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HyTEC Organ-Specific Paper

Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

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Summary

A review of published reports of spinal cord tolerance after stereotactic body radiation therapy was performed. This report presents several dose-response models, recommends dose limits for the spinal cord, and outlines standards for future reporting

Spinal cord tolerance data for stereotactic body radiation therapy (SBRT) were extracted from published reports, reviewed, and modelled. For de novo SBRT delivered in 1 to 5 fractions, the following spinal cord point maximum doses (D_{max}) are estimated to be associated with a 1% to 5% risk of radiation myelopathy (RM): 12.4 to 14.0 Gy in 1 fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions. For reirradiation SBRT delivered in 1 to 5 fractions, reported factors associated with a lower risk of RM include cumulative thecal sac equivalent dose in 2 Gy fractions with an alpha/beta of 2 ($EQD2_2$) D_{max} $\leq$70 Gy; SBRT thecal sac $EQD2_2$ D_{max} $\leq$25 Gy, thecal sac SBRT $EQD2_2$ D_{max} to cumulative $EQD2_2$ D_{max} ratio $\leq$0.5, and a minimum time interval to reirradiation of $\geq$5 months. Larger studies containing complete institutional cohorts with dosimetric data of

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of spinal cord dosimetric and clinical data.

1. Clinical Significance

Stereotactic body radiation therapy (SBRT) for spinal metastases is emerging as a clinical standard of care for patients with spinal oligometastases,[1] radioresistant histologies,[2] or prior spinal radiation therapy, both as a sole modality[3] or in the postoperative setting.[4] The main benefit of this technique is the ability to dose escalate the tumor volume while sparing the adjacent organs at risk (OARs).

At the inception of spine SBRT, owing to uncertainties regarding the response of the spinal cord to extreme inhomogeneous and hypofractionated SBRT, there was much variation in clinical practice among early adopters. Some applied traditional conservative point maximum dose (D_{max}) limits within the spinal cord, and others assumed small volumes of the spinal cord could tolerate a much greater dose as long as volumetric thresholds were respected. There was also considerable variation with respect to how the spinal cord was delineated and to what structure the spinal cord dose limit was being applied. These variations have persisted, and there is much uncertainty in the field regarding "safe" dose/volume guidelines for spinal SBRT.

With over a decade of worldwide experience in spinal SBRT and an initial spate of radiation myelopathy (RM) cases among early adopters, this Hypofractionation Treatment Effects in the Clinic (HyTEC) report aims to summarize the current understanding of the dose, volume, and outcome data for the human spinal cord specific to image guided, hypofractionated (1-5 fractions and a dose per fraction of >6 Gy) SBRT. Data and estimates are provided for patients with and without prior radiation exposure (termed reirradiation and de novo SBRT, respectively). This report provides updated recommendations based on dose, volume, and outcome data published since the American Association of Physicists in Medicine Task Group 101 (TG101) report.[5]

Several other potential spine-based toxicities associated with spine SBRT, such as vertebral compression fracture[6] and pain flare,[7] are outside of the scope of this report.

2. Endpoints

The clinical endpoint of interest in this review is RM, a diagnosis of exclusion based on neurologic signs and symptoms consistent with damage to the irradiated spinal cord segment without evidence of a recurrent or progressive tumor affecting the spinal cord.[8] Clinical manifestations range from minor sensory or motor deficits, to complete paraplegia/quadriplegia and loss of autonomic functioning. With conventionally fractionated radiation therapy, the latent time to the development of RM is approximately 18 months after de novo treatment and 11 months after reirradiation,[8] with higher total doses and doses per fraction associated with shorter latency times.[9] With SBRT, the median latent time to the development of RM in the series reviewed in this report (Tables 1 and 2) was 12 months after de novo treatment and 6 months after reirradiation. The shortened latency time to development of RM likely reflects the greater biological effect of the higher, and more extreme, doses per fraction inherent to SBRT.

In addition to clinical signs and symptoms, the diagnosis is further supported by evidence of spinal cord injury within the irradiated segment on contrast-enhanced magnetic resonance imaging (MRI).[8] Characteristic MRI findings include low signal on T1-weighted images, high signal on T2-weighted images, and focal contrast enhancement in the irradiated spinal cord segment. Experiments in rodents confirm that the high signal intensity on T2-weighted imaging correlates histopathologically with demyelination, edema, and necrosis, and enhancement postcontrast administration correlates with blood−spinal cord barrier disruption.[8]

The main histologic features of RM are demyelination and necrosis of the spinal cord, typically confined to the white matter, although they are not pathognomonic of radiation injury.[8] Other changes include varying degrees of vascular damage and glial reaction. Injury of the microvasculature, including disruption of the blood−spinal cord barrier, has been implicated in the pathogenesis of RM; although, vascular changes may be absent or inconspicuous histologically.[8]

Various toxicity grading systems exist. At present, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0[10] and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring System[11] are accepted standards. Myelitis is defined in the NCI CTCAE as a disorder characterized by inflammation involving the spinal cord with symptoms that include weakness, paresthesia, sensory loss, marked discomfort, and incontinence.[10] Using either scale, low-grade (1 and 2) RM is a challenge to diagnose in this population because spinal metastases requiring treatment are often painful and can mask the subtle signs and symptoms of motor or sensory abnormalities. Therefore, minor sensory and motor dysfunctions are easily attributed to the disease process as opposed to spinal cord radiation toxicity. However, high-grade (3 and 4) RM is clinically

Table 1 De novo spine SBRT literature that met the inclusion criteria for this review

Series	No. of patients	Dose reporting structure	Median prescribed dose in Gy (range)/ number of fractions (range)	Median spinal cord D_{max}, Gy	Median spinal cord D_{max} $EQD2_2$, Gy	Median follow-up, mo	No. of cases of RM
Chang 2012[45,*]	131	Thecal sac	Mean $EQD2_2$ 50.7/NS	NS	Mean 48.68 ± 29.97	Mean 23.7	0
Daly 2011[42]	19	Cord	20 (18-30)/1 (1-3)	1 Fx: 22.7 (range, 17.8-30.9); 2 Fx 22.0 (range, 21.3-26.6); 3 Fx: 21.9 (range, 19.7-25.4)	1 Fx: 140.17; 2 Fx: 71.5; 3 Fx: 50.92[†]	33.7	1
Gerszten 2012[53,*]	26	Cord	Mean 16 (12-24)/ 1 (1-3)	Mean 8.7 (range, 4-11.5)	Mean 23.27[†]	32	0
Sahgal 2007[54,*]	12	Thecal sac	21 (10-40)/3 (1-5)	20.9 (range, 4.3-23.1)	46.85[†]	25	0
Sahgal 2009[55,*]	14	Thecal sac	24 (7-40)/3 (1-5)	16.8 (range, 10.7-26)	28 (range, 15-57)	9	0
Sahgal 2013[33,*,‡]	66	Thecal sac	NS / (1-5)	NS	35.69	15	0
Katsoulakis 2017[34]	228	Cord	24 (18-24) / 1	13.85 (range, 9.61-15.21)	54.88 (range, 27.89-65.44)	15	2

Abbreviations: D_{max} = maximum dose; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); Fx = fraction; NS = not specified; RM = radiation myelopathy; SBRT = stereotactic body radiation therapy.

* The results from only the patients who met the inclusion criteria are reported in this row (instead of the full cohort of patients from the original study).

† Cumulative $EQD2_2$ estimated using summary data presented in paper.

‡ The data presented are the controls, not the cases of radiation myelopathy.

significant and is associated with permanent signs and symptoms of sensory dysfunction, motor weakness, and sphincter compromise. If the clinical signs are not attributable to disease progression and abnormal imaging findings are observed within the previously irradiated spinal cord, a diagnosis (of exclusion) of RM may be made. Thus, most of the cases of RM reported in the literature, and considered in this review, were high-grade ($\geq$3) cases based on the NCI CTCAE or the RTOG/EORTC Late Radiation Morbidity Scoring System.

3. Challenges Defining Volumes

Segmenting the spinal cord can be challenging on imaging and requires a stringent technique. A common approach is to fuse axial volumetric T1 and T2 MRI images to the treatment planning computed tomography (CT) and define the MRI−based spinal cord.[4,5,12] There are often inherent challenges with image fusion (eg, positional variations between the various scans) that must be recognized because they can be associated with a clinically meaningful level of uncertainty. Another approach is to visualize the spinal cord on a CT myelogram[4,12] by applying the myelogram contrast agent immediately before performing the treatment-planning CT, with the patient immobilized in the treatment position. Although a CT myelogram may be regarded as the gold standard by some, it is an invasive procedure and can be associated with complications.[13] Therefore, MRI− and CT-based approaches have their pros and cons. For both, the apparent edge of the spinal cord can change by adjusting the image viewing parameters (eg, CT window levels).[14] Importantly, CT alone (without myelogram contrast) is not considered sufficient to define the spinal cord or even the thecal sac; only the spinal canal can be reliably contoured with CT alone.

Because setup errors can alter the spinal cord position, most clinicians use a safety margin around the imaging-defined "true" spinal cord.[15] This margin can be applied by segmenting the spinal cord using one of the techniques described, and applying a uniform planning OAR volume (PRV) expansion margin (1.0, 1.5, or 2.0 mm have been used). Alternatively, a surrogate structure for the spinal cord that is larger than the spinal cord itself can be defined, such as the thecal sac or spinal canal.

The practice of constraining the entire spinal canal in SBRT treatment planning is generally not advised for several reasons. First, the clinical target volume in spinal SBRT usually extends to the edge of the spinal canal and, in the case of epidural disease, extends into the spinal canal. Defining the spinal canal as the avoidance structure upon which to apply the spinal cord dose limit will compromise coverage of disease (ie, underdose) within the canal and in the adjacent affected bone.[12,16] In most instances, the setup

Table 2 Reirradiation spine SBRT literature that met the inclusion criteria for this review

Paper	No. of patients	Dose reporting structure	Median prescribed dose (range) / number of fractions (range)	Median prescribed dose of prior RT (range) / number of fractions (range)
Chang 2012[45,*]	54	Thecal sac	Mean $EQD2_2$ 51.1 / NS	NS
Gwak 2005[44,*]	3	Cord	33 (21-35) Gy / 3	50.4 Gy (30-50.4) Gy/ 28 (10-28)
Sahgal 2009[55,*]	25	Thecal sac	24 (8-30) Gy / 3 (1-5)	36 Gy / 14
Sahgal 2012[43,*,‡]	14	Thecal sac	24 (10-30) Gy / 3 (1-5)	$EQD2_2$ = 39.8 (29.0-64.5)
Thibault 2015[35,§]	16	Cord PRV (+1.5 mm)	30 (20-35) Gy / 4 (2-5)	SBRT 24 (20-35)/ 2 (1-5)
Thibault 2015[35,§]	24	Cord PRV (+1.5 mm)	30 (24-35) Gy / 4 (2-5)	cEBRT: 22.5 (20-30); SBRT 24 (20-30)/ 2 (2-5)

Abbreviations: D_{max} = maximum dose; cEBRT = conventional external beam radiation therapy; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); NS = not specified; PRV = planning organ-at-risk volume; RM = radiation myelopathy; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

* The results from only the patients who met inclusion criteria are reported in this row (instead of the full cohort of patients from the original study).

† Cumulative $EQD2_2$ estimated using summary data presented in paper.

‡ The data presented are the controls, not the cases of radiation myelopathy.

§ The same study was broken into 2 cohorts and reported on different rows.

errors in spinal cord position with a rigorous SBRT technique are smaller than the "safety margin" applied by using the spinal canal as the PRV.

The thecal sac has been used by many practitioners as a surrogate for the true cord, with the dose limit applied to the thecal sac and no further PRV margin; that is, the thecal sac essentially represents the spinal cord with an anatomic PRV and is a dosimetric compromise to respect safety. At the level of the thoracic spine, the thecal sac typically represents a 1.5-mm margin beyond the spinal cord. However, at the level of the upper cervical spine, the thecal sac may represent a larger margin (2-3 mm) than the typically applied 1- to 3-mm PRV margin, owing to the natural enlargement of the cervical spinal canal and associated thecal sac.[17] At the level of the cauda equina, the thecal sac is contoured as the avoidance structure and is often equivalent to the canal because individual nerve rootlets are not reliably definable and motion may be an issue. It is important to note that the dose/response of the spinal cord and cauda equina cannot be assumed to be equivalent, and data from the sites generally should not be grouped together.

The most consistent and modern method of defining a spinal cord OAR may be contouring the spinal cord using a stringent technique described earlier and applying a PRV expansion margin. PRV margins of 1 mm, 1.5 mm, and 2.0 mm have been applied. However, some clinicians assume the known uncertainties associated with intrafraction patient movement (at a minimum 1 mm and 1°),[18] spinal cord motion (reported to be submillimeter),[19] image fusion, dose calculation, and image guidance systems to be negligible enough that it is safe to not apply a PRV. In fact, the spinal cord dose/response data listed in the American Association of Physicists in Medicine Task Group 101 report pertain to the spinal cord itself rather than a PRV or another surrogate structure.[5] However, because the steepest dose gradient with SBRT is almost always adjacent to the spinal cord and even small motions can be dosimetrically significant,[20,21] many prefer applying the dose limit to the spinal cord PRV structure as an additional means to respect safety. Ideally, institutions should determine the errors associated with their own setup reproducibility, contouring accuracy, and intra- and interfraction motion to determine center-specific appropriate PRV margins.[15,22]

Whichever approach is used clinically for segmenting the spinal cord, the clinician should be mindful of how past studies have reported spinal cord doses and to what structure the doses were being reported. A study by Garg et al demonstrated how different the reported doses can be depending on the structure used to specify the dose.[23] They reported the doses to both the spinal cord and a 1.5-mm PRV expansion margin around the spinal cord. The mean D_{max} was 12 Gy for the spinal cord and 14.5 Gy to the PRV. This result highlights the significance of specifying which structure is being used to report the spinal cord dose and the difficulty of pooling data when there is a lack of consistency.

4. Review of Outcomes Data

Literature search

Our literature search was limited to peer-reviewed spine SBRT papers published between January 1, 2005, and January 1, 2018. Studies were included where dosimetric data specific to spinal segments at the level of the spinal cord, and not the cauda equina, were reported; the structure used to report the spinal cord dose was explicitly defined; and, when applicable, outcomes for de novo and reirradiation SBRT were reported separately. Only series with 3 or more patients and where mean or median follow-up times were reported were included. In studies where individual patient data were reported and only certain patients met the inclusion criteria, only the data from the patients meeting these criteria were included in Tables 1 and 2. Where multiple series from the same institution reported

Table 2 Reirradiation spine SBRT literature that met the inclusion criteria for this review *(continued)*

Median spinal cord D_{max}, Gy	Median spinal cord D_{max} $EQD2_2$ for SBRT, Gy	Median cumulative spinal cord D_{max} $EQD2_2$ of all RT, Gy	Median follow-up, mo	No. cases of RM
NS	Mean 46.19 ± 35.21	Mean 83.37	Mean 21.8	0
24.1 (19.9-32.9)	60.45†	NS	24	1
12.8 (5.4-27)	18 (10-49)	41.5†	7	0
NS	12.5 (1.9-58.7)	52.4 (39.1-111.2)	12	0
NS	21.9 (12.4-25.0)	51.3	6.8	0
NS	21.9 (17.5-26.7)	73.9	6.8	0

Abbreviations: D_{max} = maximum dose; cEBRT = conventional external beam radiation therapy; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); NS = not specified; PRV = planning organ-at-risk volume; RM = radiation myelopathy; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

* The results from only the patients who met inclusion criteria are reported in this row (instead of the full cohort of patients from the original study).

† Cumulative $EQD2_2$ estimated using summary data presented in paper.

‡ The data presented are the controls, not the cases of radiation myelopathy.

§ The same study was broken into 2 cohorts and reported on different rows.

cumulative case series, we only included the most recent report that met the inclusion criteria.

On initial screen, our search identified 40 papers reporting spine SBRT outcomes. However, when applying the aforementioned exclusion criteria, the final cohort was limited to 7 papers reporting outcomes for patients with no prior radiation (Table 1) and 5 papers reporting outcomes for patients with prior radiation exposure (Table 2). Two papers that reported patient data separately for both de novo and reirradiation cohorts were included in their respective analyses. The most common reasons for papers to be excluded from our analyses were inability to segregate the dose to the spinal cord as opposed to the cauda equina, lack of segregation of previously irradiated and unirradiated patients, absence of a precise definition as to what structure was used to report the spinal cord dose, and lack of dosimetric data reported specific to the spinal cord or its surrogate structure. Seven of the selected analyses reported spinal cord dosimetry based on the thecal sac, 3 on the spinal cord itself, and 2 on the cord PRV (cord plus 1.5-mm margin). With respect to pooling the data for analysis, this lack of consistency was a major limitation. However, several papers that were excluded on the initial screen and, thus excluded from Tables 1 and 2, still contained useful data and, where appropriate, are discussed in the following sections.[24,25]

Dose-volume histogram parameters

The particular dose-volume histogram (DVH) parameters chosen for reporting the dose to the spinal cord are also essential in making comparisons among studies. The D_{max}, defined as the maximum absorbed dose as specified by a single calculation point,[26] was the most commonly reported parameter in the reviewed studies. Recent studies have shown that the D_{max} has a high degree of dose uncertainty, whereas a "near-max" dose (eg, $D_{0.03cc}$) may be associated with less uncertainty and may, therefore, be a more reliable metric for reporting the spinal cord dose.[27] Because most studies simply reported the D_{max} without a "near-max" dose, and because there is no way of reliably deducing one metric from the other in all situations,[27] we primarily summarized the data among the different studies and made recommendations using the D_{max}. We have recommended that future studies of RM report more DVH parameters such as $D_{0.03cc}$ in the "Reporting Standards for Outcomes" section such that we may be able to make recommendations using these parameters in future.

Accounting for dose per fraction

Because a variety of fractionation schedules were used in the various spine SBRT studies (Tables 1 and 2; Fig. 1), we have converted the doses to biologically effective doses (BEDs) to facilitate meaningful comparisons among different fractionation schedules. The linear quadratic (LQ) model has traditionally been used for this purpose; however, it has been postulated that the LQ model does not accurately model spinal cord biological effects at the high doses per fraction commonly used in SBRT (>10 Gy per fraction).[28,29] Several new models have been proposed that aim to more accurately model biological effects at these higher doses; however, none have been validated with clinical data with sufficient confidence to shift practice away from the LQ.[30,31] At present, the LQ model is still based on the fewest number of assumptions, easily calculated in the clinic, and the most commonly used model in current spinal SBRT literature. For these reasons, we chose to use the LQ model as the basis for our calculations.

The most important parameter for performing LQ calculations is the spinal cord α/β. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report noted that α/β values have ranged in the literature from 1 to 4 Gy.[32] The Sahgal 2013 analysis—which contains the largest number of cases of RM reported in the spinal SBRT literature—used an α/β of 2 Gy.[33] To maintain consistency with this analysis, we have chosen to use an α/β of 2 Gy for our calculations wherever possible. The 259 cases from

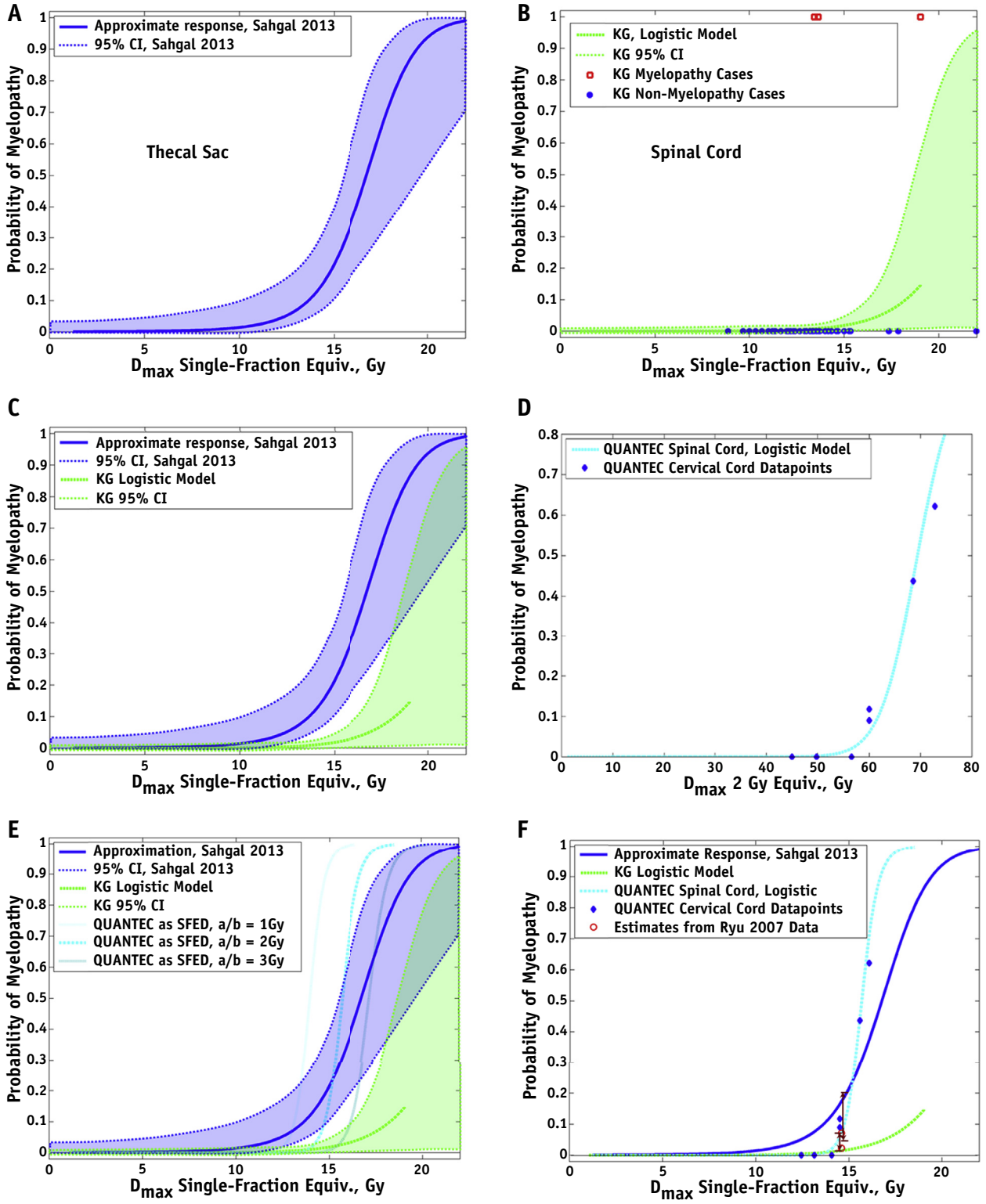

Fig. 1. Spinal cord dose tolerance models. The probabilities of radiation myelopathy are plotted against dose for the different models. In this figure, all dose conversions were performed with LQ and $\alpha/\beta = 2$ Gy, except that Gibbs et al[24] data had to be converted with $\alpha/\beta = 3$ Gy because the number of fractions for each patient was not provided and their BED values used $\alpha/\beta = 3$ Gy. (a) The dose response curve is plotted for the Sahgal model[33] and converted into the single-fraction equivalent dose. (b) The Katsoulakis–Gibbs model in single-fraction equivalent dose is shown; because the confidence intervals extend from 1% to 96% at high dose, the model itself was only plotted at lower dose. (c) The 2 curves from (a) and (b) are overlaid, demonstrating some overlap of confidence intervals for doses under 12.5 Gy. (d) The cervical spinal cord logistic model from the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report was reproduced

Katsoulakis et al[34] were delivered in a single fraction; hence, no conversions were necessary for the single-fraction dose-response model in Figure 1b. The Gibbs et al data[24] were published only in terms of BED_3, so the only possible method to convert that to the single-fraction equivalent was to use LQ with $\alpha/\beta = 3$ Gy. Of note, the maximal difference when converting this known dose to a single-fraction equivalent using any α/β ratio from 1 to 4 Gy is only 2%. Throughout this HyTEC report, the only BED conversion that was used to construct a model was the conversion of the Gibbs et al data,[24] and all other BED conversions are only for the purposes of comparing to other studies.

The LQ model was also used to convert reported doses into equivalent doses in 2-Gy fractions using α/β of 2 Gy ($EQD2_2$) for ease of comparison in Tables 1 and 2. These $EQD2_2$ values are intended to compare doses among different SBRT schedules. However, because of the aforementioned issues with the higher doses per fraction used in SBRT, we do not recommend direct comparisons of these values with the conventionally fractionated radiation therapy literature. Furthermore, it is unclear whether the data from conventional radiation therapy (<6 Gy per fraction), which typically delivers relatively more homogeneous dose distributions to larger volumes of the spinal cord (and is not necessarily intended to spare the spinal cord), are applicable to SBRT given that SBRT dose distributions are extremely inhomogeneous and the steepest dose gradient is typically adjacent to the spinal cord.

For the purposes of selecting studies for this review, if a study used a variety of dose fractionation schemes and only the absolute D_{max} was reported without reference to the fractionation, the report was deemed unusable for our analyses. However, some series accounted for the variation in fraction number by reporting the EQD2, which we considered acceptable for study inclusion. In re-treatment series, BED-based data were reported with cumulative BEDs to account for both the initial radiation delivered (typically conventional radiation) and the subsequent SBRT component. One series included patients treated with prior SBRT who were then reirradiated with subsequent SBRT (as well as patients with prior conventional radiation followed by 2 courses of spine SBRT), and used D_{max} as the metric for which the BED was calculated and summed.[35] D_{max} values in reirradiation series generally were conservatively taken from particular vertebral levels for particular plans and then summed, rather than being subjected to more sophisticated analyses such as deformable registration and plan summation.

De novo spinal SBRT dosimetric data

In patients undergoing de novo SBRT, Sahgal et al analyzed 9 cases of RTOG/EORTC Late Radiation Morbidity Scoring System grade 4 RM and a multi-institutional cohort of 66 control patients who did not have RM.[33] The thecal sac was used as a surrogate for the spinal cord in this study. Among the 9 RM cases, 1 case of SBRT as a boost (after 30 Gy in 10 fractions delivered conventionally) was included. The SBRT boost thecal sac D_{max} was 15 Gy in a single fraction, delivered within 6 weeks of conventional radiation. Six myelopathy events followed single-fraction SBRT, with the absolute thecal sac D_{max} ranging from 10.6 Gy to 16.2 Gy. RM was also observed after a thecal sac D_{max} of 25.6 Gy in 2 fractions and 30.9 Gy in 3 fractions. The mean and median $EQD2_2$ D_{max} were 70.6 Gy and 73.7 Gy, respectively, in the RM cases and 38.8 Gy and 35.7 Gy, respectively, in the control cohort. Based on this analysis, recommendations were made for thecal sac D_{max} for a 5% or lower risk of RM. A thecal sac $EQD2_2$ D_{max} of 44.6 Gy was recommended, which translates to 12.4, 17, 20.3, 23, and 25.3 in 1, 2, 3, 4, and 5 fractions, respectively (Table 3). Because the magnitude of the resulting dose responses is directly dependent on the modest number of controls included, these results represent conservative estimates. Spinal cord and thecal sac limits from a variety of sources are compared in Table 3, including estimates of risk from the "Mathematical and Biological Models" section.

Ryu et al analyzed the DVH of the MRI-defined spinal cord from 86 patients surviving 1 year after single-fraction spine SBRT, including 1 patient with RM.[25] This paper was not included in the initial screen and was, therefore, excluded from Table 1 because doses to the spinal cord and cauda equina could not be segregated. Nonetheless, this analysis does contain useful information, which is discussed in the following section. The distribution of D_{max} values of these patients was characterized by the mean (12.2 Gy) and standard deviation (2.5 Gy) compared with a D_{max} value of 14.6 Gy for the patient who developed RM. Assuming that D_{max} values are normally distributed, an upper 68% confidence interval (CI) limit for D_{max} of 14.7 Gy implies that 16% of patients ($n = 14$) received a $D_{max} \geq 14.6$ Gy (also assuming no patients with D_{max} between 14.6 and 14.7). This results in an RM rate for patients with $D_{max} \geq 14.6$ Gy of 1 in 14, or 7.1% (68% CI, 4.8%-20.3%). If we assume instead that 50% of patients received $D_{max} \geq 14.6$ Gy, this results in an RM rate of 1 in 43 or 2.3% (68% CI, 1.6%-7.3%). For a D_{max} of 14.6 Gy in a single fraction ($EQD2_2$ of 60.6 Gy), Sahgal et al,[33] QUANTEC,[32] and data from Gibbs

with dose expressed in equivalent dose in 2 Gy fractions with an $\alpha/\beta = 2$. (e) The QUANTEC logistic model data from (d) were converted to the single-fraction equivalent dose and overlaid on these 2 SBRT curves from (a) and (b). To visualize the effects of α/β uncertainty, the QUANTEC model was converted to the single-fraction equivalent dose using α/β from 1 to 3 Gy. (f) The curves from (e) are redrawn, including only the QUANTEC model conversion based on $\alpha/\beta = 2$ Gy; the data from Ryu et al[25] are also shown. The Katsoulakis–Gibbs model has about a 1% risk at 14 Gy in 1 fraction, and (f) comparison of all the data and models shows steep increases in risk above 15 Gy.

Table 3 Spinal cord and thecal sac D_{max} values recommended in previous publications compared with model-derived limits

	Existing expert-based recommendations for D_{max}		Model-based limits for D_{max} derived from clinical data		
	AAPM TG101[5]	Kim et al 2017[56]	Sahgal 2013*	Katsoulakis–Gibbs model*	Approximate
			LQ, $\alpha/\beta = 2$ Gy	LQ, $\alpha/\beta = 2$ Gy	Risk
No. fractions	Gy	Gy	Gy	Gy	of RM, %
1	14	14	12.4	14	1-5
2		18.3	*17*	*19.3*	1-5
3	21.9	22.5	*20.3*	*23.1*	1-5
4		25.6	*23*	*26.2*	1-5
5	30	28	*25.3*	*28.8*	1-5

Abbreviations: AAPM TG101 = American Association of Physicists in Medicine Task Group 101; CT = computed tomography; D_{max} = maximum dose; LQ = linear quadratic; MRI = magnetic resonance imaging; RM = radiation myelopathy.

* The spinal cord itself (from CT myelogram or MRI) was used as the dose reporting structure by Katsoulakis et al[34] and Gibbs et al,[36] and the thecal sac was used as a surrogate structure for the spinal cord by Sahgal et al.[33] Numbers in italics denote LQ-based extrapolations from the single-fraction limit. Note that because of the uncertainties involved, the decimal place may not be meaningful, and an approximately equivalent set of median rounded limits from the recommendations/models would be 14, 18, 22, 26, and 28 Gy for 1 to 5 fractions, respectively.

et al[36] predict complication rates of ~17%, ~8%, and ~3%, respectively ("Mathematical and Biological Models" section; Fig. 1f). The greater-than-expected rate of complications when applying the Sahgal et al model is likely a reflection of the limited number of controls that served to produce a safe (but perhaps overly conservative) dose-response relationship. In addition, the 1 case of RM observed among the 9 in the Sahgal et al analyses was observed at a D_{max} of 10.6 Gy, and this may have driven the more conservative estimates observed. The nature of risk has to be judged by the physician in clinical decision-making, and understanding the absolute doses at which complications occur is paramount given the inherent limitations and assumptions associated with dose conversion and modeling.

Katsoulakis et al[34] recently reported a series of 228 patients treated to 259 sites with single-fraction SBRT doses ranging from 18 to 24 Gy that included 2 RM cases. A DVH atlas[37] of RM incidence was provided by the authors in supplemental materials in line with QUANTEC recommendations.[38,39] The cumulative incidence of RM at 2 years was 0.8%. DVH-based analysis was performed for all patients in the series. Maximum doses to the CT myelogram–defined cord ranged from 9.61 to 15.21 Gy (only 3 treatments had a D_{max} >14.2 Gy). The spinal cord D_{max} for the 2 RM cases were 13.4 Gy and 13.6 Gy, both of which were lower than 13.85 Gy (the median in the series), thus suggesting that D_{max} might not be the optimal metric for predicting RM. The very small number of events limits the power to perform meaningful statistical analyses. The V7Gy <1.2 cm^3 constraint from the RTOG 0915 clinical trial[40] (for single-fraction lung SBRT) was also investigated and found not to be predictive of RM. Interestingly, 90% of treatments in the Katsoulakis et al series[34] did not meet this constraint, and the authors questioned the practicality of this particular constraint for spine SBRT. A search through the possible DVH-based metrics identified the highest rate of RM for patients with a V7Gy >5.8 cm^3 (1 of 13 = 7.7%) versus those with a V7Gy <5.8 cm^3 (1 of 246 = 0.4%). It may be that V7 Gy is a surrogate marker for other dose/volume factors because single fractions of 8 Gy to the vertebrae are not associated with spinal cord injury, albeit in patients with limited life expectancies.[41] Nevertheless, in the context of single-fraction treatment with 14 Gy maximum cord doses, a V7Gy <5 cm^3 corresponds to a very low estimated rate of RM that is likely clinically appropriate in most settings.

Gibbs et al[24] performed a retrospective review of 74 patients with 102 spinal metastases treated at Stanford University. Although this paper has been excluded from Table 1 because doses to spinal cord versus cauda equina and patients receiving de novo SBRT versus reirradiation SBRT could not be segregated, this paper does contain useful information that is discussed in the "Mathematical and Biological Models" section.

Most of the mean and median spinal cord D_{max} values reported in Table 1 are within or close to the $EQD2_2$ value of 44.6 Gy recommended by Sahgal et al,[33] albeit with broader ranges reported. The series from Daly et al represents an example of higher dose exposure.[42] In this series of patients with intramedullary hemangioblastoma, single-fraction SBRT with a median cord D_{max} of 22.7 Gy was delivered. This translates to an $EQD2_2$ of 140.2 Gy, which would be considered well beyond tolerance in other series, but only 1 case of RM was observed. Overall, it might be that the data in Table 1 broadly reflect a range of radiation tolerance in the overall population that cannot presently be quantified. It is important to understand that there may be patients for whom the risk of spinal cord damage from not achieving tumor control is higher than the risk of RM; therefore, clinical judgment is required alongside such data to inform practice.

Reirradiation spinal SBRT dosimetric data

Sahgal et al compared 5 cases of reirradiation RM to a control group of 14 reirradiated patients with 16 spinal segments treated.[43] The reirradiation RM cases were all RTOG/EORTC Late Radiation Morbidity Scoring System grade 4. The thecal sac $EQD2_2$ D_{max} for the first course ranged from 18.3 to 52.5 Gy, and the SBRT reirradiation thecal sac $EQD2_2$ D_{max} ranged from 44.1 to 104.9 Gy. In the RM cohorts, the median $EQD2_2$ D_{max} for the SBRT component and cumulative $EQD2_2$ were 61.7 Gy (range, 44.1-104.9 Gy) and 99.6 Gy (range, 77.2-154.9 Gy), respectively. In the no-RM control cohort, the median $EQD2_2$ D_{max} for the SBRT component and cumulative $EQD2_2$ were 12.5 Gy (range, 1.9-58.7 Gy) and 52.4 Gy (range, 39.1-111.2 Gy), respectively. In the no-RM cohort, there was a minimum of 5 months between initial radiation and reirradiation. With further analysis comparing the SBRT $EQD2_2$ D_{max} to the cumulative $EQD2_2$ D_{max} and time to re-treatment, recommendations have been made for SBRT given in the setting of reirradiation (summarized in the "Recommended Dose/Volume Objectives" section). The spinal cord cumulative $EQD2_2$ D_{max} values reported in the studies included in Table 2 are largely consistent with these recommendations.

However, Gwak et al[44] and Chang et al[45] treated to substantially greater reirradiation and cumulative SBRT doses than described in the Sahgal et al series.[43] Although no case of RM was reported by Chang et al,[45] the RM case from Gwak et al[44] was included in the reirradiation RM analysis by Sahgal et al.[43] At this time there are very limited data and relatively poor data quality to render any recommendations beyond what has already been reported.[43] It is also acknowledged that there are no validated means of accounting for the extent of time between courses to determine the amount of time-dependent recovery of the central nervous system tissue to accurately model tolerance in the reirradiation setting.

5. Factors Affecting Outcomes

Volume effects for spinal cord SBRT are not well understood. This issue was explored by Sahgal et al.[33] Doses to the following volumes of the thecal sac were reported: from 0 (D_{max}) to 1 cm^3 (D_{1cc}) in 0.1 cm^3 increments, and 2 cm^3 (D_{2cc}). When the doses to different volumes of the thecal sac were analyzed, significant differences between RM cases and controls were observed up to the 0.8 cm^3 volume; however, significance was greatest for the D_{max}, suggesting a serial tissue nature of the spinal cord. Similarly, Grimm et al[36] also noted that complications were best associated with similar parameters (D_{1cc} and D_{max}). Katsoulakis et al[34] reported an RM rate of 1 in 13 (7.7%) in patients with cord V7 Gy >5.8 cm^3, but this was not statistically significant. These issues are particularly important for longer targets, which inherently would lead to larger volumes of spinal cord receiving a high dose. More data are required to resolve the issue of volume effects.[46] In addition, there are no data regarding whether alternative fractionation schedules (eg, every other day vs twice a week vs daily) have any influence on the risk of RM. Last, clinical data regarding other medical factors that can influence tolerance, such as diabetes, vascular disease, or smoking are insufficient to make recommendations about modifying tolerances.

6. Mathematical and Biological Models

Models based on conventional fractionation

Schultheiss et al[47] described a logistic model for RM that was based on tabulated data points including conventional daily fractionation schemes of 1.8 to 2 Gy per fraction as well as several moderately hypofractionated (6-9 Gy per fraction) treatments. Results from this model were in agreement with the historical Emami et al paper,[48] with a 50% complication D_{max} dose estimate of 69.4 Gy (95% CI, 66.4-72.6 Gy). Efforts have been made to employ the Lyman and Schultheiss models to fit spinal SBRT data without much success.[49]

Sahgal model

With mounting unresolved questions facing NTCP modeling for spinal cord doses received in SBRT, a different approach in approximating a dose-response model was reported by Sahgal et al.[33] Because no exhaustive data set of all patients treated with SBRT was available, the 9 reported RM cases from the worldwide literature were combined with 66 control cases to approximate a dose response model. The model was fit using the maximum likelihood method, with bootstrap sampling for CI. This is an approximation because the data from the actual corresponding non-RM cases treated at the centers where the complications occurred were not available for comparison; instead, a control set of 66 non-RM cases was used (this number is almost certainly lower than the true number of controls). It should be noted that the resulting dose response is essentially inversely proportional to the number of controls included. For ease of comparison to the other models, the Sahgal[33] approximate dose response curve is shown in Figure 1a in terms of single-fraction equivalent dose (as calculated using the LQ model and $\alpha/\beta = 2$ Gy).

Katsoulakis–Gibbs model

Gibbs et al[24] reported the outcomes of 74 patients at Stanford University treated to 102 sites. Three patients developed RM, and Grimm et al[36] generated a probit dose response model using these data. Fifty of the patients were previously irradiated to a median dose of 40 Gy in 2 to 3 Gy

per fraction. Seventy-two data points were discernable, and of these 19 cases with 1 RM were from patients who received de novo SBRT and 53 cases with 2 RMs were from patients who received reirradiation SBRT. Among the 19 de novo SBRT cases, 1 had RM.

Katsoulakis et al[34] reported on the outcomes of 228 patients treated to 259 sites. We have combined the provided DVH atlas in that analysis with the maximum dose and RM data from the Gibbs series provided by Grimm et al[36] as LQ equivalent single-fraction doses using $\alpha/\beta = 3$ Gy (which we have designated the Katsoulakis–Gibbs [KG] model). Seventy-four patients were treated to maximum spinal cord doses less than 13.33 Gy, none with RM, giving a 95% confidence that the RM rate is less than 4% in similarly treated patients with cord doses under this threshold. These pooled data were also used to construct a logistic model for RM as a function of maximum spinal cord dose, reproduced in Figure 1b, with 95% CI generated by the profile likelihood method.

Although the pooled number of RM cases in the KG model was still very small (3 cases), the total number of treatments was large (278), and the P value for the dose response parameter was significant ($P = .015$). The modeled rate of myelitis at 14 Gy was consistent with overall rate of myelitis of 1% for treatments limited to $D_{max} < 14$ Gy found by Katsoulakis et al. The size of the dose response beyond 14 Gy was highly uncertain because the number of treatments beyond this dose was small. There was a modest indication that maximum single-fraction spinal cord doses >15.33 Gy were associated with increased risk of RM ($P = .043$, Fisher's exact test); only 4 treatments in the combined data set had D_{max} values over this level. A threshold of the highest 3 treatments would give $P = .032$, and the highest 2 treatments would give $P = .022$, showing that the significance of this model emanates from increasing risk at the few highest cases. This serves as a warning that dose escalation into these levels should be done with extreme caution. It is notable that neither data set alone showed a significant dose response, emphasizing the merit of publishing comprehensive, patient-specific dose volume and complication data such as the atlas by Katsoulakis et al. Notwithstanding the significant dose response, the uncertainty in the complication rate at any dose is high, as illustrated by the large 95% CIs shown in Figure 1b, which range from 1% to 96% risk at high dose.

Comparisons between the models

The QUANTEC model found that in conventional fractionation, spinal cord D_{max} values of 45 Gy had a 0.03% risk, 50 Gy had a 0.2% risk, 54 Gy had a 1% risk, and 61 Gy had a 10% risk of RM.[32] The conventional treatment range from 45 to 60 Gy therefore forms the dose range of most clinical interest in this setting. Doses under this range are known to be very safe, and doses over 60 Gy are usually not justifiable other than in rare situations such as spinal and base of skull chordoma[50] or re-treatment. In Figure 1d and 1f, the actual data points from QUANTEC[32] are included, and it may be seen that the steepness of the QUANTEC model is due in large part to the early studies from Atkins et al in 1966[51] and Abbatucci et al in 1978,[52] with $EQD2_{0.87}$ doses of 68.7 Gy and 72.8 Gy, respectively, and overall survival–corrected RM rates of 44% and 62%, respectively.[32] The lack of experience at the inception of SBRT resulted in conservative spinal cord dose constraints to avoid RM. As a result, the effort to obtain exact quantitative estimates at the higher end of the range for SBRT remains a challenge. As explained previously, it is unclear whether LQ is accurate in providing an estimate for $EQD2_2$ at the high doses per fraction used in SBRT; therefore, the QUANTEC risk estimates should not be used to directly estimate risks of RM in patients undergoing SBRT.

When the approximate dose responses of Sahgal et al[33] and the KG model are compared, as in Figure 1c, the CIs overlap up to 12.5 Gy in a single fraction and the Sahgal et al estimates are observed to be more conservative than the KG estimates at any dose. Numerical values for the 5% or less estimated dose tolerance levels from Sahgal et al[33] in 1 to 5 fractions, as well as the corresponding estimated risk levels from the KG model, are shown in Table 3, and comparisons to the KG model are shown in Figure 1c. It should be noted that the KG model is based on only 3 RM events and, therefore, the actual rate of RM is highly uncertain especially where spinal cord D_{max} exceeds 14 Gy, as shown by the CIs in Figure 1.

Making recommendations from the different models

Katsoulakis et al[34] established a spinal cord D_{max} value of 14 Gy in 1 fraction as being safe to the myelogram-defined spinal cord, with the caveat that RM was observed at spinal cord D_{max} values of 13.4 and 13.6 Gy. Both the original publication and the KG model estimate the risk of RM at this dose to be approximately 1%. Therefore, this represents a reasonable recommended upper limit of spinal cord D_{max} dose tolerance for single-fraction SBRT, with the lower limit of 12.4 Gy as per Sahgal et al. For 2- to 5-fraction SBRT, the study by Sahgal et al[33] still contains the largest cohort of patients developing RM from SBRT to a variety of fractionation schedules. Therefore, until further human data are available, recommended safe spinal cord D_{max} dose constraints for 2- to 5-fraction SBRT are 17.0 Gy for 2-fraction SBRT, 20.3 Gy for 3-fraction SBRT, 23.0 Gy for 4-fraction SBRT, and 25.3 Gy for 5-fraction SBRT. The KG model and Sahgal model estimates for risk of RM at these doses are 1% and 5%, respectively.

Considering the limitations of both models, and the overall few cases of toxicity, 1% to 5% constitutes a

Table 4 Maximal spinal cord doses for reirradiation associated with a low risk of RM according to Sahgal et al 2012[43]

Prior RT		Recommended spinal cord* D^{max} in 1-5 fractions (Gy)				
Dose, Gy/fractions	$EQD2_2$, Gy	1 fraction	2 fractions	3 fractions	4 fractions	5 fractions
20/5	30	9	12.2	14.5	16.2	18
30/10	37.5	9	12.2	14.5	16.2	18
40/20	40	N/A	12.2	14.5	16.2	18
45/25	43	N/A	12.2	14.5	16.2	18
50/25	50	N/A	11	12.5	14	15.5

Abbreviations: D_{max} = maximum dose; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); RT = radiation therapy.
* The thecal sac was used as a surrogate structure for the spinal cord in this study.[43]

reasonable estimation of RM risk at these doses to obtain adequately informed consent from patients. Although the 95% CI of the KG model itself has a tighter range of uncertainty at 14 Gy (0.5%-1.8%), the uncertainty increases to 5% at just 2 Gy higher dose, and 5% is the risk estimate from Sahgal 2013.[33] Therefore, for conservatism, we simply state 1% to 5% as the estimate of risk. Of note, a straight LQ conversion for a D_{max} of 14 Gy for 2- to 5-fraction SBRT is 19.3 Gy for 2-fraction SBRT, 23.1 Gy for 3-fraction SBRT, 26.2 Gy for 4-fraction SBRT, and 28.8 Gy for 5-fraction SBRT. These 2- to 5-fraction dose limits are not based on clinical data and are instead a straight conversion, with the inherent limitations associated with the LQ, and cannot be recommended for practice. These values can be compared with the Sahgal et al and other published recommended limits summarized in Table 3.

7. Recommended Dose/Volume Objectives

There are very few reported cases of RM after SBRT, as should be the case given the severity of RM. Because of the limitations of the currently available data, the dose and outcome estimates in this report are heavily influenced by expert opinion, based on clinical experience, and augmented by available data. Owing to these limitations, we did not generate any new dose/volume objectives but instead used the dose/volume data and response model to estimate the risk of the existing published limits. For de novo SBRT delivered in 1 to 5 fractions, D_{max} values of 12.4 to 14.0 Gy in 1 fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions appear to be associated with an estimated risk of RM ranging from 1% to 5% (Table 3). These D_{max} values generally refer to the thecal sac (which may be considered as the cord PRV), though the 14-Gy single-fraction constraint was based on a myelogram-determined spinal cord and the specific technique defined by the Memorial Sloan Kettering Cancer Center.

Table 3 also summarizes published dose limits based on protocols and clinical experience as opposed to data-driven modeling. It is up to individual physicians to determine their own practice and what limits they wish to apply; all of these tolerance limits are suggestions and are not absolute. There are significant limitations to the data that cannot be overcome unless large, prospective, multi-institutional cooperative registries of dose tolerance thresholds are created and modelled.

For reirradiation SBRT delivered in 1 to 5 fractions, the following have been recommended by Sahgal et al[43]:

1. The cumulative thecal sac $EQD2_2$ D_{max} should not exceed 70 Gy.
2. The reirradiation SBRT thecal sac $EQD2_2$ D_{max} should not exceed 25 Gy.
3. The reirradiation SBRT thecal sac $EQD2_2$ D_{max} to cumulative $EQD2_2$ D_{max} ratio should not exceed 0.5.
4. The minimum time interval to reirradiation should be at least 5 months.

Based on these recommendations, the maximum dose limits for 1 to 5 fractions that are associated with a low risk of RM for a range of prior radiation exposure are provided in Table 4. Because these recommendations are based on a low estimated risk of RM, there may be some clinical situations in which it may be reasonable to exceed these recommendations, but we cannot provide any guidance beyond the evidence. Again, the limits proposed in this paper are suggestions to help guide practice and are not absolute, given the limitations of the data.

8. Future Studies

The known cases of RM after SBRT have been reported and studied in detail; however, there have been few studies of the complete series of patients treated, including the corresponding cases that did not develop RM, and thus calculating risk estimates is challenging. In the Sahgal et al study,[33] the 66 control cases is a conservatively small number of cases; in the Gibbs et al study,[36] the 19 de novo cases is also a very small number of cases, considering that they have not had a further case of RM in the past 10 years.[36] The Katsoulakis et al study,[34] with 2 cases of RM

among 228 patients, is an improvement but is still relatively small for the purposes of accurate modeling. Because the expected risk of RM is as low as 1%, acquiring a data set with 10 complications would likely require about 500 to 2000 patients. Further studies with large cohorts of patients will likely allow us to refine our estimates of RM risk.

9. Reporting Standards for Outcomes

Published data on RM are rare and usually do not allow for systematic dosimetric analyses. The key difficulty lies in gathering complete data on large series of patients among whom there may be at most 1 or 2 cases of RM. Such data sets are incapable on their own of providing dose responses that are statistically significant, and progress in understanding spinal cord tolerance doses can only come when results from several series are combined. It is therefore vital that editors recognize the importance of the publication of such series and that the published data sets conform to rigorous reporting standards so their results can be pooled.

General recommended reporting standards for outcomes are discussed in a separate paper in HyTEC. In addition to those recommendations, we propose reporting of the following information in future studies of RM:

- SBRT prescription
  - o Dose and fractionation
- Spinal cord segmentation
  - o Whether the spinal cord itself or a surrogate structure (eg, thecal sac) was used as the OAR
  - o Imaging modality and sequence(s) used for segmentation
  - o The spinal cord and cauda equina should be segmented separately
  - o PRV margin
- Treatment-planning parameters
  - o Treatment-planning system
  - o Dose calculation algorithms
  - o Dose calculation grid size
  - o Resolution and slice thickness of the planning CT scan
- DVH parameters
  - o D_{max}, $D_{0.03cc}$, $D_{0.1cc}$, D_{1cc}, $D_{50\%}$[27]
  - o As much dosimetric data as possible should be reported—ideally, actuarial DVH atlases of complication incidence
- Prior radiation therapy
  - o Patients treated with de novo SBRT should be reported separately from those treated with reirradiation SBRT
  - o Dose and fractionation
  - o The time interval between treatments for reirradiation SBRT should be reported
- Outcome assessment
  - o Duration and frequency of follow-up
  - o Method of diagnosis of RM
  - o Grading of RM: NCI CTCAE v4.0[10] or RTOG/EORTC Late Radiation Morbidity Scoring System[11]
  - o Time from SBRT to RM
  - o Time from SBRT to death

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