Spine stereotactic radiosurgery for metastatic thyroid cancer: a single-institution experience

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OBJECTIVE Patients with metastatic thyroid cancer have prolonged survival compared to those with other primary tumors. The spine is the most common site of osseous involvement in cases of metastatic thyroid cancer. As a result, obtaining durable local control (LC) in the spine is crucial. This study aimed to evaluate the efficacy of spine stereotactic radiosurgery (SSRS) in patients with metastatic thyroid cancer.

METHODS Information on patients with metastatic thyroid cancer treated with SSRS for spinal metastases was retrospectively evaluated. SSRS was delivered with a simultaneous integrated boost technique using single- or multiple-fraction treatments. LC, defined as stable or reduced disease volume, was evaluated by examining posttreatment MRI, CT, and PET studies.

RESULTS A total of 133 lesions were treated in 67 patients. The median follow-up duration was 31 months. Dose regimens for SSRS included 18 Gy in 1 fraction, 27 Gy in 3 fractions, and 30 Gy in 5 fractions. The histology distribution was 36% follicular, 33% papillary, 15% medullary, 13% Hurthle cell, and 3% anaplastic. The 1-, 2-, and 5-year LC rates were 96%, 89%, and 82%, respectively. The median overall survival (OS) was 43 months, with 1-, 2-, and 5-year survival rates of 86%, 74%, and 44%, respectively. There was no correlation between the absolute biological equivalent dose (BED) and OS or LC. Patients with effective LC had a trend toward improved OS when compared to patients who had local failure: 68 versus 28 months ($p = 0.07$). In terms of toxicity, 5 vertebral compression fractures (2.8%) occurred, and only 1 case (0.6%) of greater than or equal to grade 3 toxicity (esophageal stenosis) was reported.

CONCLUSIONS SSRS is a safe and effective treatment option with excellent LC and minimal toxicity for patients with metastatic thyroid cancer. No association with increased radiation dose or BED was found, suggesting that such patients can be effectively treated with reduced dose regimens.

<https://thejns.org/doi/abs/10.3171/2019.12.SPINE191269>

KEYWORDS SSRS; spine stereotactic radiosurgery; thyroid cancer; metastatic; radiation; oncology

THYROID cancer is the most rapidly rising malignancy in the United States with an estimated 52,070 new cases in 2019.² Fortunately, the 5-year survival rates for thyroid cancer are among the highest of any disease site, approaching 98%.⁴⁰ Despite excellent survival rates, approximately 4% of patients with thyroid cancer develop bone metastases that can significantly affect overall

survival (OS) rates, long-term morbidity, and quality of life.^{12,31} Patients with osseous metastases have been shown to carry worse OS when compared to patients with metastatic disease not involving the bone—likely due to the high rate of symptomatic skeletal events, such as spinal cord compression and fractures.¹² The spine is the most common site of osseous metastatic disease in thyroid can-

ABBREVIATIONS BED = biological equivalent dose; CTCAE = Common Terminology Criteria for Adverse Events; CTV = clinical target volume; GTV = gross tumor volume; LC = local control; OS = overall survival; RT = radiation therapy; SSRS = spine stereotactic radiosurgery; TKI = tyrosine kinase inhibitor.

SUBMITTED October 24, 2019. **ACCEPTED** December 3, 2019.

INCLUDE WHEN CITING Published online February 14, 2020; DOI: 10.3171/2019.12.SPINE191269.

cer patients, with involvement often causing significant pain and neurological compromise.²⁷ Due to the increased survival rates compared to other malignancies, optimal local control (LC) in the spine is paramount to avoid long-term morbidity and neurological sequelae. Furthermore, with bone metastases yielding worse OS paired with the recent advancements in therapy, including targeted therapy, immunotherapy, and the oligometastatic paradigm, improved LC may result in improved survival rates. This has been demonstrated recently in the oligometastatic setting using both surgery and stereotactic body radiation therapy (RT).^{23,34} In addition, previous data have also shown excellent survival rates in patients with isolated spine disease treated with spine stereotactic radiosurgery (SSRS).²⁵

Treatment options for spinal metastases include steroids, conventional RT, SSRS, surgery, or any combination of these modalities. Decisions regarding treatment are made using a combination of factors that have been described in the NOMS (neurologic, oncologic, mechanical, and systemic) framework.²⁸ This includes neurological factors such as the presence of acute deficits, oncological factors such as tumor histology, radiosensitivity, metastatic burden, the mechanical stability of the spine, and surgical candidacy.²⁸ Patients with acute neurological compromise or mechanical instability of the spine should receive surgery if deemed to be appropriate candidates. For patients not requiring operative management, RT using a conventional or stereotactic approach can be performed. Conventional RT is often utilized in patients with significant cord compression or acute neurological deficits (in patients who are nonoperative candidates) and in patients with poor performance status or with high metastatic burden—owing to the fact RT can be performed as an urgent same-day treatment due to the simplicity of treatment planning with conventional approaches. SSRS has the advantage of delivering ablative doses of radiation with submillimeter precision, thus providing the opportunity for improved LC while reducing normal tissue toxicity. LC rates for SSRS have been shown to be approximately 90% and 80% at 1 and 2 years, respectively.^{1,5,10,17,21,43} Beyond effective LC rates, SSRS is well tolerated and toxicity rates are low.^{7,38} We previously reported our early experience in treating patients with metastatic thyroid cancer using SSRS and demonstrated effective LC.⁴ Since that study, we have experienced increased volume and therefore aim to expand upon our previous results to report outcomes of SSRS in a larger cohort of patients with metastatic thyroid cancer and to evaluate factors associated with LC.

Methods

Patients

The records of patients with metastatic thyroid cancer in whom spinal involvement was treated with SSRS from January 2004 to December 2018 were retrospectively evaluated after we obtained institutional review board approval. The study population included two cohorts of patients previously enrolled in a combined phase I/II single-institution study, in addition to patients who were treated off protocol. A total of 67 patients' medical records were

reviewed, and patient, tumor, and treatment data were extracted for analysis.

Treatment

Patients in this study were treated with image-guided intensity-modulated SSRS; the CT guidance system was the EXaCT Targeting System CT-on-rails or the Trilogy system with onboard cone-beam CT (Varian Medical Systems), as previously described.^{9,39} Since 2014, patients were treated with TrueBeam with onboard cone-beam CT and ExacTrac Dynamic (Brainlab) guidance. Patient immobilization was completed using a BodyFix stereotactic body frame system (Elekta) and aligned with a stereotactic localizer and target-positioning frame (Integra-Radiomics). Treatment planning was completed using intensity-modulated RT inverse-treatment software (Pinnacle, Philips Medical Systems). CT myelography with intrathecal injection of contrast medium (Omnipaque, Amersham Health) was performed when MRI alone was insufficient to clearly delineate the spinal cord. Thorough quality-assurance procedures were completed by a dedicated radiation physicist, and all target positions were verified by the treating radiation oncologist.

Delineation of the gross tumor volume (GTV) and clinical target volume (CTV) for primary cases was based on consensus guidelines for SSRS contouring.¹⁵ The GTV was defined as visible tumor on an MR image fused with the planning CT scan, and the CTV was defined as at-risk contiguous bone marrow or soft tissue in cases with paraspinal disease. No additional margin or planning treatment volume was utilized. In the postoperative setting, target volumes were constructed similarly to the recently published consensus postoperative SSRS guidelines.³⁶ The GTV was defined as any gross residual disease and/or the postoperative bed, with the CTV representing the contiguous bone marrow space and any additional postoperative bed at risk for microscopic disease. SSRS was delivered using a simultaneous integrated boost technique in a single-fraction regimen (18–24 Gy) or in multifraction regimens (25–30 Gy in 3–5 fractions); the multifraction treatments were delivered on alternating days. Our current practice is to utilize single-fraction treatments for cases involving radiation-naïve sites and multifraction regimens for cases involving reirradiation. Multifraction regimens in this study were performed in either patients undergoing reirradiation or patients enrolled in institutional phase I and II studies requiring alternative dose regimens. To account for and appropriately compare the various fractionation schemes, a biological equivalent dose (BED) was calculated for the prescription based on the α/β value of 10 Gy for tumor effect. A spinal cord constraint of 0.01 cm³ < 10–12 Gy was commonly utilized. An example of a treatment plan can be visualized in Fig. 1.

Follow-Up and Endpoints

Patients were followed until the last known follow-up date or the date of death. LC, defined as stable or reduced disease volume, was evaluated by posttreatment MRI, CT, and PET.

The median follow-up duration for the entire cohort

FIG. 1. A male patient with oligometastatic papillary cancer with Bilsky 1b compression at T10. Pretreatment T2-weighted sagittal (A) and axial (B) MR images displaying Bilsky 1b compression at T10. Axial (C) and sagittal (D) CT simulation slices displaying the SSRS treatment plan using a simultaneous integrated boost to 24 Gy in 1 fraction to the GTV (red target, white isodose) and 18 Gy to the CTV, including the vertebral body and pedicles (yellow target, blue isodose). Long-term follow-up posttreatment T2-weighted sagittal (E) and axial (F) MR images at 72 months post-SSRS displaying complete response, demonstrating the effectiveness and durability of SSRS for thyroid cancer. Figure is available in color online only.

was 19 months (range 1–121 months), and for all living patients it was 31 months (range 10–121 months). Acute (defined as less than 3 months) and long-term toxicities were prospectively recorded for patients treated on protocol (53%); otherwise, toxicities were retrospectively graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Patients were seen every 3 months for physical examination and MRI of the spine to assess for radiological tumor recurrence. Local recurrence-

es were defined as radiological evidence of progression, as identified by the reading radiologist.

Statistical Analysis

Data analysis was performed using Stata/MP 15.0 statistical software. The survival function was carried out using Kaplan-Meier estimates. The log-rank test was used to assess the equality of the survivor function across groups. The Cox proportional hazards model was used for multivariate analysis to assess the effect of patient, tumor, and other predictor factors of significance on OS and local tumor control. The estimated hazard is reported. The Wald test was used to assess the role of covariates in the model. All factors found to have a p value of 0.25 or less on univariate analysis were included in the multivariable analysis, with each factor eliminated in a stepwise manner until the most significant variables were identified. The Wald test was used to assess the role of covariates in the model. Competing risk regression analysis was done according to the method of Fine and Gray with a similar selection of predictive factors for multivariable analysis.¹⁸ Subhazard ratios are reported for the failure event of primary interest (local tumor control), with death without local failure as the competing event reported.

Results

Patient and Treatment Characteristics

The patient characteristics are provided in Table 1 and the treatment characteristics are included in Table 2. A total of 133 lesions were treated in 67 patients. The median follow-up was 31 months for living patients. There was nearly an equal proportion of men and women at 51% and 49%, respectively. The median age of patients was 60 years. Follicular was the most common thyroid histology at 36%, followed by papillary 33%, medullary 15%, Hurthle cell 13%, and anaplastic 3%. In terms of malignant spinal cord compression grading, the following was noted: grade 0 in 55%, 1a in 11%, 1b in 20%, and 2 in 8% of patients. SSRS treatment was the primary modality of care in 62% of cases, while 38% received SSRS in the adjunctive or salvage setting. With regard to other treatment pathways, 19% of cases underwent surgery prior to SSRS, 29% had prior external-beam RT, and 89% of patients had received iodine-131 treatment. In addition, 66% of patients were on tyrosine kinase inhibitor (TKI) therapy throughout their course of treatment. A majority of cases (76%) involved the treatment of a single vertebral body. For single-fraction treatments, a dose-fractionation scheme of 18 Gy in 1 (44%) or 24 Gy in 1 (10%) fraction was utilized. For multifraction treatments, a scheme of 27 Gy in 3 (41.4%) or 30 Gy in 5 (3.8%) fractions was utilized, with the exception of 1 patient who was treated with 25 Gy in 5 (1.5%) fractions.

Local Control

The 1-, 2-, and 5-year LC rates were 96%, 89%, and 82%, respectively (Fig. 2). Median LC was not reached. A total of 12 failures were found in this cohort. Review of the pattern of failures revealed 58% in field, 25% marginal epidural, 17% out of field, and 18% marginal paraspinal. Univariate analysis detailing factors predicting LC

TABLE 1. Patient characteristics

Characteristic	No.	%
Patients	67	
Lesions	133	
Vertebral bodies treated	179	
Median age (range)	60 (28–80)	
Sex*		
Male	34	51%
Female	33	49%
Histology*		
Follicular	24	35.8%
Papillary	22	32.8%
Medullary	10	14.9%
Hurthle cell	9	13.4%
Anaplastic	2	3.0%
Bilsky MSCC grade†		
0	73	55%
1a	15	11%
1b	26	20%
1c	0	0
2	10	8%
3	0	0
Prior treatment†		
¹³¹ I	118	88.72%
Radiation treatment	38	28.57%
Surgery	25	18.80%

¹³¹I = iodine-131; MSCC = malignant spinal cord compression.

* Percentages are based on the number of patients.

† Percentages are based on the number of lesions.

are shown in Table 3. On multivariate analysis when accounting for sex, treatment type, and progression at distant sites, progression at distant sites was the only factor that emerged as significantly associated with local failure (HR 5.0, 95% CI 1.07–23.39; $p = 0.04$). In a separate competing risk analysis that was performed to account for risk of death, the only factor that was significantly associated with LC was female sex (HR 0.18, 95% CI 0.04–0.79; $p = 0.04$).

Overall Survival

The median OS was 43 months, with 1-, 2-, and 5-year survival rates of 86%, 74%, and 44%, respectively (Fig. 3). A total of 13 patients in this analysis were deceased; all cases were attributed to progression of systemic disease. There was a trend toward worse OS in patients who experienced local failure (28 months vs 68 months), reaching near-significant significance ($p = 0.07$) (Fig. 4). The univariate analysis for factors predicting OS is displayed in Table 4. On multivariate analysis, being treated with more than 1 fraction was associated with improved OS (HR 2.28, 95% CI 1.16–4.46; $p = 0.016$).

Toxicity

Based on the CTCAE version 4.3, there were 28 treat-

TABLE 2. Summary of radiation-related characteristics

Characteristic	No.	%
Treatment intent		
Primary	70	52.6%
Adjuvant/salvage	63	47.4%
No. of vertebral bodies treated		
1	101	75.9%
2	18	13.5%
3	14	10.5%
Region of spine treated		
Cervical	20	15.0%
Thoracic	68	51.1%
Lumbar	36	27.1%
Sacral	9	6.8%
Dose-fractionation schedule (Gy/no. of fractions)		
Single fraction	71	53.4%
18/1	58	43.6%
24/1	13	9.8%
Multifraction	62	46.6%
25/5	2	1.5%
27/3	55	41.4%

ment-related acute toxicities (21%) of the 133 lesions, of which all but 1 (96.4%) were grade 1 and 2 toxicities. Fatigue was the most common among the acute toxicity cases, representing 29% of adverse events, followed by acute nausea at 21%. Two cases of grade 2 esophagitis were noted. The single case of greater than or equal to grade 3 toxicity was esophageal stenosis in a patient who received 18 Gy in 1 fraction. Pain flare was uncommon but occurred in 8 cases (6%) of the 133 lesions. With 66% of patients being on TKIs, the incidence of radiation recall was also investigated and found to occur in only 2% of patients on TKI therapy. Both cases of radiation recall were of minimal severity. In terms of late toxicity, 5 vertebral compression fractures (3%) occurred (a total of 179 vertebral bodies were treated). Two cases of mild sensory radiculopathy were noted; otherwise, no significant neurological toxicities including radiation myelopathy were observed.

Discussion

This report represents the largest study exploring the benefits of SSRS for patients with thyroid cancer. Our previous report included a total of 23 patients with 27 treated lesions, with 2- and 3-year LC rates of 88% and 79%, respectively.⁴ Our current study includes 67 patients with 133 treated lesions with similar LC rates of 96%, 89%, and 82% at 1-, 2-, and 5-year follow-up examinations, respectively. Previous data regarding the effectiveness of SSRS for spinal metastasis have shown LC rates on the order of approximately 90% at 1 year and 80% at 2 years.^{5,6,20,21,37} The improved LC rates in this cohort likely speak to the relative radiosensitivity of thyroid cancer. This holds true within our analysis as there was no benefit with increasing

FIG. 2. Local failure analysis for patients with metastatic thyroid cancer treated with SSRS. Figure is available in color online only.

radiation dose, increasing fractionation, or BED in terms of LC or OS. An example can be seen in Fig. 1, where a patient with oligometastatic papillary cancer with a grade 1b compression at T10 was effectively treated with SSRS delivering 18 Gy in a single fraction. His follow-up scans, noted in Fig. 1, showed complete resolution of epidural disease, with 72-month posttreatment imaging reflecting the effectiveness and durability of SSRS for thyroid cancer. While no data are available specifically evaluating the efficacy of conventional RT for thyroid cancer spinal metastases, the overall radiographic control rate for all histologies is quite poor, on the order of 20% at 2 years.²⁶ This is drastically lower than the LC rates achieved with SSRS and a fundamental reason why SSRS is the preferred radiation approach for appropriately selected patients. On the other hand, data regarding resection for thyroid cancer spinal metastases show excellent 5-year LC rates of 90% with total en bloc spondylectomy.¹⁶ However this drops substantially, reaching 57% when only subtotal resections are performed.¹⁶ This highlights the importance of patient selection for treatment; in cases where total en bloc spondylectomy is achievable, this would be the ideal treatment approach given the superior LC. With that being said, in cases where total en bloc spondylectomy is not achievable, such as in those with significant paraspinal disease or multilevel vertebral body involvement, SSRS would be preferred due to improved LC rates when compared to subtotal resection.

Due to the excellent LC rates seen in this study, there seems to be a limited role for biological dose escalation (e.g., 24 Gy/1 fraction) for this cohort of patients. In contrast, data regarding LC in more radioresistant histological types such as sarcomas display a strong correlation between SSRS dose and LC rates.^{6,22,29,44} In particular, renal cell carcinoma is a radioresistant histology that has been shown to have suboptimal rates of LC with conventional SSRS doses. A study comparing dose regimens for renal cell carcinoma found a statistically significant improved rate of LC with the use of single-fraction treatments of ≥ 24 Gy vs < 24 Gy with a 3-year LC rate of 88% and 21%, respectively ($p = 0.001$).⁴⁴ Our own experience as a combined phase I/II trial has been published comparing 24 Gy in 1 fraction vs 27 Gy in 3 fractions for renal cell

TABLE 3. Analysis for LC

Variable	Comparison	HR (95% CI)	p Value
Univariate analysis			
Sex			
Female	Male	4.12 (0.90–18.85)	0.07
Age			
Continuous	Continuous	1.00 (0.95–1.05)	0.89
50–69 yrs	50–69 yrs	1.27 (0.27–5.90)	0.76
70 yrs	≥ 70 yrs	0.74 (0.07–8.18)	0.81
Histology			
Papillary	Follicular	2.10 (0.59–7.48)	0.25
Other	Follicular	0.61 (0.11–3.33)	0.57
Prior RT			
Yes	No	0.68 (0.15–3.09)	0.61
Prior surgery			
Yes	No	0.40 (0.05–3.07)	0.38
Prior ¹³¹ I			
Yes	No	2.11 (0.27–16.33)	0.61
Primary treatment			
No	Yes	0.40 (0.09–1.83)	0.24
No. of vertebral bodies treated			
2	1	0.58 (0.07–4.58)	0.61
3	1	0.92 (0.12–7.26)	0.941
No. of fractions			
3	1	0.52 (0.14–1.91)	0.32
5	1	0.52 (0.14–1.91)	0.32
>1	1	0.48 (0.13–1.78)	0.271
BED			
Continuous	Continuous	1.00 (0.9–1.07)	0.99
>80	<80	0.96 (0.12–7.44)	1.0
Progression at other sites			
Yes	No	3.99 (0.87–18.32)	0.075
Multivariate analysis			
Progression at other sites			
Yes	No	5.00 (1.07–23.39)	0.041
Sex			
Female	Male	4.94 (1.07–22.82)	0.041
Primary treatment			
No	Yes	0.24 (0.05–1.13)	0.071

carcinoma and displayed statistically significant improved LC at 1 year (95% vs 71%) and 2 years (86% vs 55%) favoring single-fraction treatment.²² Comparing these rates to the current study where more than 85% of patients were treated with standard dose regimens (18/1 or 27/3), one can conclude that due to the intrinsic radiosensitivity of thyroid cancer, there is no need to utilize dose-escalated regimens, thus minimizing any long-term toxicities that these patients may develop.

In terms of factors predicting LC rates, female sex was

FIG. 3. Kaplan-Meier survival analysis for patients with metastatic thyroid cancer treated with SSRS. Figure is available in color online only.

FIG. 4. Kaplan-Meier survival analysis for patients with metastatic thyroid cancer treated with SSRS, stratified by local failure (LF; red) versus LC (blue). Figure is available in color online only.

associated with improved LC, while progression at other distant sites was associated with worse LC in the spine. Females are significantly more likely to develop thyroid cancer, and thus this finding could be reflective of the higher incidence of the disease within this population or perhaps due to underlying biology, such as hormonal differences. The association between local and distant failure in this cohort is likely reflective of more aggressive cancers with resistance to both systemic and local treatment.

Beyond being effective as a primary modality, SSRS also offers the advantage of being an effective salvage therapy in the case of failed conventional RT or surgery. Forty-seven percent of patients in this study were treated with SSRS as a second-line local therapy; despite this approach, LC remained exceedingly high. These data confirm that SSRS is an effective primary and adjuvant/salvage treatment option for patients with metastatic thyroid cancer.

The median OS for this study was 43 months, with 1-, 2-, and 5-year survival rates of 86%, 74%, and 44%, respectively. Prior studies have shown median OS rates ranging from approximately 7 to 30 months for the patients with

TABLE 4. Analysis for OS

Variable	Comparison	HR (95% CI)	p Value
Univariate analysis			
Sex			
Female	Male	0.92 (0.48–1.78)	0.81
Age			
Continuous	Continuous	1.02 (0.99–1.05)	0.25
50–69 yrs	<50 yrs	0.981 (0.45–2.17)	0.97
70 yrs	<50 yrs	1.38 (0.48–3.96)	0.55
Histology			
Papillary	Follicular	1.51 (0.70–3.25)	0.30
Other	Follicular	0.59 (0.25–1.36)	0.22
Prior RT			
Yes	No	1.97 (0.99–3.90)	0.052
Prior surgery			
Yes	No	1.14 (0.55–2.38)	0.72
Prior ¹³¹ I			
Yes	No	1.24 (0.48–3.20)	0.66
Primary treatment			
No	Yes	1.51 (0.78–2.90)	0.22
No. of vertebral bodies treated			
2	1	1.47 (0.62–3.44)	0.38
3	1	3.15 (1.26–7.89)	0.0014
Spine location			
Thoracic	Cervical	0.83 (0.33–2.11)	0.70
Lumbar	Cervical	1.14 (0.39–3.31)	0.81
Sacrum	Cervical	1.38 (0.35–5.56)	0.65
No. of fractions			
3	1	2.30 (1.15–4.59)	0.018
5	1	2.14 (0.60–7.62)	0.24
>1	1	2.28 (1.16–4.46)	0.016
BED			
Continuous	Continuous	0.99 (0.95–1.03)	0.65
>80	<80	0.99 (0.16–2.85)	0.65
Progression at other sites			
Yes	No	1.57 (0.79–3.13)	0.20
Multivariate analysis			
No. of fractions			
>1	1	2.28 (1.16–4.46)	0.016

spinal metastases undergoing SSRS.^{3,25,42} The improved OS in this cohort is likely due to the better prognosis of patients with thyroid cancer harboring spinal metastases compared to other primary histologies. However, compared to our previous study of patients with thyroid cancer, there is a 13-month increase in median OS.⁴ This finding likely reflects the improvement in systemic therapy for patients with thyroid cancer, particularly the emergence of new targeted agents and immunotherapy.³² Improved OS

was noted in patients treated with multifraction regimens compared to single-fraction treatment. Given that LC rates were not significantly different between single- and multiple-fraction approaches and that significance was lost on competing risk analysis, this difference is likely not clinically significant and may be an artifact of a higher proportion of multifraction patients being participants in clinical trials.

The incidence of thyroid cancer has been rising over the last decade.^{2,40} With excellent survival rates and the propensity for thyroid cancer to involve the spine, the importance of achieving durable LC is vital. In addition to the improvement in quality of life, recent evidence has shown overall and progression-free survival benefits from obtaining LC in the oligometastatic setting.^{23,25,34} A median OS of 76 months has also been reported in cases of solitary spinal metastasis treated with SSRS at our institution, and the presence of oligometastatic spinal disease has been incorporated into a validated prognostic scale for patients treated with SSRS.^{25,41} With a vast majority of patients in this study having fewer than 10 metastatic sites, the current data support this notion as patients with improved LC in the spine were found to have an improved OS of 68 months versus 28 months for patients with local failure, reaching near statistical significance ($p = 0.07$).

In terms of toxicity, SSRS is well tolerated. Acute toxicity rates of fatigue, nausea, and esophagitis in this report were consistent with those of prior studies.^{19,24} A pain flare was only reported in 6% of cases, representing a significant decrease from prior published rates of 20%–70%.^{11,35} The latter report utilized single-fraction doses of 20–24 Gy, providing a rationale for the exceedingly elevated pain-flare rate of nearly 70%.¹¹ One late grade 3 event (0.75%) occurred within this cohort, in which a case of esophageal stenosis was observed in a 35-year-old woman who initially received external-beam RT of 30 Gy in 10 fractions followed by salvage SSRS of 18 Gy in a single fraction to a T8 lesion. Rates of late grade 3 esophageal toxicity with SSRS have been reported to be 5% when treating lesions directly adjacent to the esophagus.¹⁴ This report utilized a median dose of 24 Gy, explaining the increased rate of esophageal toxicity noted.¹⁴ In terms of other late-onset toxicities, a 2.8% incidence of vertebral compression fractures was noted, which is significantly lower than the 12% that has been previously reported.⁷ This is likely due to the reduced dose-fractionation scheme in the present study, as previous work suggests an increased incidence of vertebral compression fractures when single-fraction doses > 19 Gy are utilized.⁷ These findings highlight the importance of effectively adjusting the dose based on the intrinsic radiosensitivity of the tumor. As in the case of this analysis, the use of low-dose, single-fraction SSRS (18 Gy) not only was adequate to provide excellent LC but also correspondingly appears to be associated with lower rates of acute and chronic toxicity. Multiple prior case reports have displayed radiation recall dermatitis related to sorafenib and other TKIs.^{13,30,33} This adverse event can be quite severe, resulting in significant morbidity for patients, and thus is a feared complication of radiation treatment for thyroid cancer patients.^{13,30,33} Given the benefits of TKIs and their increasing use in patients with metastatic thyroid cancer, it is

important to better determine the incidence and severity of this event.⁸ In the present study, the rate of radiation recall dermatitis for patients on TKIs was noted to be only 2%, with both cases resulting in a mild reaction. This provides some reassurance of the use of RT for patients receiving TKI therapy.

This study is subject to the inherent limitations of any retrospective analysis. Overall, the sample size is small to moderate ($n = 67$ patients with 133 lesions). However, when considering the available data on this subject, to the best of our knowledge, this is the largest analysis of SSRS for patients with metastatic thyroid cancer. Retrospective collections of data, particularly with regard to toxicity, are less than ideal. While a proportion of the data was retrospectively collected, more than half of the patients included in this analysis were enrolled in a combined phase I/II clinical trial at our institution, thus improving the robustness of this analysis.

Conclusions

SSRS is an extremely effective and safe treatment option for patients with spinal metastases in both the primary and adjuvant setting. The benefits of SSRS appeared to be enhanced in patients with thyroid cancer due a combination of factors, including possible intrinsic radiosensitive and improved long-term survival rates necessitating the need for effective LC. Excellent LC outcomes underscore the radiosensitive nature of thyroid cancer and suggest that escalated doses are not needed for tumor control. Due to the advancements in systemic therapy options and the corresponding improvements in OS, the demand for SSRS in patients with metastatic thyroid cancer will continue to increase.

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Disclosures

Dr. Rhines is a consultant for Stryker and Globus.

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