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Technical Report

Long-Term Outcomes After Reirradiation With Spine Stereotactic Body Radiation Therapy: Single-Institutional Retrospective Experience

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Reirradiation of spinal metastases using stereotactic body radiation therapy (SBRT) presents clinical challenges, with limited patient outcomes data to guide decision-making. We report a retrospective, single-institutional experience of 107 lesions treated in 91 patients. Of these, 88 (72%) lesions were initially irradiated with conventional radiation therapy (median equivalent dose of 33 Gy to the target, IQR, 23-35 Gy) with a median time to reirradiation of 12 months (IQR, 4-21 months). For reirradiation, most lesions received either 1 fraction (18-24 Gy) or 3 fractions (30-36 Gy) of SBRT. The median equivalent dose in 2 Gy fractions was 38 Gy (IQR, 30-41 Gy), 27 Gy (22-36 Gy), and 65 (54-73 Gy) for previous courses, reirradiation, and cumulatively, respectively. At 1 year, overall survival was 61% with a cumulative incidence of local failure at 12% and vertebral compression fracture at 9% considering death as a competing risk. None of the 79 treated lesions at L1 or above developed radiation myelitis, but 5 patients developed chronic peripheral neuropathy. In our analysis, most adverse events or local failures occur within the 2 years after retreatment. These findings demonstrate the safety and effectiveness of spine reirradiation with SBRT.

Introduction

Stereotactic body radiation therapy (SBRT) for spinal metastases is a safe, effective[1,2] and cost-effective[3] treatment. As cancer incidence and survivorship increase,[4] the role of reirradiation with SBRT (reSBRT) will likely expand. Although there is strong evidence supporting the use of reSBRT,[5-7] significant questions remain regarding the most appropriate means to safely account for previous radiation therapy (RT) dose for the spinal cord (SC). Most reports have been limited by small cohorts and limited follow-up.[2,7,8]

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As reSBRT patients make up a small fraction of all spine SBRT population, additional long-term clinical data are needed.[2,7] Recently, the Hypofractionated Treatment Effects in the Clinic project[2] reviewed published data on radiation myelitis (RM) risk in spine reSBRT, but found insufficient evidence to update prior recommendations reported by Sahgal et al[9]:

(1) Time-to-reirradiation >5 months.
(2) Maximum thecal sac equivalent dose ($EQD_{2,2}$, α/β=2 Gy) <25 Gy for reSBRT.
(3) Cumulative $EQD_{2,2}$ <70 Gy.
(4) reSBRT dose <50% of the cumulative dose.

Alternatively, Nelson et al[10] proposed applying a forgiveness-factor based on time-to-reirradiation, keeping the maximum dose to the SC ($D_{max,SC}$) to a cumulative, forgiven, biological equivalent dose of 83.3 Gy with α/β = 3 Gy ($EQD_{2,3}$<50 Gy).

To provide further data on this issue, we report outcomes from a large, retrospective, single-institutional reSBRT experience. Importantly, the planning approach reported here differs in important ways from these recommendations, providing a basis for comparison and further insight.

Methods and Materials

Patient selection

A database containing all adult patients receiving spine SBRT (2007-2019) was collected via retrospective chart review under institutional review board approval and consistent with ethical practices. Patients were included if the treated vertebral level(s) had received any dose from previous spine-directed RT, and excluded if the patient had benign histology or reSBRT was delivered using proton therapy.

Treatment

SBRT dose and fractionation were determined at the discretion of the treating radiation oncologist, with practice patterns evolving over time in line with emerging data. Specifically, we observed increasing adoption of a 3-fraction SBRT regimen, particularly after the publication of Sahgal et al[9] and related consensus recommendations. This change was most notable after 2013, with both an increase in the overall number of re-SBRT cases and in the proportion treated with multifraction regimens. Delineation of target volumes and organs at risk was determined by the treating radiation oncologist. A simultaneous integrated boost approach following consensus guidelines[11,12] was used: a high-risk planning target volume (PTV_High, gross tumor volume plus 0-2mm expansion) and a low-risk volume (PTV_Low) including all sectors containing PTV_High as well as the adjacent sector. Typical prescriptions for single-fraction SBRT were 16 to 20 Gy to PTV_Low and 18 to 24 Gy to PTV_High, and 21 to 30 Gy and 30 to 36 Gy for 3 fractions, respectively. Five fraction treatments were rare.

SC was delineated on T2-weighted magnetic resonance imaging performed in RT treatment position or computed tomography (CT) myelogram with no additional margin or planning-risk volume added. The primary planning objective was to ensure that either D_{max} or D0.03cc constraints (physician's discretion) to the SC and cauda equina were met.[9] Regarding SC constraints, these were applied at the discretion of the treating physician. There was variability in how prior SC doses were incorporated, including differences in the cumulative dose limits applied and whether any "forgiveness factor" (ie, adjustment for the time interval between treatments) was used in determining constraints. In general, SC constraints were guided by institutional practice and published recommendations at the time of treatment, with efforts made to limit the cumulative $EQD_{2,2}$ to approximately 70 Gy_{EQD2}. However, the specific thresholds varied across the cohort also influenced by individual patient and tumor characteristics. Dose calculations were performed in Eclipse (Varian Medical Systems, AAA algorithm, 2 mm dose grid size on 1.25 × 1.25 × 1 mm^3 voxels). Treatment was delivered with C-arm linear accelerators with either intensity modulated or volumetric modulated arc RT. Cone beam CT was used for primary alignment, and 2D-3D kilovoltage x-rays for intrafraction monitoring.

Data collection and clinical endpoints

Patient and treatment characteristics from current and previous treatment were collected including dose-volume histogram statistics for the PTVs and SC from for all reSBRT and any previous plans where DVH data were available. For previous conventional external beam RT without accessible dosimetric data, the PTV and SC were both assumed to be covered by the prescription dose. $EQD_{2,\alpha/\beta}$ fractions were computed assuming α/β = 10 Gy for tumor and 2 Gy for SC. Cumulative doses were computed with and without a forgiveness factor applied (25%, 33%, and 50% dose reduction after 6, 12, and 24 months).[10] For clarity, any reference to equivalent dose values in what follows will have its units labeled as Gy_{EQD2} (and specifically labeled as "equivalent-dose" in the text), while any reference to the physical dose will be reported without the subscript in the units.

Adverse events were reporting using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[13,14] Local failure (LF) was

independently assessed on imaging by a radiologist and radiation oncologist using Spine response assessment in Neuro-Oncology (SPINO) group criteria.[15] ReSBRT-related vertebral compression fracture (VCF) events were defined by either the development of new VCF or the progression of existing VCF after reSBRT.[16] Pain flare (PF) was defined as worsening spinal pain necessitating new or higher doses of corticosteroids/opiates or hospitalization.[17]

Data analysis and statistical methods

Overall survival (OS) was analyzed with Kaplan-Meier method, and time-to-event analysis for LF, VCF, and RM used death as a competing risk. Only patients treated at or above the conus medullaris (L1/L2 junction) were considered at risk for RM and at least 2 weeks of follow-up were required to be included for PF analysis. Univariate proportional hazards analysis was performed for OS, LF, VCF, and PF using age, sex, whether the previous RT was SBRT, reSBRT fractionation (single vs multiple), radioresistant histology (renal cell carcinoma, hepatocellular carcinoma, adrenocortical carcinoma, cholangiocarcinoma, melanoma, or sarcoma), and the cumulative $EQD_{2,10}$ for both PTV_High and PTV_Low. In addition, previously validated predictive models for VCF[18] and PF[17] were tested for significance in this cohort, as well minimum dose to PTV_High (D_{min,PTV_High}) using a previously identified predictive cut-off[19] of 15.3 Gy for single-fraction (equivalent to 22.2 Gy and 25.6 Gy, for 3 and 5 fractions) for LF. Statistical significance was defined with alpha ≤0.05, and 95% CIs are reported unless otherwise specified. Analysis performed using SAS v9.4 (SAS Institute Inc).

Results

Patient and treatment characteristics are given in Tables 1 and 2; 107 lesions were identified in 91 patients with a median follow-up of 22 months for all patients, and 55 months (range, 29-77 months) for surviving patients. Most patients were male (65%) with a median age of 62 years (IQR, 55-72 years). A total of 32, 73, and 2 reSBRTs were 1, 3, and 5 fractions, respectively. OS and risk of LF and VCF are shown in Figure 1 and Table 3. Sixteen patients (17%) developed PF. No variables analyzed demonstrated significant correlation with any outcomes under univariate analysis.

There were no instances of RM observed among the 79 lesions involving L1 or above, and dose-volume histogram (DVH) statistics for SC are shown in Table 4. One patient developed bilateral peripheral neuropathy. A 70-year-old woman with chondrosarcoma initially received 30 Gy in 10 fractions to T1. Twenty months later, she experienced tumor progression and underwent decompression/stabilization surgery and single-fraction reSBRT (24 Gy to PTV_High, 18 Gy to PTV_Low). Five months after treatment, she noticed progressive weakness and numbness in her right hand, ultimately complete loss of grip strength and minimal motor control in that hand.

Table 1 Patient and lesion characteristics

Age	
Mean (IQR), y	62.1 (55.1-72.0)
Sex	
Male	73 (64%)
Female	33 (36%)
Histology	
Adenocarcinoma	36 (34%)
Renal cell carcinoma	28 (26%)
IDC	10 (9%)
Other	33 (31%)
Histology	
Radioresistant	47 (44%)
Radiosensitive	60 (56%)
Primary site	
Kidney	28 (26%)
Lung	16 (15%)
Prostate	15 (14%)
Breast	13 (12%)
Soft tissue	7 (7%)
Other	25 (23%)
Unknown	3 (3%)
SINS	
≤6	58 (54%)
7-12	57 (56%)
>13	2 (2%)
Bilsky grade	
0	50 (47%)
1	37 (35%)
2-3	20 (19%)
Levels treated	
Median (IQR)	1 (1-2)
Levels involved	
Cervical	15 (14%)
Thoracic	60 (56%)
Lumbar	41 (38%)
Previous surgery	43 (41%)

Abbreviations: IDC = invasive ductal carcinoma; SINS = spinal instability neoplastic score.

Table 2 Treatment characteristics

Time to ReSBRT	
Median (IQR), months	11.6 (4.4-20.8)
Previous dose	
Median $EQD_{2,10}$ (IQR), Gy	32.5 (22.8-35.4)
Previous course	
cEBRT	88 (72%)
SBRT	19 (18%)
ReSBRT prescription $EQD_{2,10}$	
Median PTV_High (IQR), Gy	50 (50-68)
Median PTV_Low (IQR), Gy	36 (36-42)
Cumulative tumor dose	
Median $EQD_{2,10}$ (IQR), Gy	82.5 (74.5-100.5)
ReSBRT, #fx	
1	32 (30%)
3	73 (68%)
5	2 (2%)
Spinal cord D_{max} ($EQD_{2,2}$)	Median, Gy (IQR)
Previous courses	37.5 (30.0-41.3)
ReSBRT	26.7 (22.0-35.9)
Cumulative	64.8 (54.1-72.7)

Abbreviations: cEBRT = conventional external beam radiation therapy; $EQD_{2,\alpha/\beta}$ = equivalent dose in 2 Gy fractions; fx = fractions; ReSBRT = reirradiation with stereotactic body radiation therapy; SBRT = stereotactic body radiation therapy.

She also reported mild numbness in her fourth and fifth digits of her left hand, without loss of grip strength or motor control. Reflexes in her lower extremities were normal, as was her gait. Concurrent MR imaging did not have RM-specific findings, and she did not have any further MR imaging of the treated region. Her symptoms did not notably progress after this, and she died 28 months after reSBRT because of disease progression elsewhere. Given the symptomatic presentation and the lack of radiographic evidence of SC damage, this is most likely because of bilateral brachial plexus injury rather than RM or disease progression. Although current institutional practice has been to spare the brachial plexus consistent with consensus guidelines[20], this patient was trated before the adoption of the standard. The brachial plexus was retrospectively contoured, and the DVH statistics are given in Figure 2 and Table 5 (along with SC doses). This plan exceeded the cumulative SC $EQD_{2,2} < 70$ Gy $_{EQD2,2}$ recommendation from Sahgal *et al*,[9] but did meet the other 3 criteria. Applying the appropriate forgiveness factor, the cumulative SC $EQD_{2,3}$ was 53.5 $Gy_{EQD2,3}$, exceeding the 50 Gy $_{EQD2,3}$ recommendation from Nelson et al.[10] Two other patients experienced acute peripheral neuropathy (grade 2 and grade 3), whereas 4 cases of

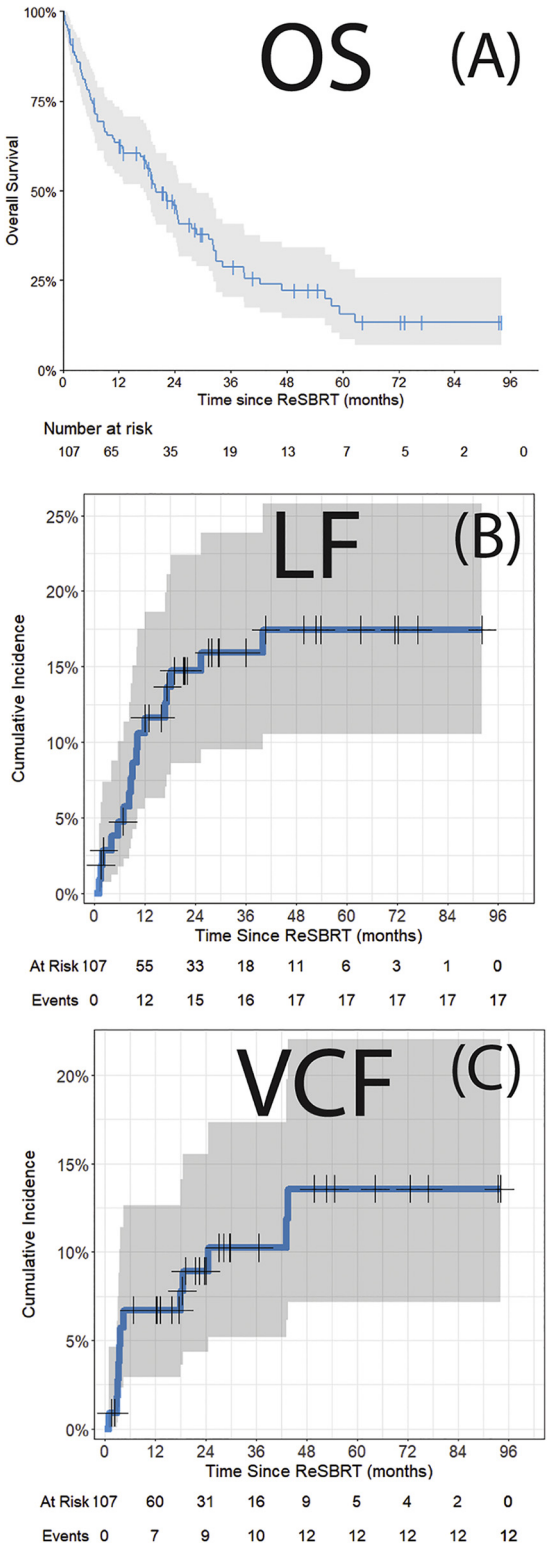

Figure 1 The (A) Kaplan-Meier estimate of overall survival (OS), and cumulative incidence of (B) local failure (LF) and (C) vertebral compression fracture (VCF) with death a competing risk for patients receiving reirradiation with stereotactic body radiation therapy for spinal metastases.
Abbreviation: reSBRT = reirradiation with stereotactic body radiation therapy.

Table 3 Select patient outcomes

Outcome	1 y	2 y	3 y	4 y
Overall survival	60.8% (51.5%-71.8%)	45.9% (36.3%-57.8%)	32.1% (23.1%-44.7%)	25.2% (16.7%-37.9%)
Local failure	11.6% (6.8%-19.8%)	4.7% (9.2%-23.5%)	15.9% (10.1%-25.0%)	17.3% (11.2%-26.9%)
Vertebral compression fracture	6.7% (3.3%-13.7%)	8.9% (4.8%-16.7%)	10.2% (5.7%-18.4%)	13.4% (7.8%-23.0%)

Table 4 Spinal cord dose-volume statistics for all patients, by fractionation

		Reirradiation with SBRT						
Metric	Previous D_{max}	D_{max}	D0.03cc	D0.1cc	D1cc	D_{max}	Total—without forgiveness D_{max}	Total—with forgiveness D_{max}
Units	$EQD_{2,2}$ (Gy)	Gy	Gy	Gy	Gy	$EQD_{2,2}$ (Gy)	$EQD_{2,2}$ (Gy)	$EQD_{2,2}$ (Gy)
All fx	21.9 (17.9-30.0)	13.6 (11.0-15.3)	11.7 (9.4-13.3)	11.1 (9.1-12.9)	9.5 (7.8-11.3)	26.7 (21.8-35.9)	64.5 (54.0-72.6)	53.0 (45.0-63.7)
All 1fx	20.0 (18.1-30.0)	11.0 (9.4-11.4)	9.3 (8.2-9.8)	9.0 (7.7-9.5)	7.4 (6.7-8.5)	35.9 (26.9-38.3)	69.7 (65.4-79.8)	64.0 (55.5-75.6)
All 3fx	30.0 (16.4-30.8)	14.7 (13.2-16.1)	12.7 (10.7-14.2)	12.1 (10.2-13.5)	10.8 (9.3-11.8)	25.4 (21.2-29.6)	59.2 (52.9-68.1)	47.4 (44.0-57.3)

Abbreviations: D_{max} = maximum dose; $EQD_{2,2}$ = equivalent dose in 2 Gy fractions; fx = fractions; SBRT = stereotactic body radiation therapy.

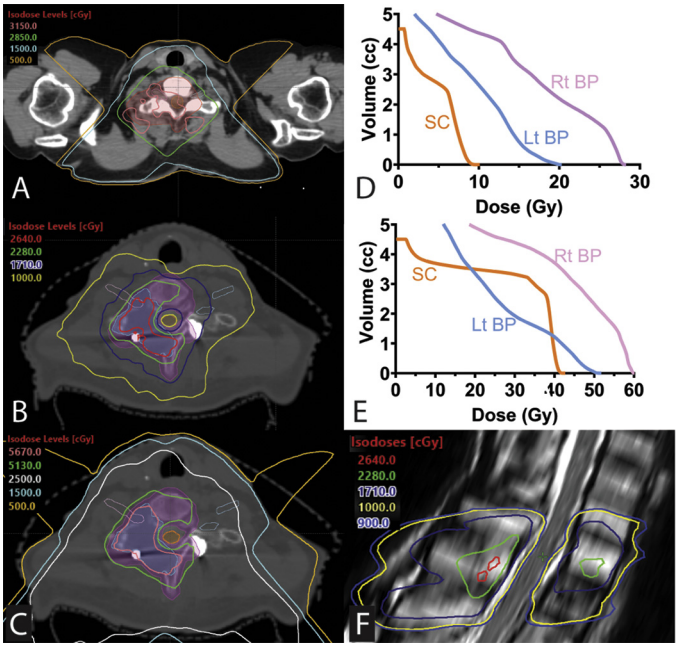

Figure 2 CT slices with plan doses, right and left brachial plexus (Rt BP and Lt BP, respectively), spinal cord (SC), and planning target volume contours for the (A) initial conventional external beam radiation therapy plan, (B) the reSBRT, and (C) the plan sum. (D, E) The dose-volume histograms for the SC for the reirradiation with stereotactic body radiation therapy for the patient who developed bilateral peripheral neuropathy. (F) Follow-up T2 magnetic resonance imaging taken 8 months after reirradiation with isodose lines from the reirradiation plan.

Abbreviations: CT = computed tomography; reSBRT = reirradiation with stereotactic body radiation therapy.

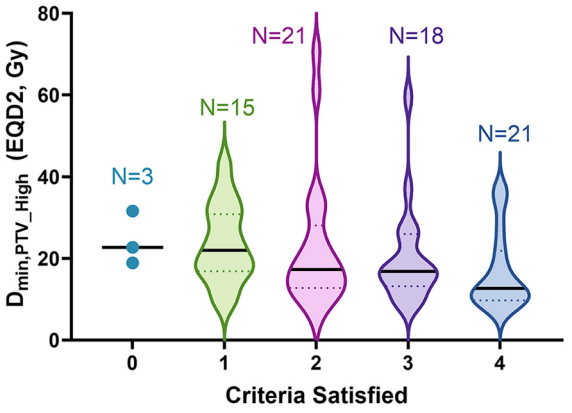

Figure 3 The minimum dose received by PTV_High (in equivalent dose in 2 Gy fractions [$EDQ_{2,\ \alpha/\beta}$] = 10 Gy) for plans at risk of radiation myelitis, classified by the number of criteria from the recommendations of Sahgal et al,[9] to minimize the risk of radiation myelitis during reirradiation with stereotactic body radiation therapy.
Abbreviation: PTV = planning target volume.

chronic unilateral peripheral neuropathy (all grade 3) were reported.

The most common acute toxicity was nausea/vomiting (N = 7, grade ≤ 2), followed by esophagitis (N = 5, grade ≤ 2), and fatigue (N = 1, grade 1). The other chronic toxicity was a grade 3 skin ulceration/wound healing complication at the site of surgery/radiation.

Discussion

These results confirm reSBRT can safely provide local control (LC) with low toxicity rates. The LF rates observed are broadly consistent with previous studies.[7,21] As expected, control rates were lower than in de novo SBRT,[22,23] likely because of radioresistant clones and target under-coverage to meet organ at risk reirradiation tolerances. Notably, 60 lesions (55%) did not meet the equivalent threshold of D_{min,PTV_High} previously identified as predictive of LF.[19] The risk of VCF is consistent with the literature in both the *de novo* setting[16] and reSBRT,[7] particularly given that many of the patients received fractional doses >20 Gy.[24] PF was relatively infrequent, though interpretation in relation to other studies is challenging because of heterogeneity in PF definitions and in limited reporting in both de novo and reSBRT settings.[7,17]

Given the seriousness of RM, strict SC dose constraints have been applied and different guidelines have been recommended for handling reSBRT cases. In particular, the recommendations from Sahgal et al[9] and Nelson et al[10] have been widely adopted. However, with advances in magnetic resonance imaging-based treatment planning, improved cone beam CT imaging, robotic couches for precise positioning, and improved intrafraction x-ray monitoring, there is potential to enhance tumor coverage —and therefore local control[19]—without compromising SC safety. Notably, in this study, RM risk remained consistent with prior reports without the use of planning-risk volume or PRV margin for the SC. Furthermore, for lesions at L1 or above, only 21 (27%) satisfied all 4 criteria from Sahgal *et al*.[9] Critically, those that did satisfy all 4 criteria had a statistically significant reduction in D_{min,PTV_High} (Fig. 3), which may compromise LC.[19] Likewise, only 33 (42%) of plans satisfied the Nelson criteria. The patient who developed bilateral neuropathy had a plan that did not satisfy the following 2 criteria: (1) the cumulative and reSBRT $EQD_{2,2}$ constraints on maximum dose (though D0.03cc did meet those constraints) and (2) a cumulative forgiven $D_{max,SC}$ $EQD_{2,3}$ of 56.8 Gy, exceeding Nelson et al's[10] 50 Gy $_{EQD2,3}$ recommendation. However, it must be emphasized that there are multiple case reports of RM for which the planned dose was not an outlier relative to the cohort (Fig. 4 and Table 4).[2,25,26] In addition, it is critical that steps are taken to ensure appropriate sparing of the peripheral nerves and that consensus guidelines are followed.[20]

Furthermore, the follow-up confirms that most LF and adverse events occur within 2 years of reSBRT. This study provides valuable evidence as recent literature reviews[2,7] only report 2 studies[27,28] with >100 lesions treated with reSBRT with shorter follow-up (<14 months) than reported here. Although limited to a single institution, it also provides a balance of patients treated with different

Table 5 Spinal cord and brachial plexus doses for patient developing bilateral peripheral neuropathy

Organ	Previous D_{max}	Reirradiation with SBRT					Total—without forgiveness D_{max}	Total—with forgiveness D_{max}
		D_{max}	D0.03cc	D0.1cc	D1cc	D_{max}		
Units	Gy	Gy	Gy	Gy	Gy	$EQD_{2,2}$ (Gy)	$EQD_{2,2}$ (Gy)	$EQD_{2,2}$ (Gy)
Spinal cord	32.8	10.0	9.0	8.8	7.5	30.0	73.7	62.4
Rt brachial plexus	32.4	28.3	27.9	27.7	26.1	214.6	257.0	235.8
Lt brachial plexus	31.2	20.1	19.6	18.7	14.3	111.3	151.6	131.5

Abbreviations: D_{max} = maximum dose; $EQD_{2,2}$ = equivalent dose in 2 Gy fractions; fx = fractions; Lt = Left; Rt = right, SBRT = stereotactic body radiation therapy.

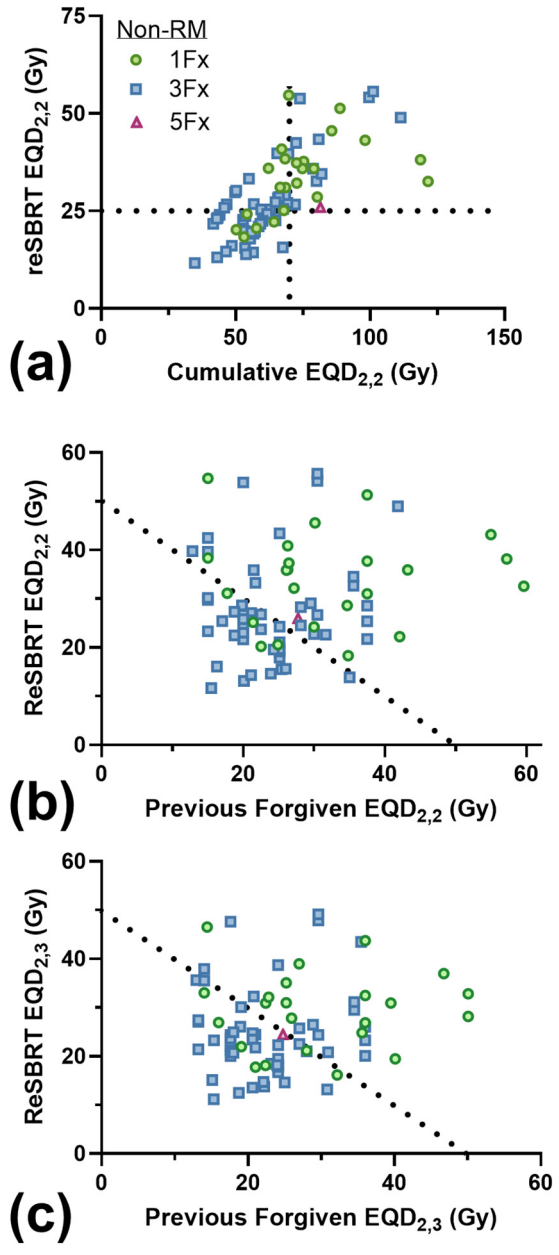

Figure 4 Comparison of the spinal cord maximum dose to spinal cord in $EQD_{2,\alpha/\beta}$ for all patients treated at vertebral body L1 and above (a) compared to the total cumulative dose to the cord (a/b = 2 Gy), with the recommendations from Sahgal et al,[9] represented by the dotted lines, and relative to forgiven dose for previous courses as outlined in Nelson, *et al*,[10] with (b) α/β = 2 Gy and (c) α/β =3 Gy, with the dotted lines representing the recommended limits from Nelson et al.[10] *Abbreviations*: $EQD_{2,\alpha/\beta}$ = equivalent dose in 2 Gy fractions; reSBRT = reirradiation with stereotactic body radiation therapy; RM = radiation myelitis.

fractionation schedules, adding to its relevance. However, the heterogeneous nature of this retrospective cohort and limited study size did not lend itself to identifying predictors of outcomes.

Conclusion

Excellent rates of local control and low rates of adverse events with reSBRT were demonstrated from a large experience with robust follow-up.

Disclosures

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