the immobilization of the cervical spine, and a stereotactic body frame and Vac-Lok bag for the immobilization of thoracic, lumbar, and sacral spine. Treatment planning was performed by fusion of the presurgery magnetic resonance imaging (MRI) and postsurgery computed tomography (CT) myelogram. The spinal cord was delineated on the postsurgery CT myelogram with a 2-mm planning risk volume (PRV). Radiation dose was prescribed so that 95% of the PTV receives at least 95% of the prescription dose. Spinal cord tolerance was based on the treatment fractionation and standard AAPM TG 101 recommendations.[20]

Systemic therapy was captured if it occurred within 4 wk of the surgery or radiosurgery. Systemic therapies included chemotherapy, targeted therapy, and immunotherapy.

Study Endpoints

The primary endpoints were LC, progression-free survival (PFS), overall survival (OS), and toxicity. Patients underwent MRI prior to surgery. Postsurgery all patients underwent a CT myelogram for radiation planning. Follow-up imaging occurred every 3 mo postradiation. MRI was retrospectively reviewed for confirmation of local failure by consensus of 2 independent neuroradiologists. Imaging-based local tumor response and progression was determined according to the SPIne response assessment in Neuro Oncology recommendations.[21] Epidural tumor was assessed using the 6-point Epidural Spinal Cord Compression Scale (Bilsky Grade).[22] Time from surgery to radiosurgery was assessed from the date of either laminectomy or vertebrectomy to the start of radiosurgery. PFS and OS were measured until the time of progression, death, or last follow-up. Toxicity was scored according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[23]

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 25 (IBM, Armonk, New York). Continuous and discrete variables were compared using the Mann-Whitney U and Pearson's chi-squared tests, respectively. Median follow-up was calculated using the reverse Kaplan-Meier method.[24] Kaplan-Meier curves were used to assess the primary endpoints: OS, PFS, and LC. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with a 2-sided significance threshold of 0.05. Univariate analysis was performed using a proportional hazards model to assess the significance of factors that may influence the primary endpoints. Cox proportional hazards modeling multivariate analyses were performed for OS, PFS, and LC.

RESULTS

Patient and Treatment Characteristics

We identified 176 patients with 217 metastatic spine sites treated with SBRT (**Figure**, **Supplemental Digital Content 1**). Of these, 63 patients underwent surgery with a median follow-up of 12.5 mo (1.23-52.4 mo). Approximately 75% of patients underwent vertebrectomy and 25% underwent laminectomy. The median dose of radiosurgery was 27 Gy. The most common regimen was 27 Gy in 3 fractions. The median time between surgery and radiation was 42 d. Radiosurgery to >2 vertebral bodies (VBs) was most common (52%), followed by 1 VB (29%). The most common preoperative Bilsky grade was grade 2 (46%), followed by grade 3 (36%). Approximately 65% of patients had space distance >2 mm between the tumor volume and spinal cord or cauda equina, whereas 35% of patients had space distance <2 mm. The most common histologies treated were renal cell carcinoma (38%), nonsmall cell lung cancer (15%), and soft tissue sarcoma (13%). The most common spinal site treated was the thoracic spine (64%). Embolization occurred in 57% of patients. Details of patient demographics can be found in Table 1.

Local Control

The cumulative incidence of local failure at 6 mo, 1 yr, and 18 mo was 11%, 19%, and 24%, respectively (Figure 1). The LC for the entire cohort at 1 yr was 81%. The 1-yr LC was significantly improved for patients receiving radiosurgery <40 d from surgery compared to that for patients receiving radiosurgery ≥40 d from surgery, 94% vs 75%, respectively (Figure 2; $P = .03$). The median LC for patients who were treated within 40 d from surgery was 15.1 mo vs 6.3 mo for patients who had delayed treatment ($P = .02$). Patients who received preoperative embolization had improved LC with 1-yr LC 88% vs 76% (Figure 3; $P = .037$). The histologies that underwent preoperative

TABLE 1. Patient Characteristics

Median age (yr)	64 (24-80)
Gender	
Male	36 (57%)
Female	27 (43%)
KPS	
≥70%	59 (94%)
<70%	4 (6%)
Surgical extent	
Vertebretomy	47 (75%)
Laminectomy	16 (25%)
Extent of resection	
≤50% or laminectomy only	42 (66%)
>50%	17 (34%)
Radiotherapy dose	27 (14-28)
Median total dose BED (Gy)	51.3 (33.6-51.3)
Median PTV minimum dose[a]	29.2 (10.76-44)
Median PTV mean dose[a]	55.23 (34.44-59.7)
Median PTV D95%[a]	51.3 (26.16-55.53)
Median PTV D90%[a]	52.54 (29.9-54.68)
Spinal cord[b]	55.77 (15.17-114)
Cauda equina[b]	68.27 (31.45-135)
PTV coverage	
95% of the dose covers at least 95% of the volume	59 (94%)
95% of the dose covers less than 95% of the volume	4 (6%)
Median treatment time (d)	42
Adjuvant therapy	
SRS	07 (11%)
SRT	56 (89%)
Median treated volume (cc)	125 (20-670)
Number of treated levels	
1 level	18 (29%)
2 levels	12 (19%)
>2 levels	33 (52%)
Radiotherapy extent	
Circumferential	38 (60%)
Standard	25 (40%)
Histopathology	
RCC	24 (38%)
NSCLC	10 (15%)
STS	8 (13%)
Breast	6 (9%)
GI	5 (9%)
Thyroid	4 (6%)
Prostate	3 (5%)
H&N	2 (3%)
Melanoma	1 (2%)
Vertebral site	
C-spine	6 (9%)
C-T spine	2 (3%)
T-spine	40 (64%)
L-spine	8 (13%)
T-L spine	5 (7%)
S-spine	2 (3%)
Systemic treatment	
No systemic treatment	36 (57%)
Chemotherapy	13 (20%)
Targeted therapy	4 (8%)
Immunotherapy	10 (15%)
Embolization	
Yes	36 (57%)
No	27 (43%)
Distance from cord/cauda	
More than 2 mm	41 (65%)
Within 2 mm	17 (35%)
Intraop blood loss (L)	
Embolization	1.65 (0.2-7.0)
No embolization	1.2 (0.1-6.5)
Systemic disease status	
Stable	45 (71%)
Progression	18 (29%)
Preop Bilsky grade	
Grade 1B	4 (7%)
Grade 1C	7 (11%)
Grade 2	29 (46%)
Grade 3	23 (36%)

C: cervical; C-T: cervical-thoracic; GI: gastrointestinal; H&N: head and neck; L: Lumbar; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; S: sacrum; SRT: stereotactic radiation treatment; T-L: thoracic-lumbar; T: thoracic.

[a]Biologically equivalent dose $(BED)_{10}$.

[b]BED_2.

embolization were vascular cancers such as renal cell and thyroid cancers (others included head and neck squamous cell carcinoma, breast, gastrointestinal, and soft tissue sarcoma). LC was significantly better for renal cell carcinoma vs other histologies (95% vs 74%, 1-yr LC, $P = .034$). LC did differ based on histology (**Figure**, **Supplemental Digital Content 2**). LC did not differ when comparing between laminectomy (84%) and vertebrectomy (81%) ($P = .975$); with treatment volume <125 cc, LC was 88% vs 78% for treatment volume >125 cc ($P = .23$); with concurrent therapy with immunotherapy, LC was 100%, with chemotherapy 50%, with targeted therapy 100%, and with no concurrent therapy 84% ($P = .076$). Furthermore, LC did not differ based on number of VBs treated with 1 VB 95%, 2 VBs 80%, and >2 VBs 75% ($P = .188$), SRS 78% vs SBRT 85%, $P = .37$. The minimum, mean, D90%, and D95% also did not show LC differences. Univariate analysis can be found in **Table**, **Supplemental Digital Content 3**. Significant predictors for LC on multivariate analysis were time from surgery to radiosurgery (HR 12.39; 95% CI 1.19-128.65; $P = .035$), preoperative embolization (HR 7.34; 95% CI 1.09-49.425; $P = .04$), and prescribed biologically equivalent dose (HR 2.99; 95% CI 1.03-8.67; $P = .044$) (Table 2).

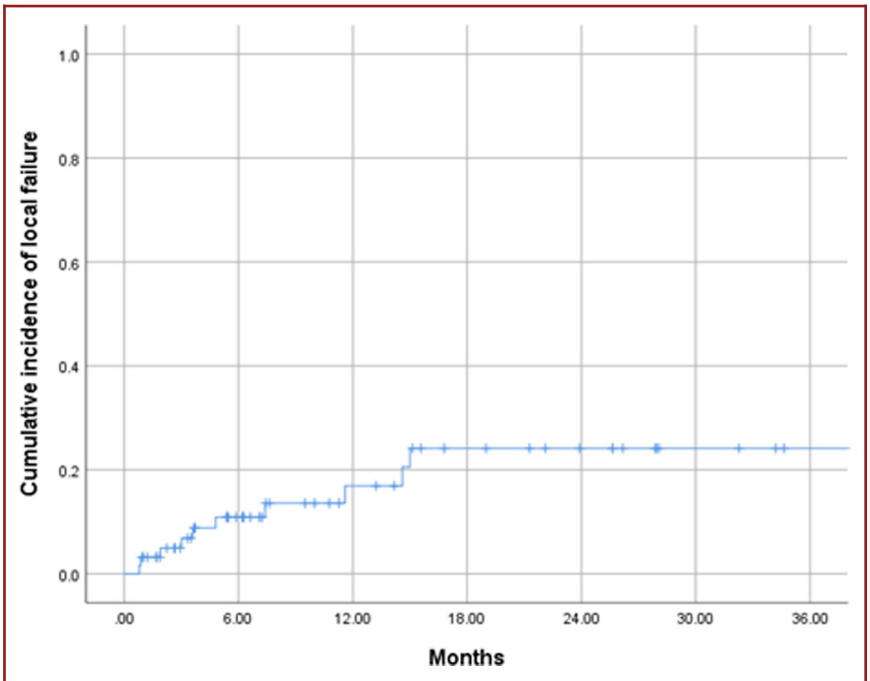

FIGURE 1. *Cumulative incidence of local failure following SRS.*

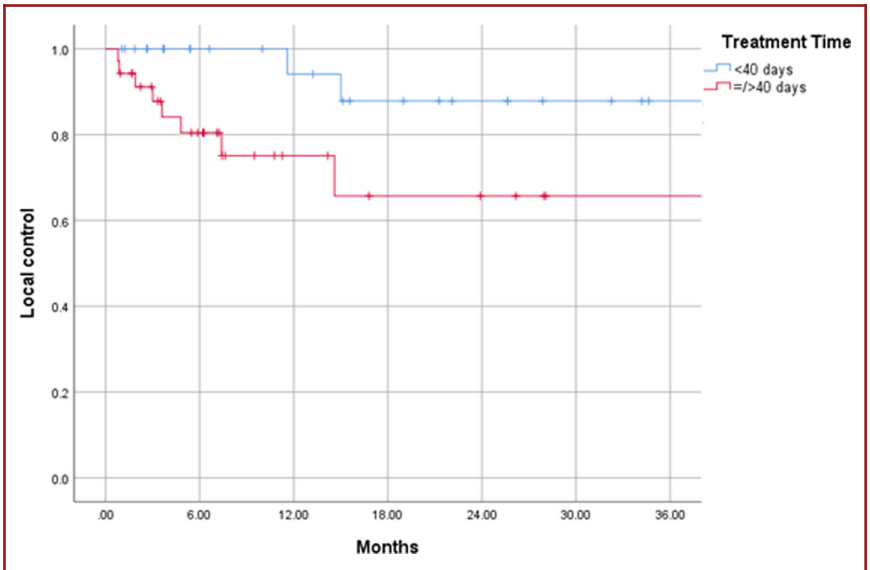

FIGURE 2. *Local control based on time from surgery to radiosurgery with 1-yr LC 94% vs 75% (P = .03).*

Progression-Free Survival

For the entire cohort, the PFS at 6 mo, 1 yr, and 18 mo was 72%, 56%, and 42%, respectively (Figure 4A). PFS was significantly different based on systemic disease status with a 1-yr PFS of 68% for patients with stable systemic disease vs 17% with progression of disease ($P = .002$). Additional univariate analysis can be found in **Table**, **Supplemental Digital Content 3**. On multivariate analysis, the significant factors for PFS were time from surgery to radiotherapy (HR 3.4; 95% CI 1.22-10.71; $P = .001$) and Karnofsky performance status (KPS) (HR 43.83; 95% CI 6.54-293.66; $P < .001$) (**Table**, **Supplemental Digital Content 4**).

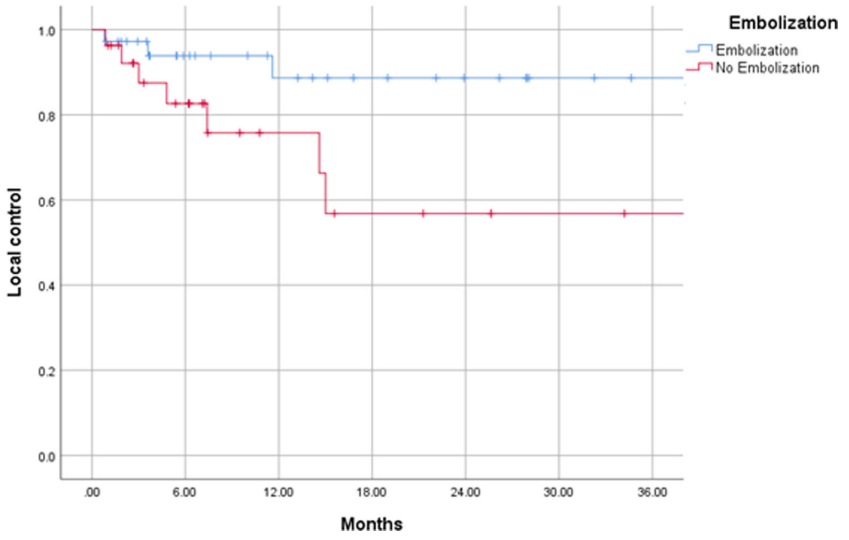

FIGURE 3. *Local control based on preoperative embolization time with 1-yr LC 88% vs 76% (P = .04).*

TABLE 2. Multivariate Analysis Local Control

Variable	HR	95% [CI]	*P* value
Surgical extent	1.978	0.214-18.327	.548
Time to radiotherapy (d)	**12.387**	**1.193-128.648**	**.035**
Age	0.984	0.892-1.086	.752
Gender	0.678	0.103-4.459	.686
SRS vs SRT	1.652	0.149-18.365	.683
Target volume (cc)	1.002	0.996-1.008	.526
Embolization	**7.345**	**1.092-49.425**	**.04**
Histology	0.420	0.003-68.963	.739
SINS score	1.540	0.892-2.661	.121
Bilsky grade (preop)	1.519	0.387-5.958	.549
Myelogram distance (postop)	1.255	0.147-10.716	.826
Prescribed dose (BED)	**2.986**	**1.029-8.668**	**.044**
Minimum PTV dose (BED)	0.957	0.852-1.074	.454
PTV D90%	0.373	0.137-1.018	.054
PTV D95%	1.063	0.652-1.734	.807

Bold values signifies statistically significant.

Overall Survival

For the entire cohort, the OS at 6 mo, 1 yr, and 18 mo was 78%, 60%, and 50%, respectively (Figure 4B). The 1-yr OS was 76% in patients with time to radiation <40 d and 48% in patients with time to radiosurgery >40 d ($P = .004$). Univariate analysis can be found in **Table**, **Supplemental Digital Content 3**. On multivariate analysis, the significant factors for OS were time from surgery to radiotherapy (HR 2.8; 95% CI 1.03-7.35; $P = .007$), systemic disease status (HR 2.51; 95% CI 1.22-5.16; $P = .012$), and KPS (HR 14.51; 95% CI 3.27-64.33; $P < .001$) (**Table**, **Supplemental Digital Content 4**).

Toxicity

Acute toxicity was noted in 28% of patients. Thirteen patients (19%) developed grade 1 to 2 fatigue. One patient developed grade 1 shortness of breath. One patient developed grade 1 skin reaction. Four patients developed pain flare within 3 mo of treatment. Eighteen patients received posttreatment steroids. One patient developed a pain flare while on steroids. No patients developed spinal cord myelopathy. No additional high-grade late toxicities were noted with a median followed up of 12.5 mo. For patients who had a delay in radiation over 40 d, the most common reasons for delays were for uncontrolled pain, electrolyte imbalance, and other nonmedical reasons, which included patient noncompliance and delays in insurance coverage and difficulty with transportation for treatment (**Table**, **Supplemental Digital Content 5**).

DISCUSSION

Key Results and Interpretation

Treatment for metastatic spinal tumors varies widely and includes surgery, radiation, and medical therapy.[25-27] Advances in systemic therapy have led to an increasing incidence of spine metastasis and longer survival.[1,5] Spinal cord decompression or surgical intervention occurs mainly in the setting of high-grade epidural spinal cord compression and/or restoration of mechanical stability.[5,28,29] Prior studies assessing practice patterns found that optimal timing of radiation following spinal stabilization and/or surgical decompression was 2 wk.[30] Previous literature reviews have determined adequate wound healing is likely between 1 and 2 wk, although reporting of wound healing was inconsistent. There is no consensus regarding the optimal

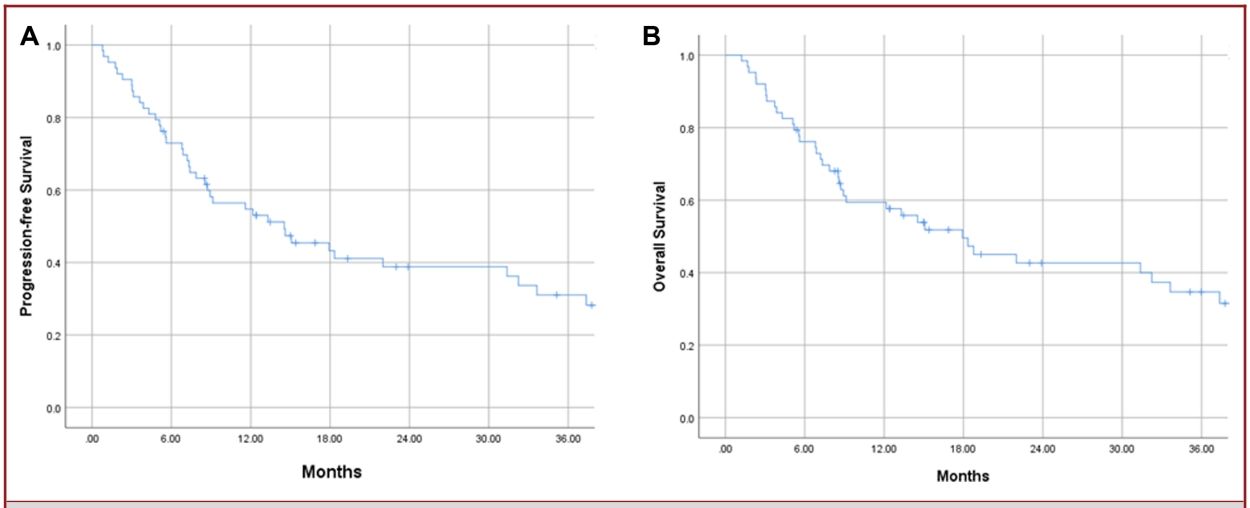

FIGURE 4. **A**, *PFS and* **B**, *OS for all patients.*

time from surgery to adjuvant radiosurgery because of limited published data.[31,32] We found that LC was improved if radiosurgery was performed within 40 d of surgery compared to a delay in radiosurgery performed after 40 d from surgery, with a 1-yr LC of 94% vs 75%, respectively ($P = .03$). Similar to prior reports, we did not find a difference in LC comparing more radical surgery, separation surgery, or vertebroplasty.[33] Interestingly, we found that preoperative embolization improved LC on multivariate analysis (HR 7.34; 95% CI 1.09-49.425; $P = .04$). These results are hypothesis generating and suggest additional LC when the tumor undergoes embolization prior to radiation. To our knowledge, this is the first report to demonstrate this association, and this differs from the arteriovenous malformation literature, which demonstrates worse obliteration rates with pre-SRS embolization.[34,35] Significant tumor vascular injury has been shown to result from stereotactic treatments, leading to hypoxic cell death after radiation,[36] possibly via the ceramide apoptotic pathway in the vascular endothelium.[37,38] Having presurgical/pre-SBRT embolization could be acting in a synergistic manner to help with the increased LC benefit. This is a hypothesis that warrants further investigations both in a prospective clinical trial setting but molecularly with tissue analysis.

We demonstrated excellent LC with a cumulative incidence of local failure of 19% at 1 yr. We found no significant high-grade toxicities, and the incidence of pain flare was low (6%), with only one patient developing pain while on steroids.

Limitations and Generalizability

Based on the retrospective nature of our study, there are several limitations. There is bias based on patient selection for surgical intervention, type and technique of surgery, dose, and volume treated based on institutional practices. We are limited by a small sample size and heterogeneity of tumor histology and systemic therapy received. Although the use of systemic therapy was not associated with LC, further validation of these findings in other retrospective and prospective data are needed to externally validate these findings.

CONCLUSION

Postoperative radiosurgery has excellent and durable LC for spine metastasis. An important consideration when planning postoperative radiosurgery is minimizing delay from surgery to radiosurgery. Preoperative embolization and higher radiation dose were associated with improved LC, warranting further study.

Funding

This study did not receive any funding or financial support.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Palmer reports consulting fees from Huron Consulting Group, outside submitted work.

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Supplemental Digital Content 1. Figure. Patient flowchart.
Supplemental Digital Content 2. Figure. Local control based on histology.
Supplemental Digital Content 3. Table. Univariate analysis for local control, overall survival, and progression-free survival at 1 year.
Supplemental Digital Content 4. Table. Multivariate analysis for PFS and OS.
Supplemental Digital Content 5. Table. Reasons for delay in radiotherapy.