



Original Article

Low incidence of late failure and toxicity after spine stereotactic radiosurgery: Secondary analysis of phase I/II trials with long-term follow-up



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ABSTRACT

Background and purpose: To characterize local control and late toxicity in long-term survivors prospectively-treated with spine stereotactic radiosurgery (SSRS).

Materials and methods: From 2002 to 2011, 228 patients were prospectively-treated on protocol for metastatic disease of 261 vertebral sites. A subset of 52 patients surviving >4 years following treatment were collectively treated for 58 sites (encompassing 69 vertebrae) and underwent secondary analysis. Of all sites, 9% received prior radiation, and 16% encompassed multiple contiguous vertebrae. Radiation prescriptions were most commonly 24 Gy in 1 and 27 Gy in 3 fractions. Outcomes were evaluated via Kaplan–Meier, and associations analyzed via logistic regression.

Results: Median follow-up was 6.7 years (range: 49–142 months). Five-year local control by site was 91%, with late failures (>2 years) occurring in 3%. Overall and Grade ≥ 3 late toxicities (>2 years) were observed in 5% and 2% of sites. The last known neurologic event (grade 2 radiculopathy) was noted 2.1 years post-treatment, while the last documented fracture occurred at 4.1 years. No Grade ≥ 3 events were witnessed after 3.1 years post-SSRS, and no toxicities were noted after 4.1 years through end of follow-up. Re-irradiation, number of segments treated per site (1 vs. 2–3), and fractionation (1 vs. 3–5) were not associated with failure or toxicity.

Conclusion: SSRS maintains excellent disease control and a favorable late toxicity profile even among long-term survivors, with very few failures or toxicities after 2 years in this prospectively-treated population. Overall, these data support the durable control and long-term safety of SSRS with extended follow-up.

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Spine stereotactic radiosurgery (SSRS) is an effective treatment modality that facilitates the precise delivery of ablative conformal doses to bone metastases. SSRS imparts excellent local control with acceptable acute toxicity rates, as demonstrated by several reports from our own institution [1–11] and others [12–14]. We have previously demonstrated local control (LC) rates of 84–88% with low incidence of Grade ≥ 3 toxicity at 12–18 months in the setting of prospective phase I/II protocols [9,10]. Summarizing the literature, systematic reviews corroborate the safety and response durability

of SSRS, supporting its utility particularly for oligometastatic disease and/or radioresistant histologies [15,16], and even in the setting of re-irradiation [17].

However, the median follow-up times of most studies are quite limited, given the traditionally short life expectancy for patients with metastatic disease. At the same time, advances in oncologic treatments have led to increasing numbers of long-term survivors (even those with metastatic disease) and thus more patients susceptible to late toxicities after radiotherapy. Local recurrence of disease also remains a concern for such patients and is associated with pain, poor performance status, and poor quality-of-life [15], as progression in these settings can result in spinal cord compression and thus rapid clinical decline if not surgically decompressed

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[18,19]. Furthermore, for these patients, ultra-late toxicities following treatments like SSRS are increasingly relevant, given the potential long-term effects on quality-of-life.

Aside from a couple of moderate-sized retrospective reports [20,21], a relative void exists in the literature regarding these concerns. To address this knowledge gap, here we report on late efficacy and safety outcomes among long-term survivors prospectively-treated with SSRS. Given the large number of patients and sites in this prospectively-treated cohort with long-term follow-up, our findings complement and improve upon the limited retrospective reports in the literature [20,21]. Furthermore, we analyzed clinical and treatment factors for potential associations with events in this largely treatment-naïve patient population.

Materials and methods

Design, patient population, and data sources

From 2002 through 2011, each patient was enrolled on 1 of 2 prospective phase I/II protocols exploring single- (NCT00492817) and multi-fraction (NCT00508443) SSRS for the treatment of spinal metastases [2,4,6–10]. Patients with histologically-confirmed malignancy and MRI findings of spinal or para-spinal metastasis, in the absence of spinal cord compression or mechanical instability, were treated on protocol. Cervical metastases were excluded from the single fraction protocol.

Of the 228 consecutively treated patients, a subset of 52 patients surviving >4 years post-treatment (with >5 years clinical and radiographic follow-up) underwent secondary analysis. The prospectively-acquired database provided demographic, treatment, site, and fractionation data. For purposes of this secondary analysis, these clinical trial data were further supplemented with additional pathologic, oncologic, clinical, dosimetric, and toxicity data acquired via retrospective medical record review.

Treatment

Details of our institutional SSRS practice have been previously described [1–8,11]. Patients were immobilized with a customized stereotactic whole-body vacuum cradle. Image-guidance entailed CT (CT-on-rails or cone-beam CT) along with orthogonal kilovoltage and megavoltage X-rays for positional correction to verify alignment and facilitate repositioning as needed.

For target definition, diagnostic MRI was fused to the planning CT. Treatment planning was performed using intensity-modulated radiation therapy inverse-planning algorithms (Pinnacle, Philips Medical Systems). Varying dose levels were prescribed to the gross tumor volume (GTV) and clinical treatment volume (CTV), which encompassed the GTV along with the contiguous volume at-risk. Patients treated on the single-fraction protocol received 16–24 Gy to the GTV, depending on histology, with cord constraint of $0.01 \text{ cm}^3 < 10 \text{ Gy}$. For the multi-fraction protocol, GTVs were prescribed 30 Gy in 5 fractions on alternating days, transitioning to 27 Gy in 3 fractions for later patients over protocol enrollment. Cord dose constraints (Dmax) were 9 and 10 Gy for 3 and 5 fractions, respectively. For both single- and multi-fraction regimens, maximum cord dose was prioritized over tumor dose if necessary, to meet constraints.

Follow-up and outcomes assessment

Patients were followed in clinic with examination and axial imaging of the spine every 3 months up to 1 year following SSRS, then every 6 months thereafter. The primary endpoint was radiation-related toxicity, graded according to the Common Termi-

nology Criteria for Adverse Events (CTCAE), version 4.0. Specifically, toxicities of myelopathy, myelitis, radiculopathy, and vertebral compression fracture (VCF) are reported here. Late toxicities were defined as occurring >2 years following SSRS. Tumor control is also reported with local failure (LF) defined as in-field radiographic progression on imaging.

All events were measured relative to SSRS completion. Toxicity development and local control (LC) were analyzed via Kaplan-Meier method with log-rank tests for comparisons. Toxicity events that occurred in the context of simultaneous tumor progression were not scored as treatment-related. Logistic regression analysis was employed to identify potential associations between clinical or treatment variables and failure or toxicity events. Given the low numbers of events, multivariable regression analyses were not performed. Statistical analyses were performed via SPSS version 23 (IBM Corp, release 2015; IBM SPSS Statistics for Windows, Version 23.0; Armonk, NY: IBM Corp). For all statistical tests, a p -value <0.05 was considered significant.

Results

Patient, treatment, and tumor characteristics

Median age was 52 years (range: 30–74) at time of SSRS (Table 1), and median follow-up was 6.7 years post-treatment (range: 49–142 months). All patients were treated for metastases. Most patients (59%) were treated for radio-resistant histology (e.g. renal, thyroid, sarcoma, or melanoma), with renal cell as the most common (41%).

Regarding treatment, fractionation schemes by site were 27 Gy in 3 ($n = 18$), 24 Gy in 1 ($n = 14$), 30 Gy in 5 ($n = 7$), 18 Gy in 1 ($n = 10$), 16 Gy in 1 ($n = 6$), 22 Gy in 1 ($n = 1$), and 24 Gy in 3 ($n = 1$) prescribed to GTV. Nine percent of sites had been treated with conventional radiation ($\leq 3 \text{ Gy/fraction}$) prior to SSRS. Of all 58 sites, 55% were thoracic, 34% lumbar, 9% cervical, and 2% sacral. While most treatments targeted single vertebral levels, 9 sites (16%) treated 2–3 contiguous segments, for a total of 69 irradiated vertebrae.

Local control

Five-year LC by site was 91%, with only 2 late failures occurring >2 years post-treatment (Fig. 1). Overall, LF occurred at a median time of 12 months (range: 8–81). Five of the 7 LFs (71%) were in-field (2 marginal), and 3 of the 7 (43%) were of radio-resistant histologies, 1 of which was previously treated with conventional radiation. Lumbosacral site was associated with LF on univariate analysis (OR 14.4, $p = 0.02$). There were no associations with respect to radio-resistant histology ($p = 0.37$), fractionation scheme ($p = 0.91$), number of segments per site ($p = 0.32$), or treatment volumes (Table 1).

Overall and late toxicities

There were a total of 15 events following treatment of 12 sites (21%) among 11 patients (21%) [Fig. 2A]. However, only 3 late events (>2 years) were observed (Table 2). Overall, nine Grade ≥ 3 toxicities occurred following treatment of 7 sites (12%) among 7 patients (13%) [Fig. 2B], but only one of these (vertebral fracture) was a late event (Table 2). On univariate analysis, there were no associations with Grade ≥ 3 events and patient age ($p = 0.42$), fractionation scheme ($p = 0.37$), re-irradiation ($p = 0.74$), treatment site ($p = 0.70$), or treatment volumes (Table 1). No toxicities were noted for the 9 sites treating multiple (2–3) contiguous segments simultaneously.

Table 1
Univariate analyses of clinical and dosimetric variables for associations with local failures and overall toxicities ($n = 58$ sites).

Variable	Number (%)	Local Recurrence		Any Toxicity		Grade ≥ 3 Toxicity	
		OR (95% CI)	p -value ^a	OR (95% CI)	p -value ^a	OR (95% CI)	p -value ^a
<i>Age at diagnosis</i>							
>50 years	33 (57)	5.33 (0.60–47.52)	0.134	1.08 (0.30–3.90)	0.910	2.05 (0.36–11.59)	0.415
≤ 50 years	25 (43)						
<i>Patient sex</i>							
Female	34 (59)	1.07 (0.22–5.29)	0.933	0.65 (0.17–2.47)	0.527	0.53 (0.09–2.98)	0.469
Male	24 (41)						
<i>Histology</i>							
Radioresistant	34 (59)	0.48 (1.0–2.39)	0.374	0.64 (0.18–2.31)	0.498	0.48 (0.10–2.39)	0.374
Radiosensitive	24 (41)						
<i>Fractionation</i>							
Multi (3 or 5)	26 (45)	0.91 (0.19–4.50)	0.911	0.33 (0.08–1.39)	0.132	0.45 (0.08–2.54)	0.366
Single (1)	42 (55)						
<i>Re-irradiation</i>							
Yes	5 (9)	1.96 (0.19–20.5)	0.575	0.96 (0.10–9.42)	0.968	1.96 (0.19–20.54)	0.575
No	53 (91)						
<i>Location</i>							
Lumbosacral	21 (36)	14.4 (1.59–130.1)	0.018	1.34 (0.37–4.91)	0.659	1.38 (0.28–6.83)	0.697
Cervicothoracic	37 (64)						
<i>Contiguous segments</i>							
Multiple (2–3)	9 (16)	2.51 (0.41–15.6)	0.322	N/A	0.999	N/A	0.999
Single (1)	49 (84)						
<i>GTV volume (cm³)</i>							
10.9 (median)	0.21–144 (range)	0.98 (0.94–1.03)	0.475	1.00 (0.97–1.02)	0.769	0.95 (0.89–1.03)	0.221
CTV volume (cm ³)							
33.7 (median)	7.6–204 (range)	1.01 (1.00–1.03)	0.171	0.99 (0.97–1.01)	0.316	0.97 (0.94–1.01)	0.199

Abbreviations: OR, odds ratio; CI, confidence interval; GTV, gross tumor volume; Gy, Gray.

^a Univariate logistic regression to assess for associations between events and clinical and treatment variables

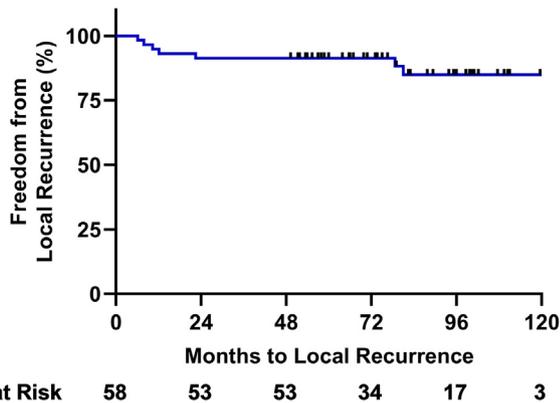


Fig. 1. Local control in 58 sites following SSRS with long-term follow-up. Late failures (>2 years) occurred in only 3% of sites.

Vertebral fractures

Eight treated sites (14%) involving 7 patients (13%) resulted in vertebral body collapse and/or endplate fracture occurring at a median 7.5 months (range 0.6–50), of which 6 required percutaneous vertebroplasty or surgical intervention (Grade ≥ 3) [Fig. 3A]. However, only 2 fractures were late events (Table 2). On univariate analysis, there were no associations with respect to age ($p = 0.28$), sex ($p = 0.32$), fractionation scheme ($p = 0.66$), re-irradiation ($p = 0.68$), treatment site ($p = 0.94$), or treatment volumes (Table 3).

Neurologic toxicities

Seven neurologic events (3 Grade ≥ 3) occurred following treatment of 6 sites (10%) among 6 patients (12%) at a median 12.7 months (range: 2.6–25.4). Of these, only 1 late event observed

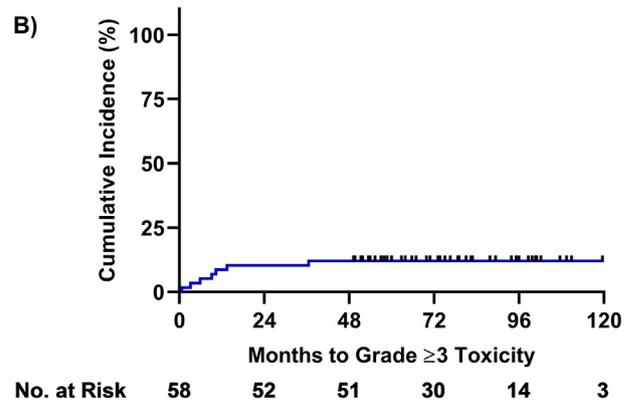
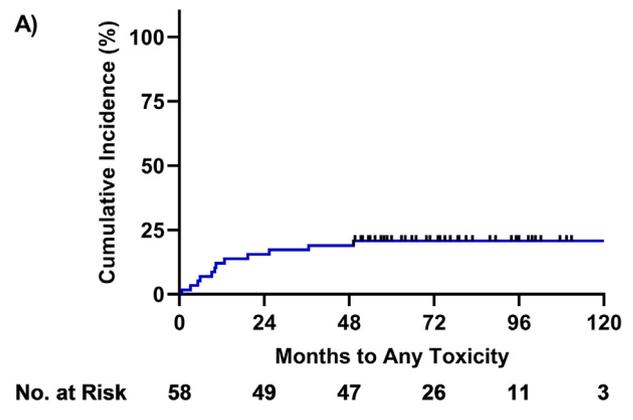
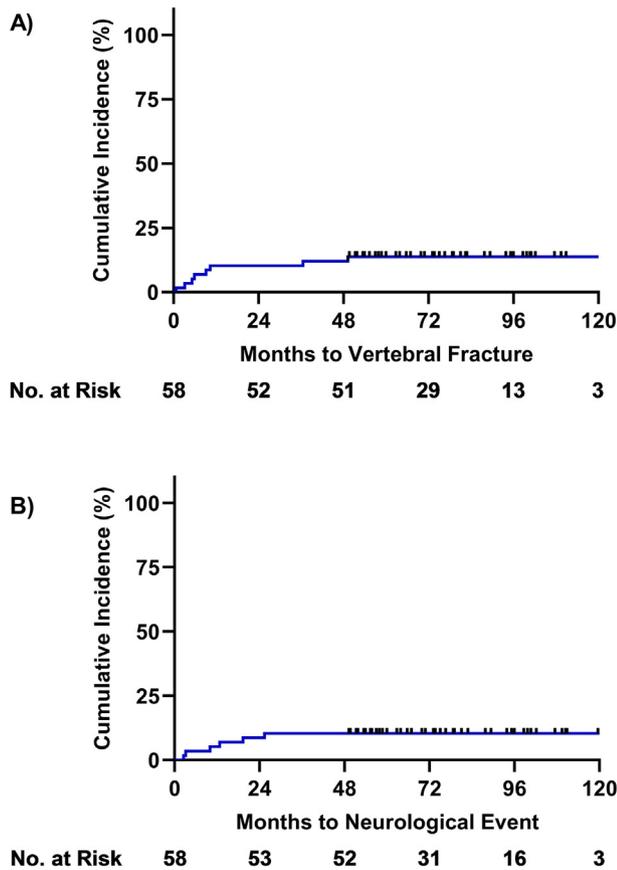


Fig. 2. (A) Overall and (B) Grade ≥ 3 toxicity outcomes in 58 sites treated with SSRS with long-term follow-up. The incidence of any Grade and Grade ≥ 3 late events (>2 years) was 5% and 2%, respectively. No toxicities were observed more than 4.1 years post-treatment (with no Grade ≥ 3 events after 3.1 years).

Table 2Toxicity events ($n = 15$), graded by Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Grade	Vertebral Fracture			Radiculopathy			Myelitis			Myelopathy		
	1	2	3	1	2	3	1	2	3	1	2	3
Acute (<3 months)	0	0	1	0	0	1	0	0	0	0	0	0
Delayed (3–24 months)	0	1	4	0	2	1	0	1	0	0	0	1
Late (>2 years)	1	0	1	0	1	0	0	0	0	0	0	0
Median Time to Onset (months)	7.5 (0.7–49.6)			12.7 (2.6–25.4)			10.0			13.5		

**Fig. 3.** Incidence of (A) Vertebral fractures and (B) Neurologic toxicities among 58 sites treated with SSRS with long-term follow-up. No neurologic events occurred after 2.1 years, while no fractures were observed after 4.1 years post-treatment.

(Grade 2 radiculopathy) [Fig. 3B]. In total, there were 5 radiculopathies, of whom 2 required intrathecal pain pumps (Table 2). Neurologic toxicity was not associated with age ($p = 0.72$), sex ($p = 0.20$), location ($p = 0.12$), or treatment volumes on univariate analysis (Table 3). No neurologic toxicities were noted among the 5 sites undergoing re-irradiation.

Of note, there was one case of clinically-apparent myelitis at 10 months, occurring at the level of T2 in a metastatic breast cancer patient and progressing to Grade 3 myelopathy by 13.5 months consistent with hemi-cord syndrome. The prescription dose was 18 Gy in a single fraction, delivered in the absence of prior radiotherapy, with maximum point dose (Dmax) of 12.67 Gy to the cord. More specifically, the maximum dose to 0.01 cm³, 0.03 cm³, and 0.1 cm³ of the spinal cord was 11.9 Gy, 11.5 Gy, and 7.9 Gy, respectively.

Discussion

In this study investigating late efficacy and toxicities in long-term survivors prospectively-treated with SSRS, our pertinent find-

ings were as follows: (a) LC remained high upon long-term follow-up, with very few failures after 2 years; (b) the incidence of late toxicity (>2 years) was quite low, with neurologic events presenting slightly earlier than fractures; and (c) overall events appeared to plateau with time, with no toxicities noted after 4.1 years through the end of study follow-up. Taken together, these data support the durable control and long-term safety outcomes of SSRS.

SSRS imparts excellent LC [1–10], and our findings confirm the durability of tumor control on long-term follow-up, with a 5-year LC rate of 91% and a late failure rate (>2 years) of only 3%. These results are further supported by a report from Memorial Sloan–Kettering [20], which cited an overall LC rate of 92% at median follow-up of 6.1 years of 36 sites treated to single-fraction 24 Gy. Comparatively, a study from the University of Pittsburgh noted a lower 5-year LC rate of 58% among 54 sites treated with SSRS [21]. However, most sites in this series received a lower single-fraction dose of 16 Gy (in the setting of re-irradiation). Of note, while median time to failure ranged from 17 to 49 months among these collective reports [20,21], a few LFs occurred as late as 81–137 months [20,21], raising the question of whether these are new bony metastases rather than true local recurrences presenting >5 years post-treatment.

In general, an optimal standard prescription for SSRS has yet to be defined, with a variety of dose and fractionation patterns shown to be effective [12,22]. However, there is a clear need of dose escalation in radio-resistant phenotypes [20,22–27]. This dose response has been well-demonstrated for renal cell carcinoma, for example, with LC increasing dramatically from 30% to 81% as single-fraction prescription dose rises above 22 Gy [28]. Likewise, relatively high dose has been shown to be necessary for durable control of other radio-resistant histologies [28,29].

In addition to these favorable control outcomes, we found a very low incidence of late toxicities (>2 years) among our patients. Specifically, the rates of overall and Grade ≥ 3 late toxicity by site were only 5% and 2%, respectively. Furthermore, although the numbers of events were limited, we failed to identify significant clinical associations with toxicities. Even “higher risk” treatment-related factors—such as re-irradiation, multiple segments treated per site (1 vs. 2–3), and fractionation scheme (1 vs. 3–5)—were unrelated to toxicities in this limited study population, suggesting that SSRS in general is accompanied by long-term safety.

As previously mentioned, Memorial Sloan–Kettering [20] and the University of Pittsburgh [21] each published retrospective studies on their long-term survivors, similar to the present study with comparable follow-up. Both of these series, however, emphasized overall toxicity rates in their reported figures including delayed events (3–24 months). While these overall rates are low and comparable with those reported here, the early toxicity profile during this timeframe (<2 years post-treatment) is already well-established by large-scale and/or prospective reports more robustly suited to address this query [1–10]. As such, the specific focus of our study was to address a literature void by characterizing true late toxicities (>2 years post-treatment) among long-term survivors—a more appropriate question for this highly-selected patient population.

Table 3
Univariate analyses of clinical and dosimetric variables for associations with vertebral fractures and neurologic events ($n = 58$ sites).

Variable	No. (%)	Vertebral fracture		Neurologic toxicity	
		OR (95% CI)	<i>p</i> -value ^a	OR (95% CI)	<i>p</i> -value ^a
<i>Age at diagnosis</i>					
>50 years	33 (57)	2.56 (0.47–13.91)	0.278	0.73 (0.14–3.98)	0.719
≤50 years	25 (43)				
<i>Patient sex</i>					
Female	34 (59)	0.42 (0.08–2.31)	0.321	3.2 (0.54–19.1)	0.202
Male	24 (41)				
<i>Histology</i>					
Radioresistant	34 (59)	0.67 (0.15–2.98)	0.596	1.47 (0.25–8.74)	0.674
Radiosensitive	24 (41)				
<i>Fractionation</i>					
Multi (3 or 5)	26 (45)	0.70 (0.15–3.27)	0.655	N/A	0.998
Single (1)	42 (55)				
<i>Re-irradiation</i>					
Yes	5 (9)	1.64 (0.16–16.9)	0.676	N/A	0.999
No	53 (91)				
<i>Location</i>					
Lumbosacral	21 (36)	1.07 (0.23–4.99)	0.935	4.12 (0.69–24.8)	0.122
Cervicothoracic	37 (64)				
<i>Contiguous segments</i>					
Multiple (2–3)	9 (16)	N/A	0.999	N/A	0.999
Single (1)	49 (84)				
<i>GTV volume (cm³)</i>					
10.9 (median)	0.21–144 (range)	0.98 (0.93–1.03)	0.376	1.01 (0.98–1.03)	0.625
<i>CTV volume (cm³)</i>					
33.7 (median)	7.6–204 (range)	0.98 (0.95–1.01)	0.258	1.00 (0.97–1.02)	0.867

Abbreviations: OR, odds ratio; CI, confidence interval; GTV, gross tumor volume; Gy, Gray.

^a Univariate logistic regression to assess for associations between events and clinical and treatment variables.

Among the very few late toxicities in this cohort, both neurologic toxicity and vertebral fractures were observed. Temporally, neurologic events appeared to present earlier than fractures. No neurologic toxicities occurred after 2.1 years, whereas fractures were observed up to 4.1 years after SSRS. These findings are consistent with the prior reports [20,21], in which fractures were among the latest occurring events. Taken together, these data suggest that the risk of neurologic toxicity falls off relatively early and poses less concern for long-term survivors with further time out from treatment.

Even following late fractures, the overall incidence of any late toxicity appears to plateau around 5 years. In the present study, no late toxicities were observed more than 4.1 years post-treatment (with no Grade ≥3 events after 3.1 years). Corroborating these findings, the University of Pittsburgh group also noted a complete absence of new toxicities after 5 years [21], while Memorial Sloan-Kettering reported only 2 low-grade events occurring >2 years post-treatment [20]. Thus, these studies collectively support the long-term safety of SSRS for patients, as well as the notion that traditional radiobiological models may be inadequately suited for predicting clinical response and/or late toxicities with hypofractionated radiotherapy [30,31].

The primary limitations of this study include its single-institution nature and the heterogeneity in prescriptions. This heterogeneity reflects our evolving practice pattern over time, as our institution gained more experience and comfort with SSRS. For single-fraction regimens, our prescription doses have increased from 16 Gy to our now standard 18 Gy and 24 Gy (to the GTV) for radio-sensitive and radio-resistant histologies, respectively. For multi-fraction treatments, prescription dose has increased from 30 Gy in 5 fractions historically to our current standard of 27 Gy in 3 fractions (which is now typically reserved for re-irradiation cases).

Additionally, while re-irradiation may be a commonly-recommended indication for SSRS [15,17,32], our study contains

only a small number of previously-treated cases. In general, the modest sample size may also limit the ability to identify significant associations between variables and outcomes. Yet, the numbers of patients and sites here are comparably greater than those of previous reports [20,21], and our study benefits from long-term follow-up (nearly 7 years) of patients prospectively-treated on protocol.

In conclusion, this is the largest study to date to investigate late efficacy and toxicity outcomes among long-term survivors prospectively-treated with SSRS. Overall, these data support the high therapeutic ratio associated with this advanced treatment modality. SSRS imparts durable local control and a favorable toxicity profile, which persist with extended follow-up.

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Declaration of Competing Interest

There are no conflicts of interest directly relevant to the specific work under consideration for publication; however, the following authors hold unrelated financial and professional relationships as disclosed: Paul D. Brown reports personal fees as contributor to UpToDate (current). Jing Li reports research funding from Medtronic.

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