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Clinical Investigation

Outcomes for Spine Stereotactic Body Radiation Therapy and an Analysis of Predictors of Local Recurrence

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Summary

Local failure after spine stereotactic body radiation therapy has significant clinical implications. Therefore, we reviewed our experience to investigate outcomes and predictors of local relapse to identify modifiable factors that may decrease the risk of local recurrence. Stereotactic body radiation therapy offers durable control, but a subset recur locally with approximately half at the margin, likely attributable to spinal cord constraints. When possible, we recommend

Purpose: To investigate local control, survival outcomes, and predictors of local relapse for patients treated with spine stereotactic body radiation therapy.

Methods and Materials: We reviewed the records of 332 spinal metastases consecutively treated with stereotactic body radiation therapy between 2002 and 2012. The median follow-up for all living patients was 33 months (range, 0-111 months). Endpoints were overall survival and local control (LC); recurrences were classified as either in-field or marginal.

Results: The 1-year actuarial LC and overall survival rates were 88% and 64%, respectively. Patients with local relapses had poorer dosimetric coverage of the gross tumor volume (GTV) compared with patients without recurrence (minimum dose [Dmin] biologically equivalent dose [BED] 23.9 vs 35.1 Gy, $P<.001$; D98 BED 41.8 vs 48.1 Gy, $P=.001$; D95 BED 47.2 vs 50.5 Gy, $P=.004$). Furthermore, patients with marginal recurrences had poorer prescription coverage of the GTV (86% vs 93%, $P=.01$) compared with those with in-field recurrences, potentially because of more upfront spinal canal disease (78% vs 24%, $P=.001$). Using a Cox regression univariate analysis, patients with a GTV BED Dmin $\geq$33.4 Gy (median dose) (equivalent to 14 Gy in 1 fraction) had a significantly higher 1-year LC rate (94% vs 80%, $P=.001$) compared with patients with a lower GTV BED Dmin; this factor was the only

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maintaining a gross tumor volume Dmin above 14 Gy in 1 fraction and 21 Gy in 3 fractions.

significant variable on multivariate Cox analysis associated with LC ($P = .001$, hazard ratio 0.29, 95% confidence interval 0.14-0.60) and also was the only variable significant in a separate competing risk multivariate model ($P = .001$, hazard ratio 0.30, 95% confidence interval 0.15-0.62).

Conclusions: Stereotactic body radiation therapy offers durable control for spinal metastases, but there is a subset of patients that recur locally. Patients with local relapse had significantly poorer tumor coverage, which was likely attributable to treatment planning directives that prioritized the spinal cord constraints over tumor coverage. When possible, we recommend maintaining a GTV Dmin above 14 Gy in 1 fraction and 21 Gy in 3 fractions.

Introduction

Spine metastases occur in 3% to 5% of all patients with a cancer diagnosis and have an incidence as high as 19% among certain histologies (1, 2). Management has typically consisted of palliative surgery or radiation therapy (RT) to aid in preventing cases of spinal cord or root compression. Traditionally, fractionated RT using conventional techniques has been sufficient in palliating symptoms for most patients with limited life expectancy, and more recent studies have shown equivalency with single-fraction, conventional RT (3-5). However, metastatic patients with radioresistant phenotypes have an increased incidence of posttreatment progression. Therefore, radiotherapeutic strategies with improved local control rates are of significant interest.

Stereotactic body radiation therapy (SBRT), also referred to by some clinicians as stereotactic ablative body radiation therapy, is a modern method for delivering precise, ablative RT doses to the target region while maximizing avoidance of nearby critical structures. Prospective trials and retrospective experiences have demonstrated SBRT to be an effective tool for treating metastatic spinal disease. Stereotactic body radiation therapy offers a favorable risk−benefit ratio, with minimal risk of myelopathy and 1-year local control rates typically above 85% (6-12). However, for patients that progress or recur after SBRT, the spinal disease may be associated with significant pain, worsening of quality of life, or a decline in performance status (8, 13). Furthermore, given the proximity of the spinal cord, treatment failure can rapidly progress to spinal cord compression, a complication associated with rapid clinical deterioration and poor prognosis (14, 15).

Despite the clinical implications of local recurrences, there are minimal data evaluating predictors of local failure for patients undergoing spine SBRT. Only 1 prospective study has reported patterns of failure, and it suggested that most recurrences occur at the margin, either in bone or in the epidural space (9). Therefore, we sought to elaborate and expand on our continued SBRT experience to report on local control and survival outcomes, and investigate predictors of local relapse to better identify modifiable factors that may optimize tumor control.

Methods and Materials

Patients

We identified 285 consecutive patients with 332 spinal metastases treated with SBRT at The University of Texas MD Anderson Cancer Center (MDACC, Houston, Texas), a regional, tertiary referral center, between 2002 and 2012. Of the 332 lesions, 210 (63%) were treated on 3 institutional phase 1 or 2 trials evaluating single- and multifraction SBRT for spinal metastases (9, 13, 16). Patients were excluded if they received postoperative SBRT or if treated at satellite centers of MDACC.

Patient, tumor, dosimetric, and outcome characteristics were extracted from the medical records for the entire group after approval was obtained from the institutional review board. Tumors were classified as radioresistant (sarcomas, renal cell carcinomas, melanoma, hepatocellular carcinomas, and chordomas) versus radiosensitive, according to histology. For comparison between marginal and in-field relapses, several additional variables were collected, including: (*1*) the recurrence location; (*2*) the pretreatment minimum distance between the tumor border (ie, clinical tumor volume [CTV]) and the spinal cord; and (*3*) the degree of epidural disease according to the epidural spinal cord compression scale (ESCC) (17).

Treatment

All patients were treated using computed tomography (CT)-guided intensity modulated SBRT using the CT-on-rails EXaCT targeting system or Trilogy treatment delivery system with On-board Cone Beam CT (Varian Medical Systems, Palo Alto, CA) as previously described (18, 19). After patients were immobilized in an Elekta BodyFix stereotactic body frame (Elekta, Stockholm, Sweden) and aligned using a CT-on-rails (GE Healthcare, Fairfield, CT) or cone-beam CT, treatments were delivered typically using a 9-field step-and-shoot intensity modulated radiation treatment plan. Each procedure was monitored by the treating radiation oncologist and a dedicated radiation physicist to verify target positioning and quality assurance.

Metastatic spinal tumors were treated with various doses and fractionations. Given that the first institutional protocols

established safety and efficacy, the regimens investigated were more conservative. However, more contemporary patients are treated with standard regimens based on tumor radiosensitivity and previous RT. Contouring of the gross tumor volume (GTV) and CTV was consistent with recent consensus guidelines (20). The GTV was defined by visible tumor on an MRI fused with the planning CT scan, and the CTV, which contained the GTV, was defined as at-risk contiguous bone marrow or soft-tissue margin in cases with paraspinal extension of disease. The planning treatment volume was defined with no margin to the CTV. The dose was commonly normalized between the 80% and 90% isodose line (19), so that the prescription line enclosed the planning treatment volume, except near the spinal cord. Institutional practice has been to not alter either dose or fractionation on the basis of tumor proximity to the spinal cord; instead, we prioritize spinal cord constraints over tumor coverage in treatment planning directives.

Follow-up and relapses

The median follow-up for the entire cohort was 19 months (range, 0-111) and for all living patients was 33 months (range, 0-111). Patients were seen every 3 months for physical examination and magnetic resonance imaging (MRI) of the spine to assess for radiologic tumor recurrence. Local recurrences were identified by the reading radiologist. After confirmation by the radiation oncologist, SBRT treatment plans were de-archived and fused with the MRI dataset showing radiographic progression, which was accomplished using the autoregistration function in Pinnacle in conjunction with manual manipulation to align bony landmarks. Using these fused plans, local recurrences were then subclassified as occurring in-field (encompassed entirely within the 95% isodose line) or marginally (relapse occurring partially or fully in the penumbra, commonly between the 20% and 95% prescription isodose lines) according to the relationship of the tumor recurrence to the prescription isodose line.

Dosimetric parameters

The GTV-related dosimetric parameters extracted for all patients included volume, percent prescription coverage, minimum dose (Dmin), maximum dose (Dmax), dose to 98% of the volume (D98), and dose to 95% of the volume (D95). The dosimetric parameters for the spinal cord included Dmax, dose to 0.1 cm^3, and dose to 1.0 cm^3.

To compare dosimetric parameters among the various fractionation schemes, the BEDs to the spinal cord and tumor were calculated. According to the linear-quadratic model of cell survival after RT, the biologically equivalent dose (BED) calculation [BED = $nd\ (1 + d/\alpha/\beta)$] allows for the comparison of the effects of different dose fractionation schemes (n = number of fractions, d = dose per fraction) (10, 21, 22). An α/β value of 2 Gy was used for spinal cord late effects and a value of 10 Gy was used for tumor effect.

Statistical analysis

Descriptive statistics were used to evaluate baseline characteristics, and categorical data were analyzed by using Fisher exact test and χ^2 analyses. The Bonferroni correction was reported to adjust for multiple comparisons. Survival times were calculated from the start date of SBRT to the first occurrence of the considered event. The Kaplan-Meier method was used to estimate rates of overall survival (OS) and local control (LC). Log-rank tests were applied to assess for equality across groups. Additionally, a competing risk analysis was performed using the Fine and Gray method; death was treated as a competing risk. Estimated subhazard ratios were reported when significant ($P \leq .05$). A 2-sided 5% significance level was used for analysis.

The Cox proportional hazard model was used for univariate and multivariate analysis. Dosimetric variables were analyzed both as continuous and as categorical variables, with the cutoff defined as the median value. Multivariate assessment was done by backwards elimination, with all factors found to have a P value of $\leq .25$ on univariate analysis included in the assessment. Estimated hazard ratios (HRs) were reported when significant ($P \leq .05$). StataCorp statistical software, version 13.1 (College Station, TX), was used for data analysis.

Results

Entire cohort characteristics

Patient, tumor, and treatment characteristics are summarized in Table 1. There were no significant differences in patient or tumor characteristics between lesions that recurred (n = 44, 13%) compared with those that did not (n = 288, 87%) (Table 1).

When comparing dosimetric coverage of the GTV, patients with local recurrences had a lower (*1*) BED Dmin (23.9 Gy vs 35.1 Gy, $P < .001$); (*2*) BED D98 (41.8 Gy vs 48.1 Gy, $P = .001$); and (*3*) BED D95 (47.2 Gy vs 50.5 Gy, $P = .004$) compared with patients without relapse, all of which remained significant using the Bonferroni correction ($0.05/9 = 0.006$) (Table 2). Furthermore, patients with marginal recurrences had significantly poorer GTV prescription coverage (86% vs 91%, $P = .002$) than those without relapse. There were no significant differences in the dose to the spinal cord between patients who relapsed and those who did not (Table 2). A Supplemental Table (avaialble online at redjournal.org) was provided for a quick reference to convert from BED to delivered total dose using 1 and 3 fraction regimens.

The only significantly different dosimetric parameter between marginal and in-field recurrences was poorer prescription coverage of the GTV in patients with marginal recurrences (86% vs 93%, $P = .01$).

Table 1 Patient and disease characteristics

Variable	All tumors (n=332)	Recurrences (n=44)	Nonrecurrences (n=288)	*P*
Follow-up time (mo)				.34
Median	19	19	19	
Range	0-111	5-93	0-111	
Age at time of SSRS (y)				.31
Median	59	59	59	
Range	17-88	34-87	17-88	
Sex				.86
Male	183 (55)	24 (55)	159 (55)	
Female	149 (45)	20 (45)	129 (45)	
Race				.33
Caucasian	266 (81)	40 (91)	226 (78)	
Black	24 (7)	1 (2)	23 (8)	
Hispanic	24 (7)	1 (2)	23 (8)	
Asian	18 (5)	2 (5)	16 (6)	
Tumor type				.70
Renal	125 (38)	12 (27)	113 (39)	
Lung	46 (14)	8 (18)	38 (13)	
Thyroid	33 (10)	5 (11)	28 (10)	
Sarcoma	27 (8)	5 (11)	22 (8)	
Breast	32 (9)	4 (9)	28 (10)	
Other	69 (21)	10 (23)	59 (20)	
Radiosensitivity of tumor				.26
Radiosensitive	169 (51)	26 (59)	143 (50)	
Radioresistant	163 (49)	18 (41)	145 (50)	
Fractionation schemes				.19
18 Gy in 1 fraction	66 (20)	10 (23)	57 (20)	
24 Gy in 1 fraction	80 (24)	5 (11)	75 (26)	
27 Gy in 3 fractions	130 (39)	21 (48)	109 (38)	
Other	56 (17)	13 (30)	47 (16)	
Tumor dose* (Gy)				.08
Median	43	43	43	
IQR	42-43	42-43	42-68	
Total dose* (Gy)				.09
<40	21 (6)	4 (9)	17 (6)	
40-60	231 (70)	35 (80)	196 (68)	
>60	80 (24)	5 (11)	75 (26)	
Vital status at last follow-up				.05
Alive	85 (26)	6 (14)	79 (27)	
Dead	247 (74)	38 (86)	209 (73)	

Abbreviations: IQR = interquartile range; SSRS = spinal stereotactic radiosurgery.

Values are number (percentage) unless otherwise noted.

* The biologically equivalent dose was calculated for all dosimetric data using an α/β value of 10 Gy for tumor effect on gross tumor volume and a value of 2 Gy for spinal cord late effects.

Local control

The actuarial 1-year and 3-year rates of LC for the entire cohort were 88% and 82%, respectively (Fig. 1). There was no difference in local control according to tumor histology ($P=.52$), radiosensitivity ($P=.41$), or total BED ($P=.21$).

Univariate analyses for LC using the Cox proportional hazard model are reported in Table 3. For a categorical analysis of dosimetric data, the median dose was used as the cut point. Categorical dosimetric variables associated with 1-year LC on univariate Cox analysis included GTV volume (81% for $\geq$18.2 cm^3 vs 93% for <18.2 cm^3, $P=.04$), GTV BED Dmin (94% for $\geq$33.4 Gy vs 80% for <33.4 Gy, $P=.001$), GTV BED D98 (93% for $\geq$47.1 Gy vs 82% for <47.1 Gy, $P=.004$), and GTV BED 95 (92% for $\geq$50.4 Gy vs 83% for <50.4 Gy, $P=.009$). Using a backwards elimination technique, the only categorical variable remaining significant on Cox multivariate analysis was having a GTV BED Dmin $\geq$33.4 Gy (equivalent to 14 Gy in 1 fraction) ($P=.001$, HR 0.29, 95% confidence interval [CI] 0.14-0.60) (Table 4). A separate model was constructed using continuous variables, and again the only significant continuous variable associated with LC on Cox multivariate analysis was GTV BED Dmin ($P<.001$, HR 0.95, 95% CI 0.93-0.98).

Table 2 Dosimetric data for all patients, comparing nonrecurrences (n=288) with all recurrences (n=44) and nonrecurrences with marginal recurrences (n=23)

Variable	Nonrecurrent	Recurrent	*P*	Marginal	*P*
GTV volume (cm^3)			.51		.27
Median	17.2	24.4		28.5	
IQR	7.5-40.4	10.0-44.8		17.1-55.4	
GTV prescription coverage (%)			.31		.002*
Median	91	89		86	
IQR	84-96	81-95		75-93	
GTV Dmin (Gy)†			<.001*		.02
Median	35.1	23.9		22.9	
IQR	23.9-47.9	17.5-33.9		16.7-26.2	
GTV Dmax (Gy)†			.91		.76
Median	61.5	61.3		61.3	
IQR	57.8-91.0	56.7-66.8		54.3-66.8	
GTV D98 (Gy)†			.001*		.02
Median	48.1	41.8		39.8	
IQR	39.1-61.3	34.3-49.1		30.9-45.6	
GTV D95 (Gy)†			.004*		.01
Median	50.5	47.2		44.8	
IQR	44.5-71.2	41.3-51.7		36.3-48.8	
Cord Dmax (Gy)†			.10		.47
Median	45.5	32.6		42.5	
IQR	26.3-66.9	22.6-57.5		24.3-56.9	
0.1 cm^3 cord dose (Gy)†			.10		.78
Median	29.9	21.7		26.9	
IQR	18.7-47.6	16.5-40.9		16.9-40.9	
1.0 cm^3 cord dose (Gy)†			.49		.49
Median	16.4	14.3		16.2	
IQR	11.7-30.16	11.5-27.1		12.9-26.5	

Abbreviations: Dmax = maximum point dose; Dmin = minimum point dose; GTV = gross tumor volume; IQR = interquartile range.
* *P* values significant using the Bonferroni correction (0.05/9 = 0.006).
† The biologically equivalent dose was calculated for all dosimetric data using an α/β value of 10 Gy for tumor effect on GTV and a value of 2 Gy for spinal cord late effects.

We also assessed the data using the competing risk regression method of Fine and Gray with death as a competing risk factor. Of the 4 variables that were significant on univariate analysis using the Cox model (GTV volume, GTV BED Dmin, GTV BED D98, and GTV BED D95), all but GTV volume were also significant using the competing risk model (Table 3). On the multivariate competing risk analysis, again using backwards elimination, the only variable associated with LC was GTV BED Dmin, both as a categorical variable ($P=.001$, HR 0.30, 95% CI 0.15-0.62) and as a continuous variable ($P=.005$, HR 0.96, 95% CI 0.93-0.99) (Table 4).

For the 44 patients (13%) with local recurrences, the median time to failure was 6 months (range, 1-40 months). There were 21 in-field (48%) and 23 marginal (52%) recurrences, with a shorter median time to local failure for marginal recurrences (6 vs 8 months, $P=.02$). Patient and tumor characteristics were compared between the 2 recurrence types (Table 5). The only significant differences between subsets included the following: marginal failures (*1*) had a shorter median distance between the tumor border (ie CTV) and spinal cord (2 vs 6 mm, $P<.001$); (*2*) a higher proportion had upfront spinal canal disease (78% vs 24% for in-field recurrences, $P=.001$); and (*3*) a higher proportion of tumors were ESCC category 1b (65% vs 19% for in-field recurrences, $P<.001$). As expected, there was a correlation between the ESCC scale and the distance between spinal cord and tumor ($P=.001$), given that both quantify the extent of epidural disease.

Overall survival

The actuarial 1-year and 3-year OS rates were 64% and 33%, respectively, with a median OS of 23 months (range, 0-111 months) (Fig. 1). Tumor histology was associated with OS, with the longest median survival among patients with breast (44 months) and thyroid cancer (29 months), followed by renal tumors (19 months), sarcomas (17 months), and finally lung histologies (14 months) ($P=.007$) (Fig. 1). On multivariate analysis, patients with breast ($P=.004$, HR 0.39, 95% CI 0.21-0.74) and thyroid metastases ($P=.04$, HR 0.57, 95% CI 0.34-0.97) had significantly higher survival rates compared with those with renal tumors, and GTV BED Dmin $\geq$33.4 Gy ($P<.001$, HR 0.59, 95% CI 0.45-0.79) was also associated with improved survival.

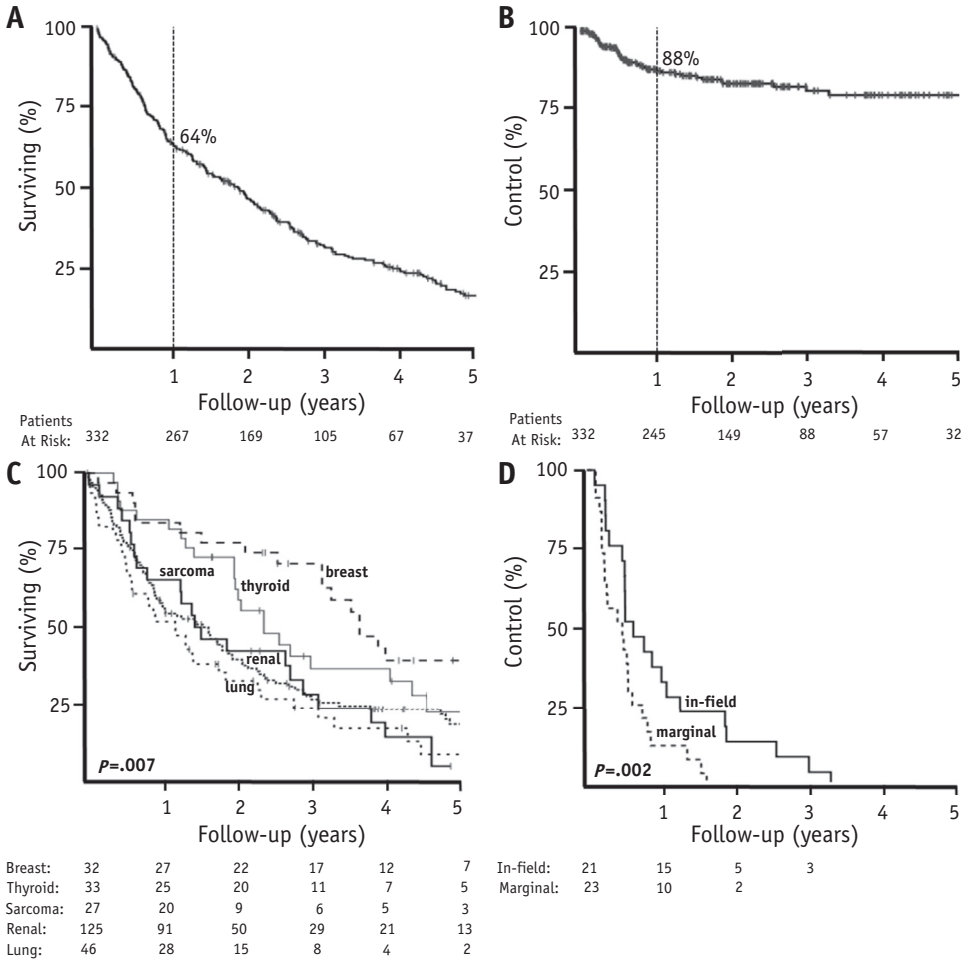

Fig. 1. Outcomes for patients with metastatic disease treated with spine stereotactic body radiation therapy. For the whole cohort, (A) overall survival was 64% at 1 year, and (B) local control was 88%. (C) Survival was significantly different according to histology ($P = .007$). (D) For patients with local failures, those with marginal recurrences relapsed earlier than patients with in-field recurrences ($P = .02$).

The median survival after local recurrence was 14 months (range, 1-86 months). There was a trend for longer median survival among patients with in-field recurrences compared with marginal recurrences (32 vs 20 months, $P = .08$) (Fig. 1).

Discussion

The present study expands on our previously published prospective experience with SBRT (9, 13) and reports on a large cohort of patients treated with spinal SBRT. We report durable local disease control with a 1-year actuarial local failure rate of 12%. Our additional analysis evaluating predictors of local recurrence is critical given the limited body of literature on this topic. We observed poorer tumor coverage by several dosimetric measures (Dmin, D98, D95) in patients with local relapse, with GTV BED Dmin as the only variable significant on both Cox regression and competing risk multivariate analyses. Furthermore, approximately half of the local recurrences were marginal, with spinal canal involvement and proximity to the spinal cord as major factors associated with this type of failure. Therefore, because of tumor proximity to spinal cord, significantly poorer tumor coverage by the prescription dose was accepted a priori owing to spinal cord constraints being prioritized over delivering tumor-ablative RT doses.

Stereotactic body radiation therapy provides excellent tumor control for the treatment of metastatic spinal disease. We observed a 1-year actuarial control rate of 88%, which compares favorably to most SBRT series reporting control rates of treated spine metastases between 85% and 90% (6-12). Despite favorable SBRT outcomes, we still observed a 1-year actuarial failure rate of 12%, which suggests opportunity for improvement given the limited salvage options and debilitating consequences of disease progression.

To better understand features that may predict for local recurrence, we examined patient and tumor characteristics, along with several dosimetric parameters of the GTV and spinal cord. Notably, the only factors associated with local relapse on univariate analysis were the GTV dosimetric

Table 3 Univariate Cox regression and competing risk analyses of factors associated with local control

Parameter	Univariate Cox analysis		Univariate competing risk	
	P	HR (95% CI)	*P*	SHR (95% CI)
Categorical variables				
Age at treatment (y)				
<60		Reference		Reference
≥60	.82	0.93 (0.51-1.70)	.75	0.91 (0.50-1.65)
Tumor type				
Renal		Reference		Reference
Lung	.09*	2.18 (0.89-5.33)	.16*	1.92 (0.78-4.77)
Thyroid	.71	1.22 (0.43-3.46)	.41	1.54 (0.55-4.31)
Sarcoma	.21*	1.96 (0.69-5.56)	.18*	2.03 (0.72-5.69)
Breast	.98	0.99 (0.32-3.07)	.65	1.29 (0.42-3.95)
Other	.40	1.44 (0.62-3.33)	.31	1.55 (0.67-3.58)
Radiosensitivity				
Sensitive		Reference		Reference
Resistant	.41	0.78 (0.42-1.42)	.26	0.71 (0.39-1.29)
Fractionation				
18 Gy in 1 fraction		Reference		Reference
24 Gy in 1 fraction	.23*	0.51 (0.17-1.52)	.14*	0.44 (0.15-1.32)
27 Gy in 3 fractions	.59	1.24 (0.57-2.71)	.65	1.20 (0.55-2.62)
Other	.82	1.11 (0.44-2.81)	.73	1.18 (0.47-2.95)
Total dose (Gy)†				
<40		Reference		Reference
40-60	.78	0.86 (0.31-2.43)	.58	0.74 (0.26-2.13)
>60	.16*	0.39 (0.10-1.45)	.07*	0.30 (0.08-1.12)
GTV volume (cm^3)				
<18.2		Reference		Reference
≥18.2	.04*	1.98 (1.05-3.72)	.15*	1.60 (0.85-2.99)
GTV prescription coverage (%)				
<90		Reference		Reference
≥90	.13*	0.61 (0.32-1.15)	.15*	0.63 (0.33-1.18)
GTV Dmin (Gy)†				
<33.4		Reference		Reference
≥33.4	.001*	0.29 (0.14-0.60)	.001*	0.30 (0.15-0.62)
GTV D98 (Gy)†				
<47.1		Reference		Reference
≥47.1	.004*	0.36 (0.18-0.73)	.004*	0.36 (0.18-0.71)
GTV D95 (Gy)†				
<50.4		Reference		Reference
≥50.4	.009*	0.40 (0.20-0.80)	.008*	0.39 (0.20-0.78)
Cord Dmax (Gy)†				
<43.2		Reference		Reference
≥43.2	.27	1.42 (0.76-2.66)	.32	1.38 (0.74-2.58)
0.1 cm^3 cord dose (Gy)†				
<27.6		Reference		Reference
≥27.6	.38	1.32 (0.71-2.47)	.40	1.30 (0.70-2.43)
1.0 cm^3 cord dose (Gy)				
<16.2		Reference	Reference	
≥16.2	.41	1.30 (0.70-2.42)	.46	1.27 (0.68-2.35)
Continuous variables				
Age at treatment	.50	1.01 (0.98-1.04)	.58	1.01 (0.98-1.03)
Total dose†	.07‡	0.97 (0.94-1.00)	.02‡	0.97 (0.94-1.00)
GTV volume	.06‡	1.0 (1.0-1.01)	.29	1.00 (1.00-1.01)
GTV prescription coverage	.03‡	0.04 (0.00-0.74)	.04‡	0.05 (0.00-0.84)
GTV Dmin†	<.001‡	0.95 (0.93-0.98)	.005‡	0.96 (0.93-0.99)
GTV D98†	.008‡	0.97 (0.94-0.99)	.007‡	0.97 (0.94-0.99)
GTV D95†	.02‡	0.97 (0.95-1.0)	.01‡	0.97 (0.95-0.99)
Cord Dmax†	.33	1.01 (0.99-1.02)	.39	1.01 (0.99-1.02)

(*continued on next page*)

Table 3 (*continued*)

Parameter	Univariate Cox analysis		Univariate competing risk	
	P	HR (95% CI)	*P*	SHR (95% CI)
0.1 cm^3 cord dose†	.63	1.0 (0.99-1.02)	.68	1.00 (0.99-1.02)
1.0 cm^3 cord dose†	.66	1.01 (0.98-1.03)	.79	1.00 (0.98-1.02)

Abbreviations: CI = confidence interval; GTV = gross tumor volume; HR = hazard ratio; SHR = sub-hazard ratio.

* Denotes variables included in categorical multivariate models owing to $P \leq .25$.

† The biologically equivalent dose was calculated for all dosimetric data using an α/β value of 10 Gy for tumor effect on GTV and a value of 2 Gy for spinal cord late effects.

‡ Denotes variables included in continuous multivariate models owing to $P \leq .25$.

parameters, including Dmin, D98, and D95. This finding emphasizes the importance of SBRT tumor coverage for maintaining local control. When accounting for confounders using multivariate analyses (for both Cox regression and competing risk), the GTV Dmin was the only parameter associated with local control, which suggests this may be a primary indicator of dose inhomogeneity. Similar findings were reported by Lovelock et al (23) from Memorial Sloan-Kettering Cancer Center. They too observed a correlation of Dmin, D98, and D95 among 7 patients with local failure. Specifically, they reported no local failures in patients with a Dmin above 15 Gy, which is notably close to our observation; the median BED Dmin in patients without relapse in our series was 35.1 Gy (equivalent to 14.4 Gy in 1 fraction) (Table 2). Therefore, our report corroborates the preliminary findings by Lovelock et al using a larger cohort. On the basis of these data, we would recommend maintaining a GTV Dmin above 14 Gy in 1 fraction and 21 Gy in 3 fractions.

We then examined our patients with local failures to determine the location in relation to the isodose lines. In doing so, we observed that approximately half of the recurrences occurred at the margin of the prescription isodose line. These findings were different from those in the report by Ryu et al (24), who noted a 5% incidence of radiologic tumor recurrence, with all 3 occurring in adjacent vertebral bodies. Their study, however, may have underreported the local recurrence rate because only 6 patients were imaged beyond 1 year to assess for tumor progression (median follow-up not reported). In a more recent prospective study by Chang et al (9), a 1-year actuarial local control rate of 84% was reported, with 17 (23%) local failures. They concluded that 10 recurrences (59% of local failures) were likely attributable to poor tumor coverage limited by spinal cord constraints; 8 tumors recurred within the epidural space, and 2 recurred at the posterior edge of the vertebral bodies. Our present series expanded on the prospective study by MDACC by pooling additional patients treated off-protocol or after protocol closure. Our analysis supports their conclusions: a large proportion of the recurrences failed at the posterior margin around the spinal cord.

Table 4 Multivariate Cox regression and competing risk analyses of factors associated with local control using backwards elimination

Parameter	Multivariate Cox analysis		Multivariate competing risk	
	P	HR (95% CI)	*P*	SHR (95% CI)
Categorical variables				
GTV Dmin *				
<33.4 Gy		Reference		Reference
≥33.4 Gy	.001	0.29 (0.14-0.60)	.001	0.30 (0.15-0.62)
Continuous variables				
GTV Dmin*	<.001	0.95 (0.93-0.98)	.005	0.96 (0.93-0.99)

Abbreviations: CI = confidence interval; GTV = gross tumor volume; HR = hazard ratio; SHR = sub-hazard ratio.

The categorical multivariate model was run separately from the continuous variable model. However, using a backwards elimination technique, only one variable emerged significant from both multivariate models, GTV Dmin.

* The biologically equivalent dose was calculated using an α/β value of 10 Gy for tumor effect on GTV.

According to further analysis, the increased risk of recurring at the posterior margin is likely a limitation of spinal cord constraints. The median prescription coverage of the GTV for patients with marginal recurrence was significantly lower than for those without recurrence. This was likely attributable to the fact that nearly 80% of patients who recurred at the margin had an epidural tumor component with a median minimum distance to the spinal cord of 2 mm. Therefore, these tumor targets were underdosed because of prioritized spinal cord constraints in the treatment planning directives (our general goal: <10 Gy to 0.01 cm^3 of the spinal cord). Previous reports have also suggested that when an epidural tumor is within 2 to 5 mm of the spinal cord, target coverage is difficult to obtain (25), which is why most SBRT investigators have excluded patients with epidural disease from prospective trials. To place this in context, our planning objectives related to the spinal cord constraints may now be viewed as overly conservative, but until recently there were limited data to develop appropriate dose constraints, especially for hypofractionated RT. Additionally, we deliberately chose conservative spinal cord dose constraints in 2002 to establish safe treatment parameters in a clinical trial setting for this previously novel indication for SBRT.

The classically accepted, conventionally fractionated tolerances for the spinal cord were derived from

Table 5 Patient and disease characteristics compared between in-field and marginal recurrences

Variable	Marginal (n=23)	In-field (n=21)	*P*
Age at time of SSRS (y)			.23
Median	61	54	
Range	28-82	41-87	
Sex			.22
Male	16 (70)	10 (48)	
Female	7 (30)	11 (52)	
Race			.35
Caucasian	19 (83)	21 (100)	
Black	1 (4)	0	
Hispanic	1 (4)	0	
Asian	2 (9)	0	
Tumor type			.78
Renal	6 (26)	6 (29)	
Lung	5 (22)	2 (9)	
Thyroid	2 (9)	3 (14)	
Sarcoma	2 (9)	4 (19)	
Breast	3 (12)	1 (5)	
Other	5 (22)	5 (24)	
Radiosensitivity of tumor			.76
Radiosensitive	14 (61)	11 (52)	
Radioresistant	9 (39)	10 (48)	
Fractionation schemes			.15
18 Gy in 1 fraction	9 (39)	4 (19)	
24 Gy in 1 fraction	2 (9)	3 (14)	
27 Gy in 3 fractions	12 (52)	9 (43)	
Other	0	5 (24)	
BED groups (Gy)			.42
<40	1 (4)	3 (14)	
40-60	20 (87)	15 (72)	
>60	2 (9)	3 (14)	
Prior radiation			.77
Yes	11 (48)	9 (43)	
No	12 (52)	12 (57)	
Tumor distance to cord (mm)			<.001
Median	2	6	
Range	1-5	2-22	
ESCC			<.001
0	1 (4)	12 (57)	
1a	3 (13)	5 (24)	
1b	15 (65)	4 (19)	
1c	4 (18)	0	
Upfront spinal canal disease			.001
Yes	18 (78)	5 (24)	
No	5 (22)	16 (76)	
Upfront neural foramina disease			1.0
Yes	13 (57)	12 (57)	
No	10 (43)	9 (43)	
Location of treated disease			.84
Cervical	4 (17)	2 (10)	
Thoracic	13 (57)	12 (57)	
Lumbar	6 (26)	7 (33)	
Number of vertebral levels involved			.47
1	13 (57)	15 (71)	
2	8 (35)	4 (19)	
3+	2 (9)	2 (10)	
Total dose (Gy)			.22
18	9 (39)	4 (19)	
24	2 (9)	5 (24)	
≥27	12 (52)	12 (57)	

Abbreviations: BED = biologically equivalent dose; ESCC = epidural spinal cord compression scale; SSRS = spinal stereotactic radiosurgery.

Values are number (percentage) unless otherwise noted.

experiments performed a half century or more ago. There has been uncertainty as to whether these historical linear-quadratic models were applicable to hypofractionated SBRT, and thus clinicians have relied primarily on anecdotal accounts of myelopathy to guide dosimetric recommendations. One of the older studies reported no events of myelopathy among 114 patients treated with palliative intent using 10 Gy in 1 fraction (26). A separate study proposed a partial volume tolerance of 10 Gy to 10% of the spinal cord volume, defined as 6 mm above and below the target, to be a safe spinal cord tolerance for single-fraction SBRT. They derived this from a series of 177 patients treated between 8 and 18 Gy in a single fraction with only 1 case of RT-induced spinal cord injury (10). Finally, a third study often referenced to justify constraints prospectively treated 63 patients using a Dmax of 10 Gy to the spinal cord. With a median follow-up of 21 months, no neuropathy or myelopathy was reported (9).

More definitive spinal cord constraints were impeded by only 4 clinical cases of myelopathy reported through 2010 (10, 27, 28). Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) reported that same year that there were insufficient data to make recommendations for single-dose or hypofractionated spinal cord constraints (28). Since then, however, Sahgal et al (22) analyzed 5 patients with post-SBRT myelopathy and compared them with matched controls. On the basis of that analysis, they recommended a point dose threshold of 10 Gy for a single fraction to the thecal sac. However, in an updated multi-institutional investigation, 9 cases of post-SBRT myelopathy were pooled, and a logistic regression model estimated the probability of RT-induced myelopathy for a given volume irradiated. This study reported a ≤5% risk of RT-induced myelopathy if the Dmax to the thecal sac was limited to 12.4 Gy in a single fraction or 20.3 Gy in 3 fractions (11).

In contrast to the previous studies that suggest thresholds around 10 Gy to the spinal cord or thecal sac, Yamada et al (6) from Memorial Sloan-Kettering Cancer Center

reported no myelopathy or other late toxicities using a Dmax of 14 Gy to the spinal cord for 93 patients treated to a median dose of 24 Gy (median follow-up 15 months). This conflicting report emphasizes the need for a prospectively designed dose escalation trial to stringently investigate dose limitations to the spinal cord for hypofractionated spine SBRT. To that end, a phase 1 spinal cord dose-escalation trial is currently accruing at our institution to aid in determining maximum spinal cord tolerance, while ensuring adequate spinal metastasis coverage for patients with epidural disease treated using SBRT.

Although we describe outcomes for a large cohort of patients treated with SBRT, this single-institution, retrospective study is prone to selection biases that are inherent in all retrospective studies, and the heterogeneity of the cohort may have underpowered the analysis. Furthermore, the relatively low number of recurrences and the multiple comparisons between groups warrants consideration when interpreting the results. Another limitation relates to dose reporting; the point dose is subject to inaccuracies due to voxel resolution, and there may be intrafractional dose uncertainty related to rotational or translational motion. Despite these limitations, this study provides additional evidence to suggest that GTV Dmin is an important surrogate of inhomogeneity and that conservative spinal cord constraints increase the risk for marginal failures. Additional data on the tolerances of the spinal cord is critical, which hopefully will be addressed by our currently accruing dose escalation SBRT phase 1 trial. Furthermore, despite the adoption of spinal SBRT, there is no current level 1 evidence proving efficacy, which underscores the importance of continuing patient enrollment on clinical trials (29).

In conclusion, SBRT continues to be a valuable tool for the treatment of spinal metastases and offers durable local control. Despite favorable outcomes, there is still a subset of patients who recur locally, and nearly half were considered marginal recurrences. This study reports hypothesis-generating results correlating tumor prescription coverage, Dmin, D98, and D95 to local recurrence, with GTV BED Dmin as the only remaining variable significant on multivariate analysis. Our data suggest a relationship between proximity to the dose-limiting spinal cord and compromised target volume coverage leading to treatment failure. Finally, the median BED for Dmin among patients without relapse was 35.1 Gy; therefore, when possible, we recommend maintaining a GTV Dmin above 14 Gy in 1 fraction and 21 Gy in 3 fractions.

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