The use of spine stereotactic radiosurgery for oligometastatic disease

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OBJECTIVE The authors investigated the outcomes following spine stereotactic radiosurgery (SSRS) for patients with oligometastatic disease of the spine.

METHODS The study was a secondary analysis of 38 of 209 patients enrolled in 2 separate institutional Phase I/II prospective protocols and treated with SSRS between 2002 and 2011. Of these 38 patients, 33 (87%) were treated for a solitary spine metastasis, with no other history of metastatic disease. SSRS was prescribed to 24 Gy in 1 fraction (8%), 18 Gy in 1 fraction (18%), 16 Gy in 1 fraction (11%), 27 Gy in 3 fractions (53%), 30 Gy in 5 fractions (8%), or 20 Gy in 5 fractions (3%). Seventeen patients (45%) received prior conventional external beam radiation therapy.

RESULTS The median overall survival (OS) was 75.7 months, and the 2- and 5-year OS rates were 84% and 60%, respectively. In multivariate analysis, patients who had prior spine surgery and a better Karnofsky Performance Scale score had an improved OS (HR 0.16, 95% CI 0.05–0.52, $p < 0.01$, and HR 0.33, 95% CI 0.13%–0.84%, $p = 0.02$, respectively), and those who had undergone prior radiation therapy had a worse OS (HR 3.6, 95% CI 1.2%–10%, $p = 0.02$). The 1-, 2-, and 5-year local progression-free survival rates were 85%, 82%, and 78%, respectively. The median time to systemic therapy modification was 41 months. Two patients (5%) experienced late Grade 3–4 toxicity.

CONCLUSIONS Patients with oligometastatic disease of the spine treated with SSRS can experience long-term survival and a long time before needing a modification in systemic therapy. In addition, SSRS leads to excellent local control and minimal late toxicity.

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KEY WORDS spine metastases; oligometastatic disease; radiosurgery; oncology

SPINE metastases are the most common site of osseous cancer metastases, with more than 180,000 new cases per year occurring in North America, and in approximately 40% of patients with metastatic cancer with spinal metastases.^{12,22,32} External beam radiation therapy (EBRT) with conventional fractionation has historically played a large role in the treatment of spine metastases, with a complete response rate for pain of about 13%–18%.^{9,15} Because patients with metastatic cancer are living longer, the incidence of spine metastases is expected to increase, creating the need for effective, durable treatment results.

Spine stereotactic radiosurgery (SSRS) is becoming accepted as a method of delivering an ablative dose of radiation therapy in a single or limited number of fractions, with a high degree of conformity allowing for treatment near the spinal cord and other critical structures. It appears to lead to improved tumor control and pain control rates compared with conventionally dosed palliative EBRT, especially for radioresistant histologies, although there has not been any randomized evidence to date.^{13,23,31} In addition, it has proven to be an effective salvage tool in patients who have progressive spinal metastases who have received prior radiation.^{11,13,31}

ABBREVIATIONS CI = confidence interval; CTV = clinical treatment volume; DFS = disease-free survival; Dmax = dose maximum; Dmin = dose minimum; EBRT = external beam radiation therapy; GI = gastrointestinal; GTV = gross tumor volume; HR = hazard ratio; KPS = Karnofsky Performance Scale; OS = overall survival; SSRS = spine stereotactic radiosurgery; STMFS = systemic therapy modification-free survival.

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In general, patients with oligometastatic disease have been shown to have better prognoses than those with multiple metastatic sites, with some able to attain very long-term survival.^{26,27} Patients specifically with spine oligometastatic disease may have a more favorable survival compared with patients with synchronous metastatic disease in other sites, and are thus likely to benefit from an ablative rather than a palliative dose of radiation. Moreover, definitive treatment of oligometastatic disease may delay the initiation of or change in systemic therapy. We therefore sought to investigate the long-term outcomes of patients treated with SSRS for oligometastatic disease, including their survival, recurrence patterns, time to systemic therapy modification, and long-term toxicity.

Methods

Patient Population

After institutional review board approval, we reviewed the records of 209 patients who were enrolled in two Phase I/II trials between 2002 and 2011, evaluating single and multifraction SSRS for the treatment of spinal metastases at our institution.^{4,10,11} Protocol inclusion criteria were a Karnofsky Performance Scale (KPS) score > 40, histopathological confirmation of cancer at our institution, and MRI identifying spinal or paraspinal metastasis < 1 month prior to enrollment. Protocol exclusion criteria were spinal cord compression and unstable spine as determined by multidisciplinary evaluation, cytotoxic chemotherapy within 1 month of enrollment, or EBRT in the prior 3 months to the same site. Before treatment, all patients were presented at a multidisciplinary tumor board to assess appropriate candidacy for the use of SSRS.

We selected 38 patients who had been treated for oligometastatic disease of the spine for this secondary analysis. Patients were included if the spinal metastasis treated with SSRS was the only known site of active progressive disease at the time of treatment. Five patients were included who had a history of previous metastases that had been treated earlier and that were no longer active at the time of SSRS.

Treatment

All patients underwent CT-guided intensity modulated stereotactic body radiation therapy with the CT-on-rails EXaCT targeting system or Trilogy treatment delivery system with On-board Cone Beam CT (Varian Medical Systems), as previously described.⁴ Patients were immobilized using an Elekta BodyFix stereotactic body frame system (Elekta). Treatment planning was performed using intensity-modulated radiation therapy inverse-treatment planning software (Pinnacle, Philips Medical Systems). Each treatment was monitored by the treating radiation oncologist and a dedicated radiation physicist to verify target positioning and quality assurance, respectively.

SSRS was prescribed to the gross tumor volume (GTV), which was delineated based on the MRI fused with the planning CT. The clinical treatment volume (CTV) included the GTV along with contiguous bone marrow that was at risk. The GTVs were prescribed to receive 20 Gy in 5 fractions or 30 Gy in 5 fractions prior to transitioning to

27 Gy in 3 fractions on the multifraction protocol, which included patients who had received up to 1 previous course of spine radiotherapy to the same region (from prior spine radiation or radiation to another site that had exposed their spinal cord at that level).¹ SSRS was not given as a boost in any case. Patients on the subsequent single-fraction protocol, which excluded patients who had undergone spine radiation in the same region, received 16 Gy to 24 Gy, depending on histology. The biologically equivalent maximum dose (Dmax) for cord constraint on the multifraction protocol was 10 Gy for the 5-fraction treatment and 9 Gy for the 3-fraction treatment. Cord constraint on the single-fraction protocol was $0.01 \text{ cm}^3 < 10 \text{ Gy}$. Multifraction treatments were administered on alternating days.

Follow-Up and End Points

Per protocol, patients underwent MRI of the spine with and without contrast and were evaluated at clinic visits 3, 6, 9, 12, 18, and 24 months following treatment, and every 6 months thereafter. Patients also had other surveillance imaging performed, such as CT, PET/CT, and bone scans, ordered at the discretion of their medical oncologist. Patients unable to return for follow-up were contacted annually to obtain information about survival, disease, and treatment status.

End points assessed included overall survival (OS), local control, disease-free survival (DFS), systemic therapy modification-free survival (STMFS), and toxicity. Local recurrences were identified on follow-up spine MRI by the reading radiologist and confirmed by a radiation oncologist after review of the original SSRS treatment plan. The date of systemic therapy modification was the date that patients were initiated on or had a modification in their systemic treatment regimen after SSRS by the treating medical oncologist, usually for progressive disease. Systemic therapy included cytotoxic chemotherapy, targeted agents, hormonal therapy, and radioactive iodine. For patients who underwent systemic therapy that was planned to begin after SSRS, the date of the next modification of systemic treatment was used. Systemic therapy modification due to patient intolerance was not scored. Toxicity was scored using the Common Terminology Criteria for Adverse Events version 4.0. Toxicity was recorded if radiation therapy was a possible cause, but complications believed to be due to progressive tumors were excluded.

Statistical Analysis

All survival rates were calculated from the date of SSRS. For local control and progression-free survival patients were censored at the date of last imaging with either MRI or CT. For OS, patients were censored at the date they were last known to be alive. For DFS and STMFS, patients were censored at the date of last follow-up. For DFS, local failure, out-of-field spine failure, distant non-spine metastasis, and death were scored as events. Local failure status was determined based on the patient's spine MRI, and distant nonspine metastasis was based on various other imaging modalities, most commonly CT or PET/CT.

Data analysis was performed using Stata/MP statistical

software (version 14.0, StatCorp). The Fisher's exact test was used to assess measures of association in frequency tables. The equality of group medians was assessed with a nonparametric test for equality. The survival function was performed using Kaplan-Meier estimates. The log-rank test was used to assess the equality of the survivor function across groups. A p value ≤ 0.05 was considered statistically significant. Statistical tests were based on a 2-sided significance level.

The Cox proportional hazard model was used to assess the effect of factors of significance on the survival end points for univariate and multivariate analysis. The estimated hazard ratio (HR) is reported. Multivariate analysis was performed on all factors found to have a p value ≤ 0.25 on univariate analysis. Backward elimination was performed with the least significant factor eliminated in a stepwise manner until the most significant variables were identified.

Results

Patient, Tumor, and Treatment Characteristics

Baseline patient characteristics and treatment characteristics are listed in Table 1. The most common primary histology was renal cell carcinoma (26%), and 42% of patients had radioresistant histology (defined as renal cell, sarcoma, and melanoma). The most common dose and fractionation was 27 Gy in 3 fractions (53%). Seventeen (45%) and 16 (42%) patients had prior radiation therapy and surgery to the same site, respectively. Eleven patients received a prior course of radiation therapy for spinal metastatic disease at the same level and underwent SSRS for progressive disease. Six patients received a previous course of nonspine radiation (such as for the primary cancer) that had exposed their spinal cord at the same level as that in patients receiving subsequent SSRS. Thirty-three patients (87%) had solitary spine metastases, with no prior history of any other metastasis besides the site undergoing SSRS. The other 5 patients (13%) received SSRS for a single spine metastasis as the only site of active/progressive disease, and had a history of a prior metastasis treated with radiation or surgery.

Three patients (8%) were receiving systemic therapy within the 2 months prior to the date of SSRS. Twenty-five patients (66%) were not receiving any systemic therapy within this time period. Ten patients (26%) were started on a systemic therapy shortly after the completion of SSRS, which was planned prior to SSRS (endocrine therapy, $n = 5$; targeted agent, $n = 2$; chemotherapy, $n = 2$, radioactive iodine, $n = 1$).

Overall Survival

At a median follow-up of 69 months (range 9–145 months), 21 patients (55%) had died. Among patients still alive at the time of this analysis ($n = 17$), the median follow-up was 75 months (range 53–145 months). The median OS was 75.7 months (Fig. 1). The 1-, 2-, and 5-year survival rates were 95% (95% CI 81%–99%), 84% (95% CI 68%–93%), and 60% (95% CI 43%–74%), respectively. Patients with a KPS score of 70–80 (compared with 90–100) had a worse OS (HR 3.0, 95% CI 1.2%–7.5%,

TABLE 1. Patient and treatment characteristics

Variable	Value (%)
Median age in yrs (range)	60 (22–88)
Race (%)	
White	31 (82)
Hispanic	4 (11)
Black	2 (5)
Asian	1 (3)
Radioresistance (%)	
Radioresistant*	16 (42)
Radiosensitive	22 (58)
Primary site (%)	
Renal	10 (26)
Breast	7 (18)
Sarcoma	4 (11)
Lung	3 (8)
Thyroid	3 (8)
Other	11 (29)
KPS score (%)	
90–100	20 (53)
70–80	18 (47)
Prior spine surgery (%)†	16 (42)
Prior spine radiation (%)†	17 (45)
Systemic therapy prior to SSRS (%)‡	3 (8)
Chemotherapy	1 (3)
Targeted therapy	2 (5)
Type of metastasis (%)	
Solitary§	33 (87)
Single¶	5 (13)
Spine location (%)	
Cervical	4 (11)
Lumbar	13 (34)
Sacral	1 (3)
Thoracic	20 (53)
Median tumor vol in cm ³ (range)	28.4 (1.6–98.3)
Fractionation schemes (%)	
24 Gy in 1 fraction	3 (8)
18 Gy in 1 fraction	7 (18)
16 Gy in 1 fraction	4 (11)
27 Gy in 3 fractions	20 (53)
30 Gy in 5 fractions	3 (8)
20 Gy in 5 fractions	1 (3)
Median time from cancer diagnosis to SSRS in mos (range)	40.8 (0.9–201)

* Defined as renal cell carcinoma, melanoma, and sarcoma.

† Prior treatment at the same site that underwent SSRS.

‡ Given within 2 months of SSRS.

§ Only known site of metastatic disease.

¶ Only active metastasis with history of previously treated metastasis.

FIG. 1. Kaplan-Meier curves demonstrating OS (upper) and local progression-free survival (lower) in all patients.

$p = 0.02$; Table 2, Fig. 2). Patients who had prior spine surgery had a better OS (HR 0.33, 95% CI 0.12%–0.92%, $p = 0.03$; Table 2, Fig. 2). Other factors assessed were not significant, including age, sex, tumor volume, radioresistance, spine location, fractionation, and prior radiation. On multivariate analysis, prior radiation (HR 3.6, 95% CI 1.2%–10%, $p = 0.02$), prior surgery (HR 0.16, 95% CI 0.05%–0.52%, $p < 0.01$), and higher KPS score (HR 0.33, 95% CI 0.13%–0.84%, $p = 0.02$) was a significant predictor (Table 3).

Spinal Recurrence

The median local progression-free survival was 130.7 months, and the 1-, 2-, and 5-year rates were 85% (95% CI 68%–94%), 82% (95% CI 64%–91%), and 78% (95% CI 59%–89%), respectively (Fig. 1). No variables were identified as predictive of local failure in univariate (Table 2) or multivariate analysis (Table 3).

The patterns of spinal recurrence and the subsequent management strategies are summarized in Table 4. Among the 10 patients (26%) with local progression, 4 underwent surgery, 2 had further surgery and EBRT, 3 had systemic

therapy alone, and 1 patient had a repeat course of SSRS (27 Gy in 3 fractions, given 1 year after the initial SSRS). Thirteen patients (34%) experienced out-of-field spine metastases following SSRS at a median of 27.6 months (range 8.5–91.3 months) after SSRS. Three of these 13 patients' subsequent out-of-field spine metastases were located in spinal levels directly adjacent to the site of SSRS and were treated with SSRS in 1 patient, EBRT in 1 patient, and surgery in 1 patient. In the 10 other patients, their distant spine failures were managed with SSRS ($n = 5$), EBRT ($n = 1$), surgery followed by SSRS ($n = 1$), and systemic therapy or best supportive care ($n = 3$).

Disease-Free Survival

The median DFS was 19.0 months. The 1- and 2-year DFS rates were 62% (95% CI 44%–75%) and 44% (95% CI 28%–60%), respectively. Patients with a lower KPS score (70–80 vs 90–100) had a worse DFS (HR 2.3, 95% CI 1.1%–4.7%, $p = 0.03$; Table 2). Patients aged 60 years or older had a better DFS (HR 0.43, 95% CI 0.20%–0.94%, $p = 0.03$; Table 2). Seven patients (18%) did not experience any local or distant failure after SSRS, at a median follow-up of 75 months (range 20–119 months). On multivariate analysis, higher KPS score (HR 0.37, 95% CI 0.17%–0.81%, $p = 0.01$) and older age (HR 0.36, 95% CI 0.16%–0.82%, $p = 0.02$) were also found to be significant (Table 3).

Systemic Therapy Modification-Free Survival

The median STMFS was 41.2 months (Fig. 3), and the 1- and 2-year rates were 83% (95% CI 67%–92%) and 65% (95% CI 47%–79%), respectively. Patients with a lower KPS score (70–80 vs 90–100) and lumbar or sacral disease (compared with cervical or thoracic) were more likely to experience a modification in systemic therapy (HR 2.9, 95% CI 1.2%–6.8%, $p = 0.02$, and HR 2.4, 95% CI 1.0%–5.3%, $p = 0.04$, respectively, Table 2). Twenty-four patients (63%) had a modification in systemic therapy for progressive disease at a median of 29.0 months (range 3.0–144.4 months). Fourteen patients (37%) never had an initiation of or modification in systemic therapy (median follow-up 69 months, range 10–145 months). On multivariate analysis, higher KPS score (HR 0.21, 95% CI 0.08%–0.57%, $p < 0.01$), older age (HR 0.21, 95% CI 0.08%–0.59%, $p < 0.01$), and lumbar/sacral spine location (HR 5.6, 95% CI 2.1%–15%, $p < 0.01$) were found to be significant predictors (Table 3).

Toxicity

Three patients (8%) experienced acute toxicity: 2 patients had Grade 2 gastrointestinal (GI) toxicity, and 1 patient had Grade 3 GI toxicity. One patient (3%) experienced late Grade 4 GI toxicity. This patient received 18 Gy in 1 fraction to T-8, T-8 laminectomy and vertebrectomy, EBRT (30 Gy in 10 fractions) to T7–9, and finally 16 Gy in 1 fraction to T-7, over the course of 2 years, and developed an esophageal fistula and stricture 29 months after the first instance of SSRS (4 months after the last SSRS). One patient (3%) experienced late Grade 3 myelopathy 12 months after SSRS. Six patients (16%) developed a compression

TABLE 2. Univariate analysis for OS, local control, DFS, and STMFS

Variable	No. (%)	OS		Local Control		DFS		STMFS	
		HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age									
Continuous									
≥60 yrs	20 (53)	1.0 (0.99–1.1)	0.12	0.99 (0.95–1.0)	0.74	1.0 (0.97–1.0)	0.72	1.0 (0.97–1.0)	0.95
Sex									
Male	15 (39)	0.64 (0.26–1.6)	0.33	0.79 (0.22–2.8)	0.72	0.65 (0.31–1.4)	0.26		
Female	23 (61)							1.1 (0.48–2.4)	0.86
KPS score									
Continuous									
90–100	20 (53)	0.95 (0.91–1.0)	0.05	0.97 (0.90–1.0)	0.36	0.97 (0.93–1.0)	0.11	0.95 (0.91–0.99)	0.02
70–80	18 (47)	3.0 (1.2–7.5)	0.02	1.7 (0.46–6.5)	0.41	2.3 (1.1–4.7)	0.03	2.9 (1.2–6.8)	0.02
Median tumor vol in cm ³ (range)									
Continuous									
>25	15 (39)	1.0 (0.99–1.0)	0.40	1.0 (0.98–1.0)	0.47	1.0 (0.99–1.0)	0.40	1.0 (1.0–1.0)	0.13
Radioresistance*									
Radioresistant	16 (42)	1.5 (0.51–4.1)	0.48	2.1 (0.38–11)	0.40	1.1 (0.48–2.5)	0.84	1.3 (0.51–3.2)	0.60
Radiosensitive	22 (58)	0.88 (0.36–2.1)	0.79	1.1 (0.32–3.9)	0.88	0.82 (0.39–1.7)	0.59	0.96 (0.43–2.2)	0.92
Tumor location									
Lumbar/sacral	14 (37)	1.5 (0.62–3.5)	0.38	2.4 (0.66–8.4)	0.18	1.5 (0.70–3.0)	0.32	2.4 (1.0–5.3)	0.04
Cervical/thoracic	24 (63)								
Fractionation									
Multiple	24 (63)	1.6 (0.60–4.2)	0.35	2.4 (0.49–11)	0.28	1.3 (0.59–2.7)	0.56	1.0 (0.44–2.3)	0.98
Single	14 (37)								
Prior spine radiation†									
Yes	17 (45)	1.8 (0.77–4.4)	0.17	2.5 (0.70–9.1)	0.16	1.3 (0.61–2.6)	0.53	1.1 (0.47–2.5)	0.86
No	21 (55)								
Prior spine surgery†									
Yes	16 (42)	0.33 (0.12–0.92)	0.03	1.2 (0.31–4.5)	0.81	0.71 (0.34–1.5)	0.36	0.85 (0.37–1.9)	0.70
No	22 (58)								

* Defined as renal cell carcinoma, melanoma, and sarcoma.

† Prior treatment at the same site that underwent SSRS.

FIG. 2. Kaplan-Meier curves comparing the OS of patients with a KPS score of 90–100 (solid line) versus 70–80 (dashed line; left), and the OS of patients with prior spine surgery (solid line) or no prior spine surgery (dashed line; right).

fracture in the area treated with SSRS at a median of 3.8 months (range 0.7–10.2 months). Five of these patients had symptomatic fractures and subsequently underwent vertebral augmentation procedures. The SSRS doses prescribed in these 6 patients who developed fractures were 24 Gy in 1 fraction ($n = 3$), 18 Gy in 1 fraction ($n = 1$), and 27 Gy in 3 fractions ($n = 2$).

Discussion

Our results represent the largest published series of patients ($n = 38$) with oligometastatic spinal metastases treated with SSRS and demonstrate that these patients have an excellent long-term OS with limited toxicity. In addition, we showed that these patients did not need a change in systemic therapy for years following SSRS and that a significant portion had excellent survival after SSRS without the need for systemic therapy.

Significant variability exists in the prognosis for pa-

tients treated with SSRS. A recent analysis of patients treated with SSRS identified 7 pretreatment variables that grouped patients into 4 survival groups, with a 5-year overall rate of 66% for the excellent survival group compared with 0% for the poor survival group, with 1 of the variables being the SSRS site as the oligometastatic site of disease.²⁸ Our results show that as a group, these patients with oligometastatic spine metastases do have an excellent prognosis with a median survival of 76 months and a 5-year survival rate of 60%. Although all of the patients in this series had a KPS score of at least 70, those with a KPS score of 90–100 had a significantly improved survival compared with those with a score of 70–80, consistent with previously reported data.^{5,28} In addition, those patients receiving prior surgery had improved survival in our series, which may represent both the advantages of debulking as well as a healthier selected population.

Patients with oligometastatic disease potentially represent a distinct group with a better prognosis than those

TABLE 3. Multivariate analysis

Variable	OS		Local Control HR (95% CI)	DFS		STMFS	
	HR (95% CI)	p Value		HR (95% CI)	p Value	HR (95% CI)	p Value
KPS score							
90–100	0.33 (0.13–0.84)	0.02	—	0.37 (0.17–0.81)	0.01	0.21 (0.08–0.57)	<0.01
70–80	Reference			Reference		Reference	
Prior radiation*	3.6 (1.2–10)	0.02	NS	—		—	
Prior surgery*	0.16 (0.05–0.52)	<0.01	—	—		—	
Age (yrs)							
≥60	NS		—	0.36 (0.16–0.82)	0.02	0.21 (0.08–0.59)	<0.01
<60				Reference		Reference	
Spine location							
Lumbar/sacral	—		NS	—		5.6 (2.1–15)	<0.01
Cervical/thoracic						Reference	
Radiation dose	—		NS	—		—	

NS = nonsignificant; — = variable not included in the multivariate analysis.

* Prior treatment at the same site that underwent SSRS.

TABLE 4. Patterns of spine failure and salvage therapy

Type of Spine Failure	No. (%)	Surgery	Surgery + EBRT	Surgery + SSRS	SSRS	EBRT	Systemic Therapy Alone
In-field failure	10 (26)	4	2	—	1	—	3
Out-of-field	13 (34)						
Adjacent level	3 (8)	1	—	—	1	1	—
Distant level	10 (26)	—	—	1	5	1	3

who develop multiple sites of metastases, and targeted therapy with surgery or ablative radiation may be warranted over the traditional use of only systemic therapy. Several reports of resection of pulmonary, hepatic, or adrenal metastasectomies in select patients have demonstrated excellent long-term survival rates.^{3,21,29} Stereotactic body radiation therapy is a less-invasive alternative to surgery and appears to offer acceptable local control and survival rates for patients with limited metastatic disease.^{16,17,30} It is currently the subject of several ongoing clinical trials, examining the value of stereotactic body radiation therapy in oligometastatic disease for various primary sites.

However, the literature on the outcomes of SSRS for oligometastatic spinal disease is limited, and, to our knowledge, ours is the largest series to date. Thibault et al. reviewed patients with renal cell cancer treated with SSRS and showed that patients with oligometastatic disease had an improved survival compared with those with more numerous metastases (1-year survival of 84% vs 53%).³⁰ Gill et al. reported on 20 patients with oligometastatic spinal metastases treated with Cyberknife SSRS to a median dose of 30 Gy in 5 fractions.¹⁴ Another report of 4 patients with solitary spine metastases showed excellent survival and control.¹⁸ Our study stands out as the highest quality evidence, because it is the largest and a reanalysis of Phase I/II trials. In addition, oligometastatic disease has been variably defined in the literature, which makes comparison between studies challenging. Thibault et al. defined it as fewer than 5 sites of metastatic involvement, while Gill et al. did not define it at all.^{14,30} Our analysis specifically was more stringently limited to those patients with

only 1 site of disease: those who either had solitary spine metastases (in 87% of patients), or those with single spine metastases (13%) who had prior other metastases that were not progressive. Our series also compared favorably to Gill et al. in terms of survival and local control, with 1- and 2-year survival rates of 95% and 84% compared with 80% and 57%, and 1- and 2-year local control rates of 85% and 82%, compared with 80% and 73%.¹⁴ The extended long-term OS of our cohort is likely partially due to the fact that the 2 most common primary sites in our study were renal cell and breast, which have a slower natural course and better prognosis than many other primary sites. Our local control rates were acceptable and comparable to larger series, with a median local failure-free survival of 130.7 months, and a 1- and 2-year rate of 85% and 82%, respectively.^{13,31} Bishop et al. reported that patients with a GTV biologically equivalent minimum dose (Dmin) of at least 33.4 Gy had significantly better local control, recommending that, when possible, the GTV Dmin should be maintained above 14 Gy in 1 fraction and 21 Gy in 3 fractions.¹

In addition to excellent survival and acceptable local control, we have shown that these patients with oligometastatic spine disease had extended time intervals before the initiation of or a modification in systemic therapy, with a median time of 41.2 months. Eighteen percent of patients in this series did not develop any subsequent local recurrences or distant metastases at a follow-up of 75 months and never required systemic therapy (except for 1 patient who started leuprolide shortly after SSRS). This supports the notion that in select patients with oligometastatic spinal metastases that are treated definitively with SSRS, close monitoring without the need for the immediate start of systemic therapy could be a reasonable option. However, it cannot be concluded from this study whether systemic therapy should be initiated sooner or later, because it is possible that it could improve DFS in some patients. In addition, many targeted therapies have low toxicity profiles and may not affect quality of life. A thorough discussion between the medical oncologist and patient should take place regarding this decision.

As an alternative to SSRS, en bloc radical resection is a surgical technique with potentially curative intent that can be offered for oligometastatic spinal disease.^{7,8,20} However, surgical treatment of spine metastases can lead to morbidity and a postoperative complication rate of around 20%–30%.⁶ In particular, older patients have a higher risk of cardiopulmonary and infectious complications from surgery.^{19,20} In contrast, SSRS, as an outpatient noninvasive treatment, is generally very well tolerated and carries minimal morbidity and toxicity, with excellent local control rates. Because most patients will ultimately develop

FIG. 3. Kaplan-Meier curve showing the STMFS of all patients.

further metastases (we reported a median DFS of 19.0 months), SSRS is a practical alternative to en bloc spondylectomy, as it provides durable local control for patients who may ultimately have further progression of disease.

Minimization of late toxicity is especially important after SSRS for these patients with excellent long-term survival. We reported one instance of late Grade 3 myelopathy, and one instance of late Grade 4 GI fistula in a patient who had received multiple courses of radiation and surgery. In addition, 16% of patients developed compression fractures, consistent with previous reports.^{2,24} There have been variable reports on the dose limitation to the spinal cord using SSRS, with 1 recent analysis reporting a $\leq 5\%$ risk of myelopathy with a 12.4 Gy Dmax,²⁵ or even no reported myelopathy with a Dmax of 14 Gy.³³ In general, we limit the spinal cord receiving 10 Gy to 0.01 cm³ or less for single-fraction SSRS.

Our study is limited by its small sample size, patient heterogeneity, and potential selection bias. However, to our knowledge, it represents the largest analysis of and the highest level of evidence for patients with oligometastatic spine disease treated with SSRS. Because our data are based on a secondary analysis of Phase I/II clinical trials, we have eliminated some of the biases inherent in retrospective analyses, such as information bias and poor follow-up data. Instead, our rigorous and standardized follow-up, with a median follow-up duration of 69 months, allowed us to carefully assess long-term outcomes.

Conclusions

SSRS for the treatment of oligometastatic spinal metastases is a safe and very effective treatment option with excellent long-term survival, local progression-free survival, and STMFS, and should be offered over palliative radiation regimens for these patients. Further prospective study is warranted to confirm these findings.

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Disclosures

Dr. Rhines is a consultant for Stryker and Globus.

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Conception and design: Ghia, Ho, Brown. Acquisition of data: Ghia, Ho, Tang, Deegan, Jonasch, Amini, Wang, Li, Tatsui, Rhines, Brown. Analysis and interpretation of data: Ghia, Ho, Tang, Allen, Wang, Brown. Drafting the article: Ghia, Ho, Allen. 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: Ghia. Statistical analysis: Allen. Administrative/technical/material support: all authors. Study supervision: Ghia.

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