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Scientific Article

Dosimetric analysis of varying cord planning organ at risk volume in spine stereotactic body radiation therapy

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Abstract

Background: Spine stereotactic body radiation therapy (SBRT) is becoming widely accepted as first-line treatment of oligometastatic spine disease as well as in the postoperative setting. The reported incidence of myelopathy is very low and guidelines vary widely on the maximum tolerable dose of the spinal cord and thecal sac.

Methods and materials: Between April 2008 and December 2010, radiation parameters were exported for 46 patients treated with spine SBRT at the Mayo Clinic. Using an in-house data mining program, dose-volume histogram constraints were extracted, including dose prescription, dose fractionation, planning target volume, planning target volume coverage, maximum dose to the cord, D2cc thecal sac, and D2cc spinal cord. Diagnostic magnetic resonance imaging scans and/or computed tomography myelograms were fused with the planning set to delineate the cord and thecal sac for receiver operating characteristic analysis of cord and thecal sac subvolume doses. A high-resolution planning at-risk volume was created in 1-mm increments for cord (1-7 mm) and the thecal sac (1-2 mm) to examine dose gradients that might be correlated with toxicity.

Results: No patients experienced myelopathy with a median follow-up of 14 months. The most common toxicities were pain and nausea. Median values of D2cc maximum dose (maximum dose received by 2 cc of the organ at risk; biologically equivalent 2-Gy dose maximum [EQD2]) for cord and thecal sac were 38.5 Gy (range, 7.5-67.9 Gy) and 67.7 Gy (range, 15.5-155.8 Gy), respectively. Median values for high-dose subvolumes for cord and thecal sac were 2 times higher than the doses for 5% predicted grade 3 cord toxicity as recommended in the current literature. Cord D0.1cc[EQD2] $\geq$23.8 Gy was correlated with pain flare (n = 5). Thecal sac D2cc [EQD2] $\geq$29.3 Gy was a significant indicator of nausea.

Conclusion: Current guidelines may overestimate the risk of myelopathy from spine SBRT. The current study's population included both radiation-naïve and retreatment cases, but no myelopathy was observed despite exceeding recommended spine limits.

Conflicts of interest: None.

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Introduction

Spine stereotactic body radiation therapy (SBRT) has been shown to confer excellent local control and pain control in both the radiation-naïve and reirradiation settings.[1-4] Spinal cord tolerance in SBRT has been the subject of debate. The incidence of myelopathy is exceedingly low. Attempts to delineate the actuarial risk as well as characterize the cord doses that best correlate with myelopathy have been difficult. Sahgal et al have published extensively on this issue, but given the rarity of this occurrence, to generate an estimate of cord/thecal sac tolerance in spine SBRT, a pooled multiple institutional analysis was performed.[1,5] Because of differences in target delineation techniques, limitations in reviewing magnetic resonance imaging (MRI) data as well as differences in treatment planning techniques, the authors propose a maximum point dose (Pmax) to the thecal sac of 12.4 Gy for single-fraction regimens, 17 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23 Gy in 4 fractions, and 25.3 Gy in 5 fractions for which the estimated a risk of 5% myelopathy in the radiation-naïve setting.[1] In the reirradiation setting, estimates are understandably much more conservative and depend on the prior dose to the cord.[5]

In contrast, single-institution reports have suggested myelopathy is rare even with doses to the true cord of 15.7 Gy in the reirradiation setting.[4] A recent review of multiple institutions again confirmed that myelopathy was very rare even though the maximum dose to the cord varied widely, to as high as a single point dose of 19 Gy in a single fraction delivery, even in the reirradiation setting.[6] To date, it has been difficult to precisely predict which patients will have myelopathy based on maximum dose to the cord.

In the current single-institution study, we examine dose metrics to both the thecal sac and spinal cord using a high-risk planning at risk volume (PRV) and correlations with toxicity in patients treated with spine SBRT.

Methods

We have previously published on the Mayo Clinic experience with spine SBRT in both the reirradiation and radiation-naïve setting.[4] Between April 2008 and December 2010 (to allow for adequate follow-up of late toxicity), the radiation plans and dose-volume histogram (DVH) parameters from 46 of these patients were exported. These patients were selected because they were the only patients treated during that period with both adequate follow-up and available diagnostic MRI for accurate delineation of the spinal cord and thecal sac. Diagnostic MRI and/or computed tomography (CT) myelograms, from each patient, were fused with the CT planning set to contour the spinal cord and thecal sac. Previous authors have referenced doses to cord, thecal sac, or a PRV. High-resolution PRV structures were created using 1-mm increments for the cord (1-7 mm) and the thecal sac (1-2 mm). Constructing the PRV set enabled examining which cord + PRV margin resulted in distributions similar to thecal sac. Using an alpha/beta of 2 Gy, the biologically equivalent 2-Gy dose (EQD2Gy) maximum (Max(2) [EQD2Gy]) and high-dose subvolumes (Dxcc(2) [EQD2Gy]) were calculated for x = 0.1 mL to 1.0 mL in 0.1-mL increments from the DVHs.

Toxicities for pain, nausea, myelitis, fatigue, fracture, and radiation necrosis were assessed using the Common Terminology Criteria for Adverse Events, c4.0, criteria. Although clinical data were available in a prospectively collected database, all data were verified by retrospective chart review. Acute and late toxicity data were documented at every follow-up in a prospective manner. Additional information was gleaned from follow up notes and notes documenting effects during the treatment course.

DVH metrics were calculated for all patients in the study using an in-house program, DataMiner. Dependencies of toxicity scores on DVH metrics were examined using receiver operator characteristics (ROC) curve analysis, carried out with R (The R Foundation for Statistical Computing, www.r-project.org) using an in-house program, DataMole.[7,8] For each DVH metric and toxicity level, an ROC curve was created and the area under the curve calculated. A threshold value for each DVH metric to use in calculating 2 × 2 contingency tables for each toxicity level was determined as the value maximizing the Youden Index on the ROC curve. For each table, the sensitivity, specificity, positive predictive value and negative predictive value were calculated. The significance of the association of groups was calculated using Fisher exact test ($P < .01$). Differences in mean values for groups with and without toxicity were assessed using t tests for significance ($P < .05$).

Results

Patient demographics

Forty-six patients were available for analysis (Table 1). Most patients were male (38/46). Only 9/46 patients had prior external beam radiation therapy to the spine SBRT site. All patients included in the study had a single course

Table 1 Demographics of spine SBRT patients (N = 46)

Gender	
Male	38
Female	8
Spine level	
C spine	8
T spine	27
L spine	11
Prior EBRT to SBRT spine level	
Yes	9
No	37
Dose prescriptions	
16 Gy/1 fraction	2
18 Gy/1 fraction	8
21 Gy/1 fraction	1
22 Gy/1 fraction	1
24 Gy/1 fraction	4
18 Gy/3 fractions	2
21 Gy/3 fractions	2
24 Gy/3 fractions	17
28 Gy/4 fractions	1
30 Gy/3 fractions	7
35 Gy/5 fractions	1

EBRT, external beam radiation therapy; SBRT, stereotactic body radiation therapy.

of SBRT to the spinal level documented. Sixty-five percent (30/46) patients were treated with a 3-fraction regimen, whereas most of the remaining patients (16/46) received a single-fraction regimen. The most common dose fractionation was 24 Gy/3 fractions.

Acute and late toxicity

With respect to acute toxicity, five patients developed pain with spine SBRT (four with grade 1, one with grade 2). Four patients developed nausea (three with grade 1, one with grade 2). Two patients had documented grade 1 fatigue. One patient experienced acute myelitis and one developed acute paresthesias.

No patients developed late myelopathy. This was true even for patients who had more than a 6-month survival with SBRT (37 of 46 patients lived beyond 6 months from the end of SBRT). The patient who initially developed acute myelitis passed away 17.5 months after spine SBRT with no recurrence in the area treated and no symptoms of myelopathy. She died of unrelated causes. Two patients experienced vertebral compression fracture and one patient developed osteoradionecrosis. Characteristics of the patients with acute and late toxicities are further characterized in Table 2.

Dosimetry and correlation with toxicity

The mean and median values for the Max(2)[EQD2Gy] to the research cord (0, 1, 2, 3, 4, and 5 mm) and to the thecal sac (0, 1, and 2 mm) were calculated. Sample delineation of these structures are shown in Figures 1 and 2. The median values of the Max(2)[EDQ2Gy] to the spinal cord and thecal sac were 38.5 Gy (range, 7.9-67.9 Gy) and 67.7 Gy (range, 15.5-155.8 Gy), respectively. Distribution of Max(2)[EQD2Gy] values for the thecal sac corresponded most closely to spinal cord + 3.5-mm margin (Figure 3). These values were plotted against the Pmax values published by Sahgal et al[1] in Figure 4. Our median values for high-dose subvolumes (Dxcc(2)[EQD2Gy] were two times higher than the doses for 5% predicted distribution of Max(2)[EQD2Gy] values for the PRV 1 and 2 mm were also evaluated. These values were also plotted against the suggested Pmax values[1] in Figure 4. Our median values for

Table 2 Demographics of spine SBRT patients with acute and late toxicity

Toxicity	CTCAE grade	Gender	Prior RT	Spine level	SBRT dose/fractionation
Fatigue	1	Male	No	T9	24 Gy/3 fractions
Fatigue	1	Female	No	T6	30 Gy/3 fractions
Nausea	1	Male	Yes (54 Gy/30 fractions)	L5	24 Gy/3 fractions
Nausea	1	Male	No	T10-11	24 Gy/3 fractions
Nausea	1	Male	No	T10	18 Gy/1 fraction
Nausea	2	Male	No	L2	18 Gy/1 fraction
Pain	1	Male	Yes (20 Gy/5 fractions)	T5-6	30 Gy/3 fractions
Pain	2	Male	No	T10-T11	30 Gy/3 fractions
Pain	1	Male	No	L2	30 Gy/3 fractions
Pain	1	Male	No	T3	18 Gy/1 fraction
Pain	1	Female	No	C7	24 Gy/3 fractions
Myelitis	3	Female	No	C6	24 Gy/3 fractions
Paresthesia	3	Male	No	C5	22 Gy/1 fraction
Fracture	3	Male	No	L2	18 Gy/1 fraction
Fracture	3	Male	No	L3	24 Gy/1 fraction
Radionecrosis	3	Male	No	T12	24 Gy/3 fractions

CTCAE, Common Terminology Criteria for Adverse Events; SBRT, stereotactic body radiation therapy.

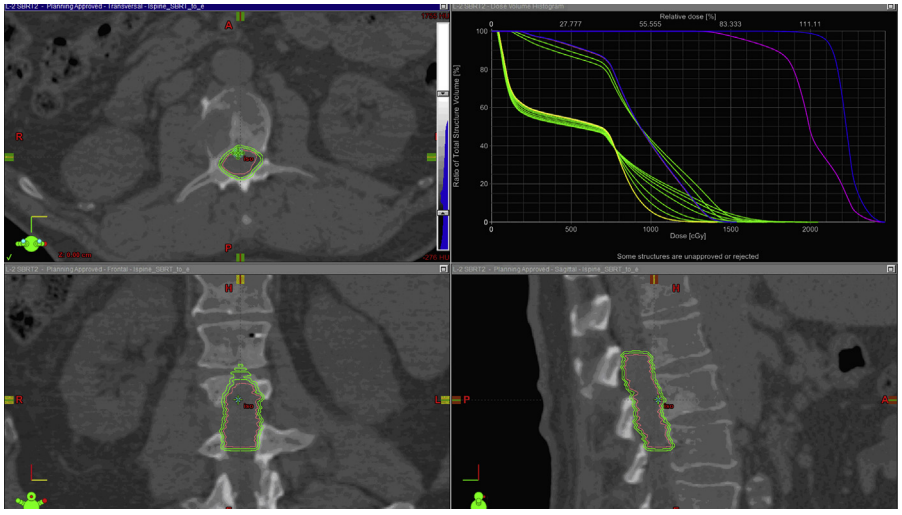

Figure 1 Sample thecal sac 0-, 1-, and 2-mm structures with sample dose-volume histogram.

high-dose subvolumes (Dxcc(2)[EQD2Gy] in PRV 1 mm and 2 mm were two times higher than the doses for 5% predicted.

The patients who developed myelitis and paresthesia each had a Max(2)[EQD2Gy] to the cord of 54.7 Gy and 24.8 Gy, respectively. The Max(2)[EQD2Gy] levels to the thecal sac were 72 Gy and 92.7 Gy. Neither patient had prior radiation therapy to the sites treated. Both patients had complete resolution of symptoms within 1 month of treatment.

Spine SBRT was very well-tolerated and acute effects were uncommon, as described previously. The most common acute events were acute back pain (5/46 patients) and nausea (4/46 patients). ROC analysis demonstrated freedom from pain $\geq$1 was significant for cord Dxcc [EQ2Gy] $\leq$ volume ($\times$) dependent thresholds. Cord D2cc [EQ2Gy] $\leq$ 15.2 Gy was most significant (Fisher exact test $<$0.0004) with highest ROC area under the curve (0.85). Thecal sac D0.1cc[EQD2Gy] $\geq$29.3 Gy was a significant indicator for nausea $\geq$1.

Local control and overall survival

Median follow-up was 14 months and median survival from the end of SBRT spine treatment was also 14 months (range, 1-64 months). At the time of analysis, 34 of 46 patients had died of causes unrelated to spine SBRT. Only one patient of 46 in the current series had documented local progression.

Discussion

The current study raises questions about the sensitivity and tolerance of the spinal cord to high doses of radiation. Despite our patients receiving 2 times the limit that may

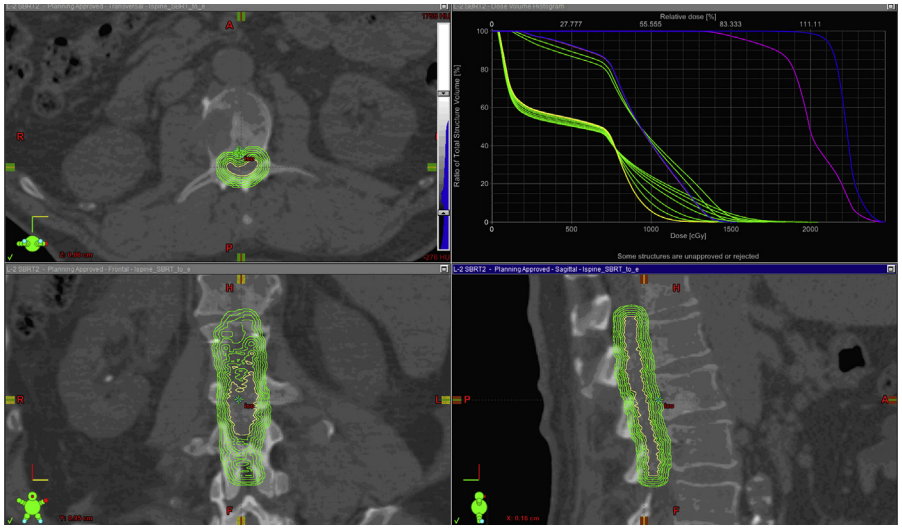

Figure 2 Sample cord 0-, 1-, 2-, 3-, 4-, 5-, 6-, and 7-mm structures with sample dose-volume histogram.

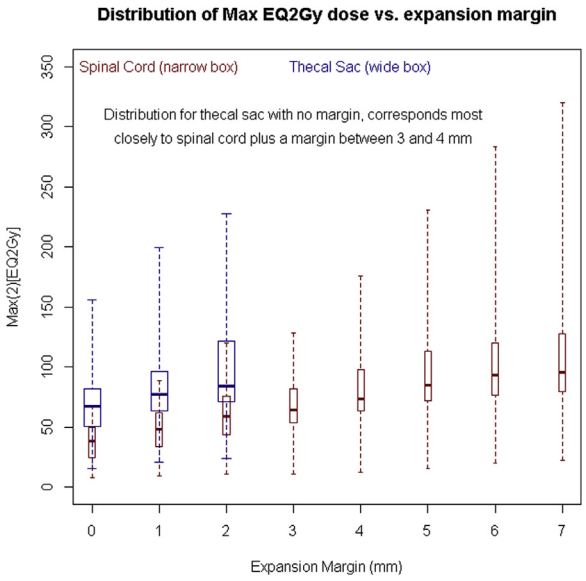

Figure 3 Determining thecal sac dose correlation with spinal cord expansion margin. EQ2Gy, equivalent dose in 2 Gy/fraction; Max(2), maximum dose in 2 Gy equivalent fractions to the spinal cord or thecal sac.

confer a 5% or greater risk of myelopathy, we did not observe any patients with this complication after spine SBRT. The majority of our patients lived well beyond 6 months with adequate follow-up to assess for these complications.

The seminal study in delineating the risk of myelopathy from spine SBRT was derived from Sahgal et al's retrospective review.[1] In that series, spine metastases SBRT databases from MD Anderson Cancer Center, University of Toronto, and University of California at San Francisco were used to identify a cohort of 66 controls and nine patients who developed myelopathy. In that study, median survival was 15 months, which is comparable to our current patient population. Normalized biological equivalent dose or 2 Gy biologically equivalent doses (nBED) was calculated and a logistic regression model was generated to predict 1% and 5% radiation myelopathy. This study suggested that the maximum dose to the thecal sac (nBED Gy2/2) for a single-fraction spine SBRT treatment was 12.4 Gy and 20.3 Gy for a 3-fraction regimen. However, this study is limited by the heterogeneous population across three different institutions and that 7/9 radiation myelopathy patients had dose parameters to the thecal sac that were well below the dose constraints proposed by the authors. The authors also report that the thecal sac actually corresponds to a cord PRV of the cord + 1.5-mm margin, which is more rigorous than our correlation of dose that may reflect contouring differences in the thecal sac between our institutions.

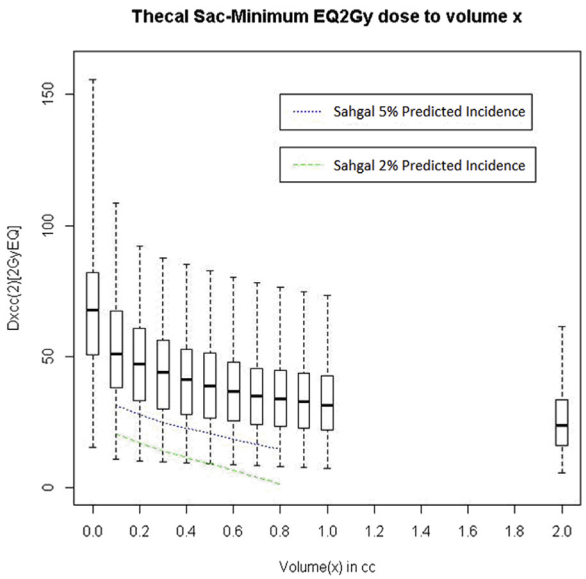

Figure 4 Myelopathy risk per Sahgal et al and Mayo Clinic minimum EQD2 to thecal sac. 2GyEQ, dose in equivalent 2-Gy fractions; EQ2Gy, biologically equivalent dose in 2-Gy fractions.

In the current study, our maximum thecal sac doses were twice those reported by Sahgal et al. The median values for high dose subvolumes (Dxcc(2)[EQD2Gy] assuming a 2-mm PRV to more closely align with the suggested guidelines were two times higher than the doses for 5% predicted. We have previously reported on 85 spine lesions treated with SBRT in 66 patients with a median follow-up of 8.2 months, none of whom developed myelopathy. The 46 patients included in this study were from the same cohort who had spinal cord and thecal sac contours available for analysis and with further follow-up and median survival of 14 months, there were still no patients who have developed myelopathy. The risk of myelopathy is truly unknown. One recent review examined 1400 patients, mostly reported in retrospective reviews, and proposed that the risk of myelopathy is less than 1%.[9] Chang et al demonstrated no myelopathy with a 21.3-month median follow-up among 63 patients treated with spine SBRT on a phase 1/2 trial.[10] The University of Pittsburgh has extensive experience, with 1075 patients treated with spine SBRT between 1996 and 2005.[11] In that series, they identified only 6 patients who developed late radiation myelopathy.[11] The low incidence of myelopathy may be correlated with poor survival in spinal metastases.

In the past 10 years, chemotherapy has markedly improved systemic control and radiation oncologists are entering an era of aggressive oligometastatic treatment. Median survival after spine SBRT varies but has been reported to be as high as 30 months.[12] However, survival in spinal metastases depends on a variety of factors, including performance status, neurological compromise before treatment, control of the primary and systemic disease, histology, age, and comorbidities. A recent study generated a recursive partitioning study for predicting survival after SBRT.[13] Their model of 174 patients

focused on favorable histologies (breast and prostate) and unfavorable histologies (renal cell, melanoma, sarcoma) as well as gender, age, Karnofsky performance scale, primary control, extraosseous metastases, time from primary diagnosis, dose of SBRT, extent of spine disease, and prior spine surgery. The limitation of this study was its short median follow-up of 8.9 months. Class 1 patients were defined as time to diagnosis of spinal metastasis from primary disease >30 months, Karnofsky performance scale >70 and had a median survival of 21.1 months. Class 3 patients were diagnosed <30 months from initial primary diagnosis and age >70 with a median survival of 2.4 months. Class 2 had a median survival of 8.7 months. The difference in median survival between radiation-resistant and radiosensitive disease was 11 and 14 months, respectively.[13] In the current study, 75% of the patients had already died at the time of analysis after spine SBRT despite excellent local control.

Given the low incidence of myelopathy and variable survival of patients after spine SBRT, it is very difficult to definitively correlate dosimetric data with adverse outcomes and to accurately predict which patients may develop myelopathy. Our study is limited by small numbers as well as its retrospective nature. However, it does confirm that adherence to current guidelines confers a low risk of myelopathy and that in patients whose survival may be limited but who may benefit from spine SBRT, such as in the reirradiation setting, the risk of myelopathy may be low even if cord limits are above current recommendations. Prospective trials such as Radiation Therapy Oncology Group 0631 will help provide insight into ongoing debates about the safety and tolerability of spine SBRT and possible clinical predictors of rare events such as late radiation myelopathy.

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