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Clinical Investigation

A Detailed Dosimetric Analysis of Spinal Cord Tolerance in High-Dose Spine Radiosurgery

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Summary

Dose-volume histograms (DVHs) of the spinal cord were used to create a DVH atlas of myelitis incidence. No dose-volume relationship attributable to myelitis was found. A median SC Dmax of 13.85 Gy is safe and supports that a Dmax limit of 14 Gy carries a low <1% rate of myelopathy. This is the only study examining comprehensive dosimetric data and radiation spinal cord myelitis in de novo spine radiosurgery. Readers can use information in the atlas to assess the safety of a candidate treatment at any point along its DVH.

Objective: Dose-volume tolerance of the spinal cord (SC) in spinal stereotactic radiosurgery (SRS) is difficult to define because radiation myelitis rates are low, and published reports document cases of myelopathy but do not account for the total number of patients treated at given dose-volume combinations who do not have myelitis. This study reports SC toxicity from single-fraction spinal SRS and presents a comprehensive atlas of the incidence of adverse events to examine dose-volume predictors.

Methods and Materials: A prospective database of all patients undergoing single-fraction spinal SRS at our institution between 2004 and 2011 was reviewed. SC toxicity was defined by clinical myelitis with accompanying magnetic resonance imaging (MRI) signal changes that were not attributable to tumor progression. Dose-volume histogram (DVH) atlases were created for these endpoints. Rates of adverse events with 95% confidence limits and probabilities that rates of adverse events were <2% and <5% for myelitis were determined as functions of dose and absolute volume.

Results: Information about DVH and myelitis was available for 228 patients treated at 259 sites. The median follow-up time was 14.6 months (range, 0.1-138.3 months). The median prescribed dose to the planning treatment volume was 24 Gy (range, 18-24 Gy). There were 2 cases of radiation myelitis (rate $r=0.7\%$) with accompanying MRI signal changes. Myelitis occurred in 2 patients, with Dmax >13.33 Gy, and minimum doses to the hottest 0.1, 0.2, 0.5, and 1 cc were >10.66, 10.9, and 8 Gy, respectively; however, both myelitis cases occurred below the 34th percentile for Dmax and there were 194 DVHs in total with Dmax >13.33 Gy.

Conclusions: A median SC Dmax of 13.85 Gy is safe and supports that a Dmax limit of 14 Gy carries a low <1% rate of myelopathy. No dose-volume thresholds or relationships between SC dose and myelitis were apparent. This is the largest study

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examining dosimetric data and radiation-induced myelitis in de novo spine SRS.

Introduction

Radiosurgery to the spine is beneficial to patients with metastatic disease and results in both rapid and durable pain control, with excellent local control rates ≥90% (1). Continued advances in systemic therapy have led to improved survival in metastatic patients. In a study of long-term (≥5 year) survivors after spine SRS, tumor control was maintained, and no grade ≥3 toxicities were associated with high-dose single-fraction spine radiosurgery (2). Whereas radiosurgery is highly effective, it also carries the potential for delivering large doses of radiation to adjacent normal structures such as the spinal cord (SC). Thus, the possibility of adverse events to normal tissue is significant and warrants further investigation.

The SC is one of the most critical organs at risk. The overall risk of delayed myelopathy with radiosurgery is thought to be <1% (3-7). Although this toxicity is rare, the consequences to the patient are devastating. Spinal dose constraints and tolerance limits vary substantially in the literature; over 59 have been reported (8, 9). The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) found multiple methods of defining the cord, which further confound the problem of a consensus SC constraint and suggest that a Dmax of 13 Gy in SRS is likely associated with a <1% risk of injury. Unfortunately, owing to a lack of dose-volume data, there were no definitive recommendations for SC constraints with radiosurgery (10, 11), and additional multi-institutional data collection was encouraged to accurately estimate SC injury (12, 13). The most meaningful method of analysis is to create a comprehensive dose-volume histogram (DVH) atlas of the risk of myelitis (14).

DVH atlases can incorporate dose-response modeling and statistically estimate risk levels at each dose limit based on clinical outcomes. The safety and risks of SC injury have not been well characterized. In a literature review spanning over 2 decades of publications and 200 articles, only 1 study incorporated dose-volume data (9) on 24 patients with de novo treatment. Other limitations included intramedullary lesions, follow-up time of 9 months, wide range of dose, and a conservative SC Dmax of 10 Gy (3). Dose constraints vary significantly in the literature, and higher SC Dmax is permitted, as in Radiation Therapy Oncology Group (RTOG) 0915, where SC Dmax was 14 Gy (15). It is critical to add more SC dosimetric data analysis to the literature from de novo treatments with high dose delivered to the SC. We report the largest analysis of SC dose limits using a prospectively collected cohort of DVH data with the longest follow-up time.

Patients and Methods

Patient characteristics

Data on all patients treated with high-dose single-fraction linear accelerator–based radiosurgery for spinal metastases at Memorial Sloan-Kettering Cancer Center between June 2004 and January 2011 were prospectively collected. Institutional review board approval was obtained to examine the dosimetric parameters of this patient cohort. All patients had pathologic review of tumor and radiographic evidence of spinal lesions. Patients were offered radiosurgery based on the neurologic, oncologic, mechanical, and systemic decision framework (16). Treatments were excluded from the analysis if there was prior radiation therapy (RT) involving the current treatment site or if there were intramedullary lesions.

Radiation technique

The decision to treat with radiosurgery was made by a multidisciplinary tumor board. The planning technique at Memorial Sloan-Kettering Cancer Center has been previously described (17). Patients underwent myelogram and computed tomographic (CT) simulation with 2-mm intervals. The clinical target volume (CTV) was contoured using international consensus contouring guidelines (18). The planning treatment volume (PTV) was generated by expanding the CTV by 2 mm, excluding the SC. The true SC was identified using computed tomographic (CT) myelogram, and no additional expansions were made for SC contours. Intensity modulated radiation therapy treatment plans using dynamic multileaf collimation were generated using an in-house optimization algorithm. Typically, 7 to 9 coplanar beams to treat the PTV to a prescription of 18 to 24 Gy were prescribed to the 100% isodose line. The SC Dmax (maximum point/voxel) was initially 12 Gy and was later extended to 14 Gy. The maximum dose constraint could be exceeded when medically necessary after departmental review.

The Memorial Sloan-Kettering Cancer Center body cradle was used to immobilize the patient, which uses pressure plates applied laterally to the pelvic bones and ribs under the arms, with adjustable hand grips. At treatment, patients were immobilized and aligned to in-room lasers before pretreatment 3-dimensional kilovoltage cone beam CT imaging to match target bony anatomy to the simulation scan. Rotational and translational errors were corrected with further cone beam CT imaging. Two-dimensional kilovoltage orthogonal verification scans were obtained immediately before treatment to confirm patient alignment.

Infrared imaging of reflective markers was used to monitor patient movement. For motion >2 mm, treatment was stopped and the positioning process was repeated.

Follow-up and clinical endpoints

The patients were seen at regular intervals and followed up every 12 to 16 weeks using total spine magnetic resonance imaging (MRI). Myelopathy was defined as grade 3 or higher per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, which includes severe weakness or sensory loss limiting the patient's activities of daily living. For a diagnosis of myelopathy, there had to be no evidence of tumor progression on MRI. All encounters were used to assess myelopathy, including radiographic imaging and rehabilitation visits. Time to myelopathy was calculated from the time of radiation until the development of symptoms.

Dosimetric analysis and statistical modeling

All treatment plans were reviewed, the accuracy of SC contours was confirmed, and DVHs were retrospectively collected. Given the rarity of myelitis, we did not expect conventional analysis to yield statistically significant dose-volume tolerance thresholds for myelitis. We concentrated on using our dataset from a large number of patients without myelitis, to provide limits on the rate of adverse events as a function of the dose and volume of SC treated. The dose-volume atlas of incidence of adverse events, as previously described (13), documents the incidence of adverse events for a given percentage of an organ at risk receiving more than a particular dose, for any choice of organ volume and dose. Here we used our spinal cord DVH and myelopathy data to create a dose-volume atlas of myelopathy incidence (DVAMI), and we investigated how confident we could be of the safety of various potential spinal DVH constraints at dose-volume intervals of 1/3 Gy and either 0.25 cc or 0.1 cc.

Given the observed incidence of myelitis above or below various potential dose-volume constraint positions in the DVAMI, binomial statistics show that confidence intervals on the true rate of myelitis (TRM) can be calculated with the β distribution (19). For DVHs that violate a potential constraint, we would like to know, with 95% confidence, how high the TRM could be and how confident we are that the TRM is higher than 2% or 5%. For DVHs that respect a potential constraint, we would like to know with 95% confidence how low the TRM could be, and how confident we are that it is less than 2% or 5%. These incidence levels of myelitis were chosen because the rate of myelitis in the patient population was <1%. Hence, regions where the myelitis rate is >2% and >5% indicate DVH positions of excessive risk.

Specifically, in DVHs that violate a given constraint, we have maps of the 5th percentile on the TRM ($M_{5,+}$) over the constraint position. We are 95% confident that the TRM is $>M_{5+}$. Conversely, in DVHs that respect a given constraint, we have maps of the 95th percentile on the TRM (M_{95-}). We are 95% confident that the TRM is $<M_{95-}$.

Additionally, in DVHs that violate a given constraint, we have maps of the probability that the TRM is greater than 2% (p2%+) or 5% (p5%+) over the constraint position. Conversely, in DVHs that respect a given constraint, we created maps of the probability that the TRM is less than 2% (p2%−) or 5% (p5%−). We have tabulated similar quantities around the positions of the DVHs of the myelitis cases.

To facilitate further use of these data in meta-analysis, we provide the DVAMI and its format description in electronic form (Appendices E1 and E2; respectively, available online at www.redjournal.org). Readers can also use the information provided to perform their own calculations using their own choices of confidence levels or rates of adverse events. The DVAMI can be used to assess the safety of a candidate treatment at any point along its DVH.

Results

Cord DVH and myelitis information were available for 228 patients treated at 259 sites (47 cervical, 202 thoracic, 10 lumbar). The patient characteristics are shown in Table 1. The median prescribed dose to the PTV was 24 Gy (range, 18-24 Gy). The majority of lesions treated included radioresistant histologies, with renal cell 19%, sarcoma 12%, and melanoma 9%. Radiosensitive histologies included prostate (11%) and breast (5%). The median follow-up time was 14.6 months (range, 0.1-138.3 months). At last follow-up, 18% of the patients were alive. The Kaplan-Meier (KM) estimate for the overall survival (OS) of the patient cohort is shown in Figure 1. The rate of either death or myelitis is shown in Figure 2a, along with the rate of myelitis, estimated either with death as a competing risk (CR) or using the KM method. The estimated rate of myelitis at 2 years was low and <1.5% using either KM or CR estimates. The low probability region of Figure 2a is magnified in Figure 2b to show the rate of myelitis more clearly. The 2-year rate of myelopathy was 1.4% with KM and 0.8% with CR estimates.

The median SC Dmax was 13.85 Gy (range, 9.61-15.21 Gy). Only 3 treatments had Dmax >14.2 Gy. There were 2 cases of radiation myelitis (0.7%). Their treatment plans are shown in Figures 3a and 3b. The time to myelopathy was 12.2 months and 11 months, respectively. The first patient was a 55-year-old woman with a chordoma and burst fracture requiring posterior segmental fixation from occiput to C6. She received adjuvant SRS to C1-3 to a dose of 24 Gy; the SC Dmax = 13.43 Gy, D0.35 cc = 11.54 Gy, V10 Gy = 2.13 cc, and V14 Gy = 0 cc. One year after radiosurgery she developed experienced instability and falls. She was hyperreflexic in all groups, with progressive motor weakness in the upper and lower extremities bilaterally. Imaging revealed T2 hyperintense abnormality and T1 postcontrast

Table 1 Baseline clinical characteristics (overall n=228 patients, 259 lesions)

Parameter	Value
Age at IG-IMRT, y	
Median	60.8
Range	20.8-87.8
Median follow-up period, mo	14.6
Sex	
Male	139
Female	89
Radiation-resistant metastases	(% of treatments)
Renal	48 (19)
Sarcoma	31 (12)
Melanoma	23 (9)
Thyroid	22 (8)
Lung NSCLC	20 (8)
Colon	21 (8)
Radiation-sensitive metastases	
Prostate	29 (11)
Breast	12 (5)
Other	53 (20)
Levels treated	
Thoracic	47
Thoracolumbar	202
Lumbar	10
RT IG-IMRT dose	
18 Gy	30 (12)
21 Gy	13 (5)
22 Gy	5 (2)
24 Gy	211 (81)

Abbreviations: IG-IMRT = image guided intensity modulated radiation therapy; RT = radiation therapy.

enhancement, as shown in Figures 3c and 3e. She started steroid therapy and acute rehabilitation. Unfortunately, she ultimately became quadriplegic and died less than 3 months after a diagnosis of myelopathy.

The second patient was a 62-year-old woman with locally advanced gastroesophageal junction adenocarcinoma who received neoadjuvant chemoradiation with cisplatin/irinotecan followed by resection 3 years before

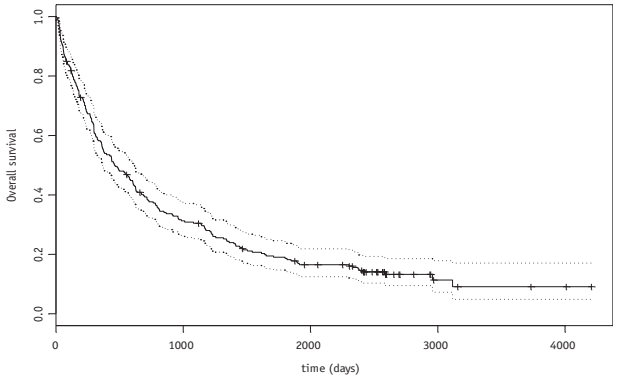

Fig. 1. Kaplan-Meier actuarial estimate of overall survival for high-dose stereotactic radiosurgery to the spine.

the development of a T1 spine metastasis. The patient underwent SRS to a dose of 24 Gy to T1 with SC Dmax = 13.63 Gy, D0.35 cc = 9.54 Gy, V10 Gy = 0.21 cc, and V14 Gy = 0 cc, and subsequent capcitabine for 6 months. At her 11-month follow-up visit, she experienced an unsteady gait with 3+/5 right hip flexor and 4/5 left hip flexor strength, with hyperreflexia. She also had sensory deficits at T7 down to the left lower extremity. MRI revealed right intramedullary T1 postenhancement with cord edema and T2 hyperintense signal changes as shown in Figures 3d and 3f. The patient initiated steroid therapy and aggressive physical therapy with minimal improvement. She continued systemic therapy and died 1 year and 9 months after the myelopathy.

A dose-volume atlas of myelitis incidence was created using the absolute SC DVHs from all treatment plans. This information is provided, with an explanation of the data format (Appendix E1; available online at www.redjournal.org), in an electronic supplement (Appendices E2 and E3; available online at www.redjournal.org) as suggested by QUANTEC (12, 13). This DVAMI provides comprehensive dose-volume and toxicity data that can be used to assess the safety of candidate treatments and the potential utility of dose-volume constraints. Both myelitis cases occurred in patients with Dmax >13.33 Gy and minimum doses to the hottest 0.1 cc, 0.2 cc, 0.5 cc, and 1 cc >10.66 Gy, 10 Gy, 9 Gy, and 8 Gy, respectively. Both myelitis cases occurred below the 34th percentile for Dmax.

In comparison with the RTOG 0631 constraint for the SC of V10 <0.35 cc, in the 77 treatments that met this limit, there was 1 case of myelopathy. For V10 <0.2 cc, there were no myelopathies, but only 56 treatments met this limit. In comparison with the RTOG 0915 (single-fraction lung SBRT) constraint for SC, V7 <1.2 cc, there were no cases of myelopathy in the 26 treatments that met this limit. It is notable that 233 treatments (~90%) did not meet this, and we expect that it would be very difficult to impose this limit on spine SRS. However, for SC DVHs with V7 Gy >5.8 cc, the myelitis rate is 1/13 = 7.7%. This is the highest rate of myelitis for any potential DVH constraint.

For our institutional SC constraint of Dmax <14 Gy (also used by RTOG 0631 and 0915), 15 treatments had Dmax >14 Gy; however, none of these had V14 Gy >0.05 cc, and only 3 treatments had Dmax >14.2 Gy. The majority of treatments had both higher SC DVH curves and SC Dmax values than the lowest myelitis case: a total of 194 treatments had Dmax >13.33 Gy, of which 2 patients had myelitis, whereas 65 treatments had Dmax <13.33 Gy, with no myelitis. Using the Fisher exact test, Dmax >13.33 Gy was not significantly associated with myelitis.

Table 2 shows the dose-volume statistics for treatments respecting potential DVH constraints. Locations of the potential constraints investigated were chosen to bracket the DVHs of the 2 myelitis cases. Inferences regarding the safety of treatments without myelitis may be made from the left-hand columns. Thus, when Dmax <13.33 Gy, with

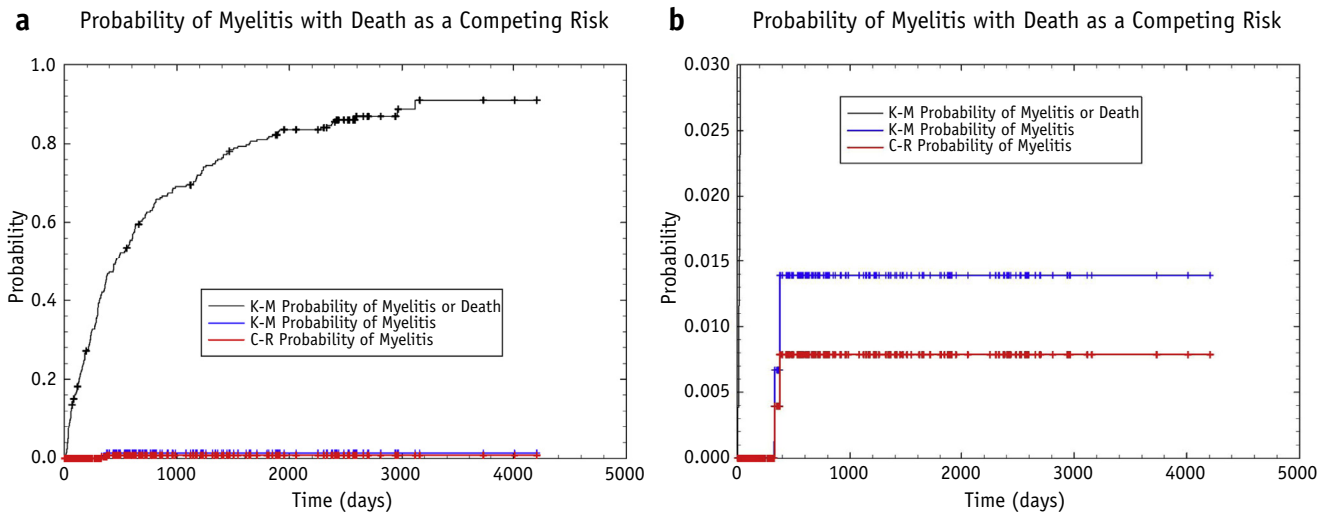

Fig. 2. (a) Black line: Kaplan-Meier (K-M) actuarial estimate of rate of death or myelopathy. Blue curve: K-M estimate of the rate of myelopathy. Red curve: rate of myelopathy with death as a competing risk (C-R). (b) Magnification of the low-incidence region of Figure 2a to show both the K-M and C-R estimates for the rate of myelopathy. The estimated rate of myelitis at 2 years is low using either the K-M or C-R estimates: 1.4% and 0.8%, respectively. (A color version of this figure is available at www.redjournal.org.)

99% confidence the TRM is <6.7%. When D 0.2 cc <10 Gy, with 99% confidence TRM is <7.8%. These values are relatively high, mainly because of the low numbers of DVHs that respect these potential constraints and the high degree of confidence used. The map in Figure 4a illustrates the 95% confidence limit on the TRM for treatments respecting potential DVH constraints (M_{95-} as defined in Methods and Materials). Also given in Table 2 are the probabilities that the TRM is <2%. Thus, when Dmax <13.33 Gy, the probability of the TRM being <2% is 74%, and when D 0.2 cc <10 Gy, the probability of the TRM being <2% is 68%. Figure 4b maps p2%−, the probability that the TRM is <2%, for treatments respecting potential DVH constraints.

Table 3 shows the dose-volume statistics for treatments violating potential DVH constraints (at the same locations as in Table 2) from which we can make statistical inferences regarding the TRM. Thus, when Dmax >13.33 Gy, with 99% confidence the TRM is <4.2%; when D 0.1 >10.66 Gy, with 99% confidence the TRM is <4.1%. Counterintuitively, these confidence limits on the TRM are lower than their counterparts from Table 2. This results from the larger number of patients treated above the myelitis positions, which more tightly constrain the TRM compared with the relatively small numbers treated below them. When Dmax >13.33 Gy, the probability of the TRM being <2% is 75%, and when D 0.2 cc >10 Gy, the probability of the TRM being <2% is 78%. In Figure 5a we have maps of the 5th percentile limit on the TRM ($M_{5,+}$) for treatments violating potential DVH constraints (we are 95% confident that the TRM is greater than $M_{5,+}$). Figure 5b shows p2%+, the probability that the TRM is >2%, for treatments violating potential DVH constraints. The red regions just under the highest myelitis DVH seen in Figures 5a and 5b confirm the high relative risk of myelitis at V7 Gy = 5.8 cc, they and show that this belongs to a surrounding region of similar risk.

Discussion

The SC dose tolerance and institutional constraints have important consequences. Injury to the SC is devastating. Radiation myelopathy clinically manifests as slowly progressing severe sensorimotor impairment, including paraplegia and quadriplegia. The latency period for the onset of myelopathy is typically after 6 months, but can it range to 20 months after RT (20). On the other hand, tumor recurrence from underdosing can be just as devastating, so elucidating the proper balance of tumor control and probabilities of adverse events is essential in spinal radiosurgery.

The pathogenesis continues to remain elusive; however, vascular injury appears to play a role (21). In addition to delivered RT dose (including effects of setup variability and intrafraction motion), other contributing factors include drug-radiation interactions, patient comorbidities, and even epigenetic changes in normal tissue adjacent to the tumor.

In a comprehensive review on SC dose limits by Grimm et al (8, 9), more than 200 articles on spine radiosurgery were reviewed from over 2 decades. Unfortunately, only 1 article contained dose-volume data and treatment outcomes. Patients received SRS 16 to 25 Gy in 1 to 5 fractions with SC Dmax 10 Gy. Scatterplots of SC volume versus BED_3 for 80% of prescription dose were developed for 90 lesions including the 3 patients with myelitis. Their median follow up was only 9 months and 74% had prior RT. Only 24 patients had de novo spine SRS and neither

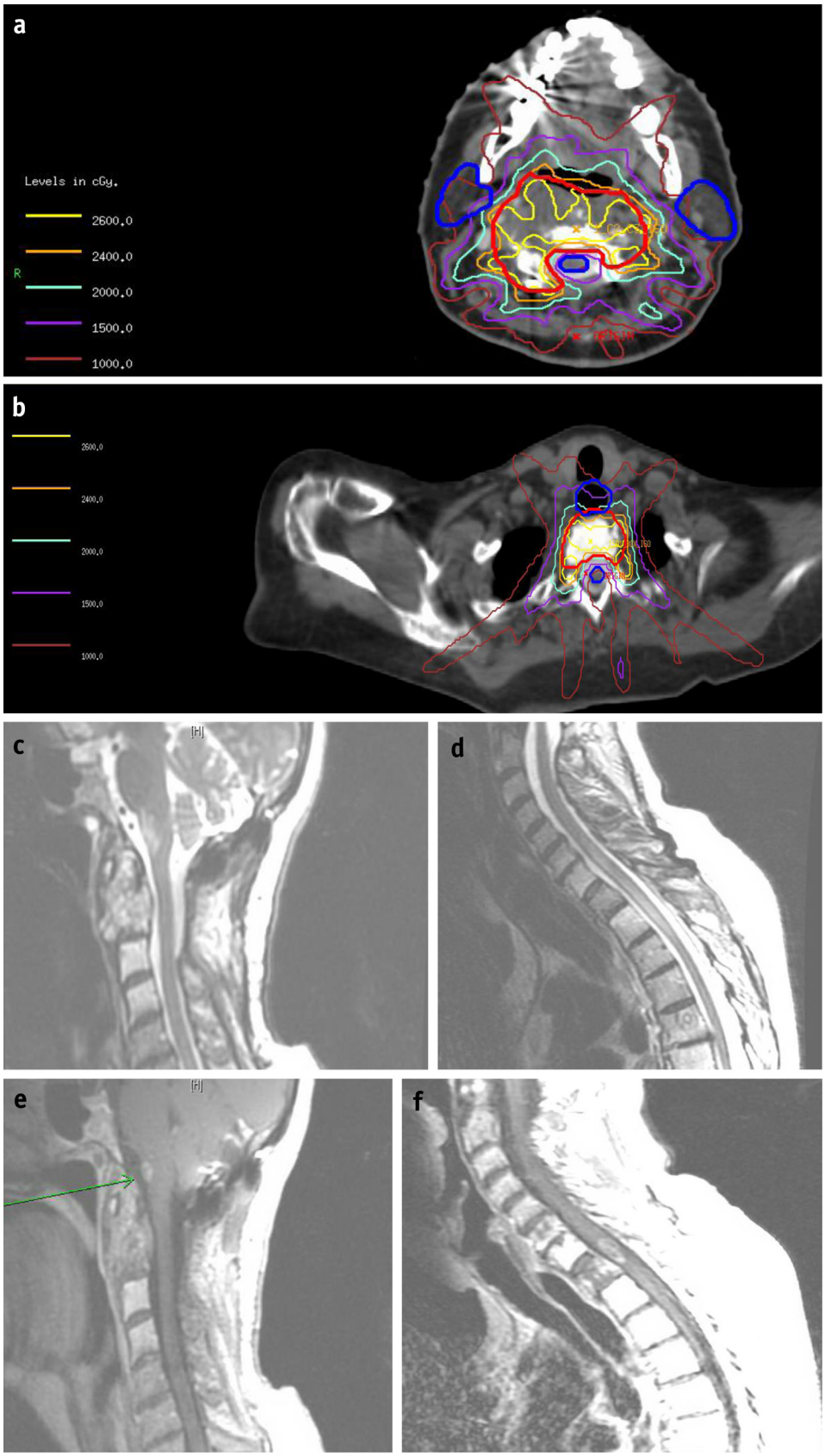

Fig. 3. Radiation treatment plans for myelitis cases. (a) Stereotactic radiosurgery (SRS) to C1-C3. (b) SRS to T1. (c, d) Sagittal magnetic resonance image (MRI) of T2 series showing signal intensity in the spinal cord (SC) segments treated. (e, f) Sagittal MRI of T1 postcontrast images showing enhancement in the SC segments treated.

Table 2 Summary statistics from DVAMI for treatments with DVHs respecting potential DVH constraints

Vol V, cc	Dose D, Gy	No. comp	No. tot	99% confident that TRM <	Probability TRM <2%	Dose D, Gy	No. comp	No. tot	99% confident that TRM<	Probability TRM <2%
0	13.33	0	65	0.067	.74	13.66	2	89	0.09	.27
0.1	10.66	0	60	0.073	.71	12.33	2	184	0.04	.72
0.2	10	0	56	0.078	.68	12	2	191	0.04	.74
0.5	9	0	45	0.095	.61	11.33	2	195	0.04	.75
1	8	0	39	0.109	.55	11	2	211	0.04	.80

Abbreviations: comp = number of myelitis cases; DVAMI = dose-volume atlas of myelopathy incidence; DVH = dose-volume histogram; tot = total number of treatments; TRM = true rate of myelitis.

Constraint locations are determined by the DVHs of 2 myelitis cases. The table is divided into 2 column groups: the group on the left reflects DVH locations immediately below the lowest myelitis case; the group on the right reflects locations immediately above the highest myelitis case, within dose-volume resolution of 1/3 Gy and 0.1 cc.

Dmax nor average SC dose was predictive of adverse events. It is noteworthy that 2 of the 3 myelitis patients received prior RT while the radiation-naïve patient received anti-angiogenic therapy. The authors concluded that no adverse event occurred when the volume of SC receiving Biological Effective Dose BED_3 $\leq$58 Gy was $\leq$0.15 cm^3, corresponding to 12 Gy in a single fraction, and that reir-radiation is safe with SRS. They expanded the study to include benign disease (4) and concluded that caution should be used when the volume of SC receiving $\geq$8-Gy dose equivalent exceeds 1 cm^3. At $\geq$8 Gy dose to 1 cc, our reported myelitis rate is $\sim$1% (2/220). The 2 patients with myelitis in our series both received Dmax >13.33 Gy, and the rate of myelitis was $\sim$1% (2/194) when Dmax was >13.33 Gy. In addition, 170 treatments were of Dmax at >13.66 Gy, with no myelitis cases. Similarly, our study demonstrated no dose-volume threshold that was predictive of adverse events. This is secondary to the fact that there

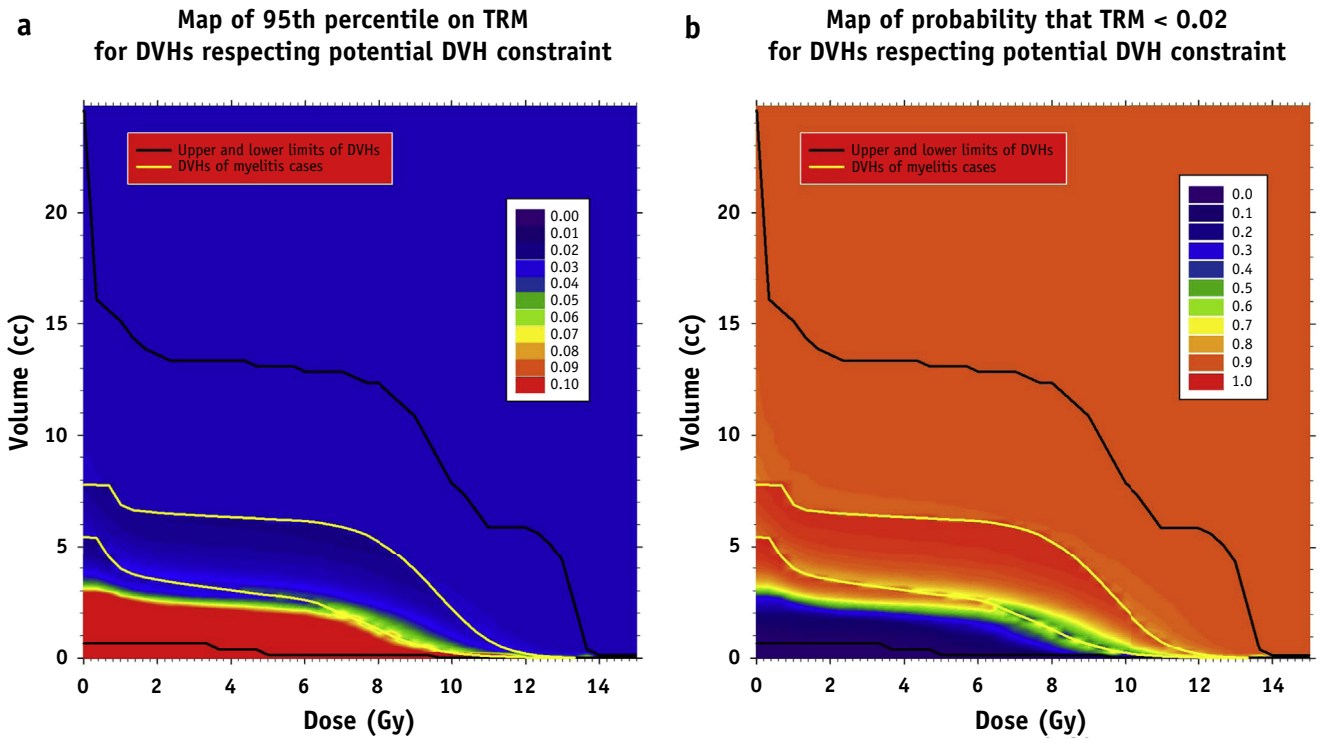

Fig. 4. (a) Map of the 95th percentile on the true rate of myelitis (TRM) for dose-volume histograms (DVHs) that respect a potential constraint at the map position (defined as M_{95-} in Methods and Materials). We are 95% confident that the TRM is $<M_{95-}$. This myelitis rate is encoded by the color value in the graph. Range for the myelitis rate (color) in the map is restricted to between 0.0 (indigo) and 0.10 (red). Yellow lines: DVHs of the cases of myelopathy. Black lines: outer envelope of all DVHs in the dataset. (b) Map of the probability that the TRM is <2%, for DVHs that respect a potential constraint at the map position (defined as p2%− in Methods and Materials). The probability is encoded by the color value in the map. Range for the probability (color) in the map is between 0.0 (indigo) and 1.0 (red). Yellow and black lines are as in Figure 4a. (A color version of this figure is available at www.redjournal.org.)

Table 3 Summary statistics from DVAMI for treatments with DVHs violating potential DVH constraints

Vol V, cc	Dose D, Gy	No. comp	No. tot	99% confident that TRM <	Probability TRM <2%	Dose D, Gy	No. comp	No. tot	99% confident that TRM <	Probability TRM <2%
0	13.33	2	194	0.042	.75	13.66	0	170	0.026	.968
0.1	10.66	2	199	0.041	.76	12.33	0	75	0.058	.784
0.2	10	2	203	0.041	.78	12	0	68	0.064	.751
0.5	9	2	215	0.038	.81	11.33	0	64	0.068	.731
1	8	2	220	0.037	.82	11	0	48	0.089	.628

Abbreviations: comp = number of myelitis cases; DVAMI = dose-volume atlas of myelopathy incidence; DVH = dose-volume histogram; tot = total number of treatments; TRM = true rate of myelitis.

Constraint locations are determined by the DVHs of 2 myelitis cases. The table is divided into 2 column groups: the group on the left reflects DVH locations immediately below the lowest myelitis case; the group on the right reflects locations immediately above the highest myelitis case, within dose-volume resolution of 1/3 Gy and 0.1 cc.

were only 2 myelitis cases, and the myelitis DVHs were in the 34th percentile for Dmax.

In a pooled multi-institutional study, 9 cases of grade 4 myelopathy resulting in paraplegia or quadriplegia were pooled and compared with a selected cohort without myelopathy (6). The thecal sac (cord + 1.5-mm margin) was contoured as a surrogate for the SC. The study included a heterogeneous population. Only two-thirds of the myelitis patients received SRS, and the Dmax to the thecal sac varied, ranging from 10.6 to 16.5 Gy. The myelitis patient with a Dmax of 10.6 Gy was particularly unexpected because early studies using parallel opposed fields found a 0% risk of myelitis with a 10-Gy single fraction (22). The 2 cases of myelitis with a relatively low Dmax of 10.6 Gy and

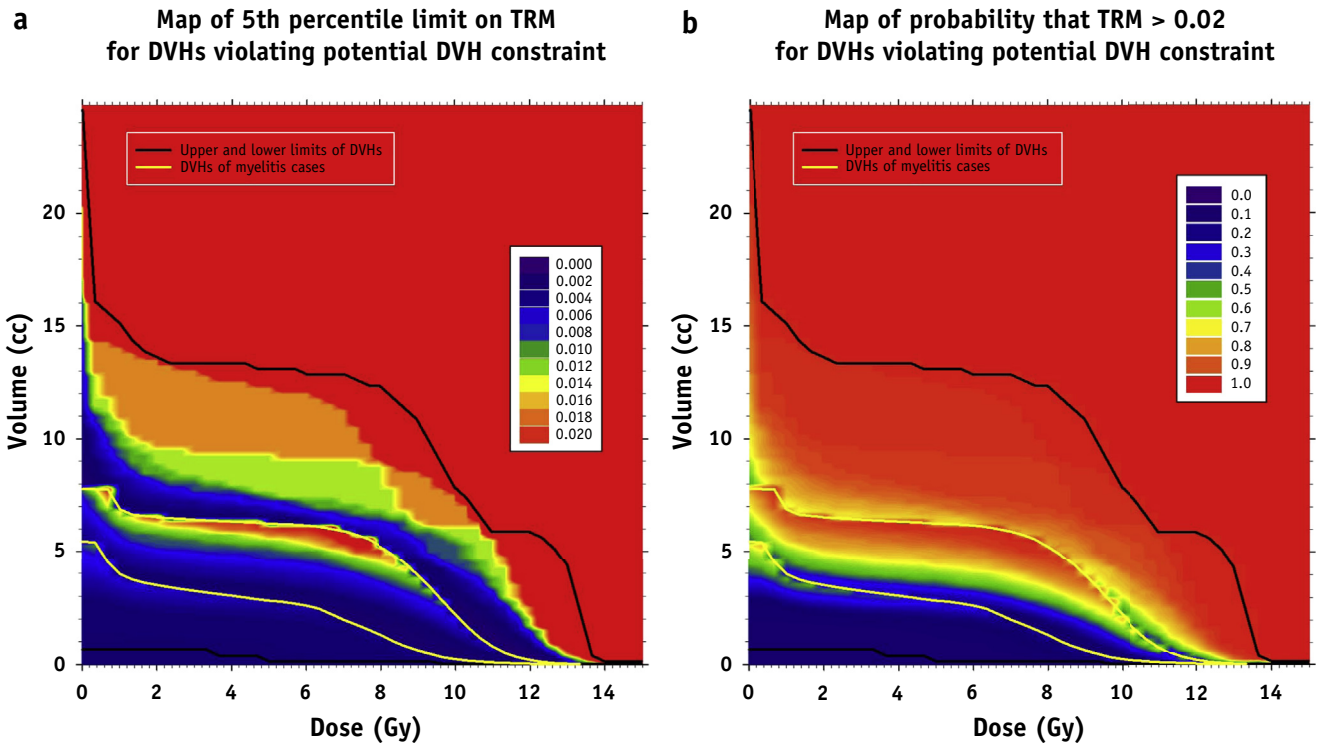

Fig. 5. (a) Map of the 5th percentile on the true rate of myelitis (TRM) for dose-volume histograms (DVHs) violating a potential constraint at the map position (defined as M_{5+} in Methods and Materials). We are 95% confident that the TRM is $>M_{5+}$. This myelitis rate is encoded by the color value in the map. Range for the myelitis rate (color) in the map is restricted to between 0.00 (indigo) and 0.02 (red). Yellow lines: DVHs of the cases of myelopathy. Black lines: outer envelope of all DVHs in the dataset. (b) Map of the probability that the TRM is >2%, for DVHs that violate a potential constraint at the map position (defined as p2%+ in Methods and Materials). The probability for both Figures 5b is encoded by the color value in the map. Range for the probability (color) in the map is between 0.0 (indigo) and 1.0 (red). Yellow lines: DVHs of the cases of myelopathy. Black lines: outer envelope of all DVHs in the dataset. (A color version of this figure is available at www.redjournal.org.)

13.1 Gy, while surprising, impacted the calculated risk of myelitis. Moreover, the model probability was directly linked to the size of the selected control cohort. The calculated risk of radiation myelopathy was extremely conservative (reflecting the small control cohort); it was $\leq$1% with thecal sac Dmax 9.2 Gy/1 fraction, 12.5 Gy/2 fractions, and 14.8 Gy/3 fractions and $\leq$5% with Dmax of 12.4 Gy/1 fraction, 17 Gy/2 fractions, and 20.3 Gy/3 fractions. Seven of 9 myelitis patients received doses below the above limits, which were proposed as constraints. The myelitis rate reported here was 0.7%. Our SC constraint of 14 Gy appears safe using a myelogram contoured cord and results in an acceptable <1% risk of toxicity.

In another study examining partial volume tolerance of the SC with SRS, a total of 230 lesions were treated, and only 1 case of radiation myelopathy was observed (5). The prescribed dose ranged from 8 to 18 Gy with only 6.4 months of follow-up. For patients receiving 18 Gy, the average dose to 10% SC was 9.8 $\pm$ 1.5 Gy. The myelopathic patient received Dmax within 1 standard deviation of the average of the long-term survivors. This phenomenon was similar to our dataset in which the myelitis cases were unremarkable. The authors conclude that the partial volume tolerance of the SC is at least 10 Gy to 10% of the SC volume.

Another potential causative factor of radiation myelopathy is spinal cord motion (both setup error and interfraction motion). Spinal cord motion has been reported to be 0.5 mm in the thoracic spine, with more motion in the cranial direction and decreasing motion caudally. Small errors may be introduced with MRI image fusion. In many studies of spinal cord dose tolerance, the thecal sac is used as a surrogate for the spinal cord and is contoured based on an estimated 1.5-mm expansion on the true cord to account for all spinal cord shifts. Our practice involves CT myelography as part of the treatment planning; injection into the subarachnoid space and visualization of the true cord eliminate any errors introduced by MRI fusion. The clinical use of maximum dose constraints derived using a myelogram-defined cord would be conservative when used with a Planning Organ at Risk Volume PRV or thecal sac−defined cord, inasmuch as maximum doses in the PRV-defined cord could be up to 20% higher than the maximum dose on the myelogram-defined cord, assuming a dose falloff of 10% per 1 mm.

In addition to substantiating the safety of Dmax of 14 Gy, our study suggests that more data are needed to assess the utility of the RTOG constraint of V10 <0.35 cc; however, our dataset does not indicate that the rate of myelitis for treatments respecting this constraint is lower than that for treatments violating it: 1 of 77 patients with V10 <0.35 cc experienced myelitis compared with 1 of 182 patients with V10 >0.35 cc. For spine SRS, it may be important to use both a SC Dmax constraint and a constraint at lower doses such as V7 Gy <5.8 cc. Although the Fisher exact test for this constraint is not significant ($P = .098$), it should not be difficult to implement because only 13 treatments violated it in our dataset. The atlas can be further used in the clinic with the physician plotting various dose-volume SC doses and examining the probability of myelitis.

Although it is difficult to reconcile SC tolerance with the heterogenous studies above, our results are in concordance with QUANTEC, which reports that the risk of myelopathy is <1% when the Dmax is limited to 13 Gy. Our study represents the most comprehensive SC dose-volume dataset to date with Dmax dose points greater than 14 Gy and with a very low myelitis risk of approximately 1%.

In conclusion, we report the first and largest dose-volume analysis of a prospectively collected patient cohort, estimating risk of myelopathy specific to de novo high-dose single-fraction radiosurgery. No dose-volume threshold or relationship attributable to myelitis was found. A median SC Dmax of 13.85 Gy is safe and supports that a Dmax SC limit of 14 Gy carries a low <1% rate of myelopathy.

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