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NORMAL TISSUE TOLERANCE

Estimating normal tissue toxicity in radiosurgery of the CNS: application and limitations of QUANTEC

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Minimizing radiation-induced normal tissue damage in the central nervous system (CNS) is a key objective and primary impetus for stereotactic radiosurgery and radiotherapy. The recently published Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study provides updated dose/volume/outcome data on normal tissue tolerance for sixteen anatomic sites, including the CNS. Most of the data used to develop the relationship between dose, volume and normal tissue toxicity derived from large field, conventionally fractionated regimens, and quantitative dose/volume/outcome data at high doses per fraction to limited volumes is much sparser. Nonetheless, QUANTEC provides some limited recommendations for dose constraints in stereotactic radiosurgery/radiotherapy of the CNS. This paper critically reviews the findings, recommendations and limitations of QUANTEC as they apply to radiosurgery of the CNS, as well as presenting suggestions to establish and validate clinically meaningful dose/volume/toxicity relationships in this setting.

Key words: Stereotactic radiosurgery, Hypofractionated stereotactic radiotherapy, Normal tissue toxicity, Central nervous system, Brain, Brainstem, Optic apparatus, Auditory apparatus, Hearing, Radiation-induced optic neuropathy, Spine, Myelopathy

INTRODUCTION

Stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT) can effectively treat CNS lesions in one day to a few weeks with relatively-modest risks to normal tissue. Nevertheless, the choice of SRS and HFSRT is often dominated by this risk of CNS injury. Furthermore, for both SRS and HFSRT, the dose and fractionation is often largely based on minimizing the risk of a radiation-induced CNS injury.

Seminal papers by Rubin [1] and Emami [2] et al provided rational guidelines for the dose tolerance limits of normal tissues under *conventional* fractionation (Typically <3Gy/faction); recommendations for patients receiving radiosurgical treatments were absent since the use of such hypofractionated approaches was limited at the time of these publications. In 2006, leaders in the American Association of Physics in Medicine (AAPM) and American Society of Therapeutic Radiology and Oncology (ASTRO) recognized that an increasing amount of dose/volume/outcome data for normal tissues had been generated. A joint AAPM-ASTRO effort - "Quantitative Analysis of Normal Tissue Effects in the Clinic" or QUANTEC [3-5] - has since summarized these dose/volume/outome data for 16 anatomic

"sites" (*International Journal of Radiation Oncology, Biology and Physics* in March, 2010).

The QUANTEC papers essentially present a critical review of the literature on radiation dose/volume/outcome for normal tissue, and attempt to quantitatively analyze these data and present recommendations on dose-volume limits and futures studies of normal tissue toxicity. While all of the papers dealing with the CNS address the issue of radiosurgery and normal tissue toxicity, the data on dose/volume/toxicity in the CNS at high doses/fraction were diverse and disparate, and thus quantitative models could not be established. Herein, we critically review and summarize the findings and limitations of QUANTEC as applied to SRS/HFSRT in the CNS on an anatomic site basis. In doing so, we propose further studies to better define dose/volume/toxicity that could be of value to the clinical application of radiosurgery in the CNS.

DEFINING NORMAL TISSUE TOXICITY IN THE CNS

A broad range of endpoints are used to describe normal tissue toxicity in the CNS, as discussed for each anatomic site below. The CNS is amenable to radiographic imaging. MRI scans are frequently obtained for pre-treatment planning on a regular basis and post-treatment to monitor the response to therapy. Radiographic imaging post radiosurgery can provide a quantitative measure of post-treatment changes at the treatment site which have been equated with damage, i.e., radionecrosis. However, the clinical significance of these changes is not always clear, as transient radiation-induced inflammation, radionecrosis and tumor progression can be seen in radiosurgery [6].

Focal symptoms attributable directly to SRS/HFSRT may be more clinically relevant, such as spinal cord myelopathy, visual deficits and hearing loss. Deficits involving specific cranial nerves, such as the optic [7] or auditory [8] apparatus, can also be quantitatively measured. Global problems arising from radiosurgery, such as diminished neurocognition, quality of life and the ability to carry out activities of daily living, are also relevant, and may be particularly important in patients receiving radiosurgery in the palliative setting. Unfortunately, these are often the most difficult outcomes to measure, and there is a paucity of data in this regard.

In QUANTEC, an effort was made to select those studies that used clinical endpoints most appropriate for both the anatomic site and disease being treated. The clinical context for radiosurgical treatment will be quite different, for example, for an otherwise healthy patient with an AVM or benign meningioma versus multiple brain metastases and poorly controlled extracranial disease. In the former situation, avoiding long-term symptomatic expression of radiation-induced injury may be the dominant issue [9], while in the latter, acute palliation without incurring severe neurocognitive deficit may be the objective. The severity of the deficit also influences the selection of appropriate endpoint. For example, a relatively high (20%) risk of unilateral hearing loss might be considered acceptable in some situations and a very low (1-2%) risk of complete blindness unacceptable. Similarly, the degree of acceptable risk will depend on the disease being treated, e.g., a 5% risk of transverse myelopathy could be considered reasonable when treating a malignant tumor in the spinal cord with short survival expectancy, but unacceptable when treating a low-grade tumor involving the vertebral body.

Finally, the issue of normal toxicity cannot be divorced from the need to effectively treat the target lesion. Every practitioner (and their patient) balances the risks of the treatment against the benefit of curing/controlling the lesion. A radiosurgery treatment which severely compromises target coverage and/or prescribed dose may limit damage of normal tissue damage at the expense of rapid disease progression and attendant disability. Knowledge of the known risk/reward relationship, as well as the many uncertainties regarding radiosurgery and CNS toxicity, may aid the clinician in developing and discussing an appropriate treatment plan with each patient. Without such communication, it is difficult to obtain an informed consent.

CEREBRAL HEMISPHERE

Radiosurgery is used for treatment of a broad range of malignant and benign brain lesions, including malignant tumors metastasized from extracranial sites ("brain metastases"), meningiomas, recurrent malignant gliomas, vestibular schwannomas and arteriovenous malformations (AVMs.) The endpoints for assessing radiation-induced complications are typically radiation necrosis or asymptomatic radiologic changes as seen on serial MRI scans[10]. Other measures have included steroid usage, preservation of performance status and neurocognitive function[11-13].

In SRS of brain lesions, normal tissue toxicity appears to be a function of dose, volume and location in the brain. The Radiation Therapy Oncology Group conducted a dose-escalation study (RTOG 9005) of radiosurgery to recurrent brain metastases and primary tumors in patients who previously received whole- or partial-brain irradiation[14]. The goal of this study was to determine the maximal tolerated dose as a function of maximum diameter of the lesion. Unacceptable

toxicity was defined as acute irreversible severe neurologic symptoms, requiring inpatient or outpatient medications, any life-threatening neurologic toxicity or death. This study found a maximum tolerated prescription dose to the tumor margin of >24Gy, 18Gy and 15Gy for tumors of maximal diameter <2.0, 2.1-3.0 and 3.1-4.0 cm, respectively. The rates of acute and late unacceptable toxicities in patients treated at these doses were 0 and 10%, 0 and 14% and 0 and 20%, respectively. The dose limits appear to be validated by the results of the RTOG 9508, a randomized study of SRS + WBRT versus WBRT alone in 333 patients with brain metastases[11]. Using the dose constraints developed in RTOG 90-05, this study found a 3 and 6% rate of Grade 3 and 4 acute and late toxicities in the group of 167 patients receiving radiosurgery.

The results of dose-volume studies of the development of "radionecrosis" following single-fraction radiosurgery are shown in Table 1 [10, 15-24]. While a common element in many of these studies is the volume receiving a dose of 10 or 12Gy or more (V_{10} or V_{12}, respectively), there is a broad variation in the crude rate of radionecrosis as a function of volume irradiated. This is likely due to difference in the definition of "radionecrosis," the location irradiated, the proximity to and sparing of critical structures, and the length of and intensity of clinical follow-up.

These results suggest that the rate of complications increases rapidly as the V_{12} increases beyond 5-10 cm^3. Note, however, that V_{12} will far exceed these limits for lesions 2 cm or greater in mean diameter when the RTOG guidelines are utilized. For example, assume that spherical lesions of 1, 2, 3 and 4 cm diameter are treated under the RTOG guidelines with single-fraction radiosurgery with the plans yielding V_{12}'s of 6, 5, 4 and 3 times the lesion volume, respectively. Then, the calculated V_{12}'s are 3, 21, 57 and 101 cm^3, respectively.

The location of the lesion is important as the severity of expressed damage is greater in the more eloquent parts of the brain. For example, for a V_{12} of 10 cm^3 Flickinger et al found a <5% of symptomatic post-radiosurgery injury for AVM's in the frontal, temporal and parietal lobes versus >20% for AVM's in the brainstem, thalamus and basal ganglia [9].

It is common practice to utilize hypofractionated stereotactic radiotherapy in the treatment of large tumors, previously irradiated sites, or targets in or adjacent to critical structures, as a means to ostensibly reduce the risks. However, there is little systematic reporting on normal tissue toxicity for hypofractionated regiments using fraction sizes in the 5-8Gy range.

Based on the available data, it is prudent to minimize the volume of normal brain receiving >10-12 Gy in a single fraction, and to consider both target diameter and anatomic location when prescribing dose. However, a clear dose-volume-clinical toxicity relationship has not been established. Key questions that would benefit from systematic study include:

1. What is the dose-volume-location-clinical toxicity relationship for brain metastases and other common lesions treated with single-fraction SRS?
2. What is the rate of local and distant failure for the above sets of patients as a function of prescribed dose?
3. How does the GTV to PTV expansion influence the incidence of normal tissue toxicity and failure rates in single-fraction SRS?
4. How is the incidence of normal tissue toxicity affected by previous large field irradiation to the brain, particularly, the combination of WBRT and SRS in the treatment of brain metastases?
5. How do systemic treatments affect the incidence of normal tissue toxicity?

To better understand these issues, studies of SRS and HFSRT should capture the data, including neurocognitive and neurologic dysfunction (e.g. per the Common Terminology Criteria for adverse events, version 4.0 (CTCAE v. 4.0 [25]), report the prescription dose, dose/fraction, target volume, V_{12}, anatomic location treated, and clinical outcome data (*e.g.* adverse events, patterns of failure).

BRAINSTEM

While lesions in the brainstem are occasionally the targets for radiosurgery, the issue of radiation-induced brainstem injury is more frequently encountered when treating lesions immediately adjacent to this structure, particularly vestibular schwannomas [26]. The brainstem is comprised of the midbrain, pons and medulla, and care should be taken to segment the superior extent and cerebral/cerebellar peduncles as these borders are often indistinct. Coronal and sagittal views, in addition to axial images, are frequently helpful in visualizing the brainstem and its interfaces. The adult brainstem volume is on the order of 35 + 8 ml [27].

A limited number of studies report brainstem toxicity in single-fraction SRS or HFSRT [28-32]. A broad range of prescription isodose levels and dose metrics are reported, making it difficult to develop a predictive dose-volume model for brainstem toxicity [26]. In the study with the largest number of patients, Foote et al analyzed the outcome in 149 vestibular schwannoma patients treated with SRS between 1988 and 1998; 41 were treated before 1994 when radiosurgery was primarily based on CT imaging and 108 after 1994

Table 1. Summary of published reports of radionecrosis in patients receiving brain stereotactic radiosurgery

Reference	Diagnosis	n	Mean Dmin, Gy (range)	Overall Incidence of RN	Subgroup	Incidence of RN in Subgroup	Primary predictor of toxicity	Other risk factors
Lax, 1996 [20]	AVM	823	?	5%			Average dose in $20cm^3$	
Voges, 1996 [24]	Mixed	133	15.0 (7.0–25.0)	12.8%	V_{10} <10cc V_{10} >10cc	0% 23.7%	V_{10}	Location
Flickinger, 1997 [17]	AVM	307	20.9 (12–30)	10.7%,			V_{12}	Location
Miyawaki, 1997 [21]	AVM	73	16 (10–22)	14%	Tx volume: <1cc 1–3.9cc 4–13.9cc >14cc	 0% 15% 14% 27%	Tx volume	Dose, Prior brain insult
Chin, 2001 [16]	Mixed	243	20 (10–30)	7%			V_{10}	Repeated radiosurgery, glioma
Nakamura, 2001 [22]	Mixed	749	18 (16–19)*	?	Rx volume : 0.05–0.66cc 0.67–3cc 3.1–8.6cc 8.7–95.1cc	 0% 3% 7% 9%	Rx volume	
Barker, 2003 [15]	AVM	1250	10.5 (4–65)	4.1%			Dose & volume combined.	Age, Location
Friedman, 2003 [18]	AVM	269	?	4.7%			V_{12}	
Varlotto, 2003 [23]	Brain metastases	137	16 (12–25)	11.4%	Tx volume: <2cc >2cc	 3.7% 16%	Volume	
Korytko, 2006 [19]	Tumor	129	17.3 (11–25)	30%	V_{12}: 0–5cc 5–10cc 10–15cc >15 cc	 23% 20% 54% 57%	V_{12}	Location, previous WBRT, male

*Range refers to 25^{th}–75^{th} quartile

Abbreviations: AVM= Arteriovenous malformation, RN = Radionecrosis, Rx = Prescription, Tx = Treatment, V_{10} = Volume receiving 10Gy, V_{12} = Volume receiving 12Gy, WBRT = Whole brain radiotherapy

when planning was MRI-based. Large single fraction doses (10-22.5Gy) were used. Their analysis revealed a ''learning curve'' with a 5% and 2% actuarial 2-year rate of facial and trigeminal neuropathies, respectively, for patients treated after 1994 compared with 29% for both neuropathies for the earlier patients. This study found a significant increase with a 2-year actuarial rate of facial and trigeminal neuropathies of 29% and 7% for patients treated before and after 1994, respectively. The authors ascribe this difference to the use of MRI rather CT-based imaging and lower prescription doses in the latter years. A univariate analysis showed an incidence of cranial nerve neuropathy of 2% for <12.5 Gy vs. 24% for >12.5 Gy ($p<0.0003$). On multivariate analysis, the prescription dose >12.5 Gy, prior surgery, and treatment prior to 1994 were significant variables.

It appears that a maximum brainstem dose 12.5-13 Gy is associated with a low (<5%) risk of cranial

neuropathy in patients with vestibular schwannomas treated with single-fraction SRS. The risk appears to increase rapidly when the marginal prescription dose >15Gy or when the target volume exceeds 4 cm^3 [26, 28, 33]. However, doses of 15-20Gy have been used to treat brainstem metastases with a low reported rate of complications, potentially because of the limited survival time for these patients [32, 34].

As shown in QUANTEC paper [26], there is little dose-volume data in the hypofractionated portion of dose-volume versus toxicity curve. Only a single study is available in this region [35]. Clearly, more data with detailed dose-volume metrics is required before the absolute risk of H-FSRT to the brainstem can be assessed.

OPTIC NERVES AND CHIASM

The optic nerves and chiasm frequently receive a substantial dose of radiation during therapeutic irradiation of the brain, base of skull and head-and-neck structures, and the optic apparatus is frequently the dose-limiting structure in these cases. The primary endpoint for radiation-induced optic neuropathy (RION) is visual impairment, defined by visual acuity and the size/extent of visual fields [36]. Of course, damage to the lens (development of cataracts), retina (retinitis), and lacrimal apparatus and trigeminal nerve (dry eye syndrome) can also produce visual impairment [37]. While toxicity may be objectively scored using CTCAE version 4 [25] and LENT-SOMA criteria [38, 39], it is important to obtain a comprehensive ophthalmological exam of patients with suspected RION.

The optic nerve originates roughly at the posterior center of the globe and is bracketed by the rectus muscles as it tracks posteriorly through the orbit to pass through the optic notch, just medially to the anterior clinoid process. The optic nerves join and decussate to form the optic chiasm, an œ shaped structure which sits just superiorly to the sella turcica with the center immediately anterior to the pituitary stalk [40]. The optic nerves and chiasm are thin (<5mm diameter) and visualization is best performed using thin-cut (≤3mm) T1- or T2-weighted magnetic resonance imaging. Contouring the optic nerves/chiasm is challenging and it is important to ensure that these structures are drawn in continuity, i.e., there is not a gap in the contours. Appropriate contouring of these structures is facilitated by visualizing this region in multiple planes and using multiple, fused imaging modalities, e.g., utilizing the MRI images in the axial and coronal planes to track the optic nerves/chiasm and sagittal CT views to see the sella turcica.

Because of the small size of the optic nerves/chiasm and steep dose gradients in radiosurgery, most studies of RION involving SRS use the maximum point dose (Dmax) to the optic nerves/chiasm as the critical dose metric [7]. As shown in Table 2, single-fraction SRS studies describe a range of threshold D_{max} for RION. In analyzing their early experience with radiosurgery, Tishler et al [41] reported RION at D_{max} as low as 9.7Gy and recommended 8Gy as the dose limit for the optic nerves/chiasm in SRS. Stafford et al [42] found RION in 4 of 215 patients receiving a median D_{max} of 10Gy. The D_{max} in the patients ranged from 0.4-16Gy and 3 of the 4 had received previous external beam radiotherapy to this area. They estimated a 1.7%, 1.8%, 0% and 6.9% incidence of RION for D_{max} of <8, 8-10, 10-12 and >12

Table 2. Summary of published reports of radiation-induced optic neuropathy in patients receiving stereotactic radiosurgery adjacent to the optic apparatus

Reference	Disease	n	Prescribed Dose, Gy (range)	Dose Subgroup	Incidence of RION in Subgroup
Foote, 1993 [38]	Meningioma	62	10-40	<8 Gy	0/35 (0%)
				8-10 Gy	1/2 (50%)
				>10 Gy	3/15 (20%)
Leber, 1998 [41]	Mixed	45	14.3 (8-25)	<10 Gy	0/31 (0%)
				10-<15 Gy	6/22 (30%)
				>15 Gy	10/13 (77%)
Stafford, 2003 [39]	Mixed	215	18 (12-30)	<8 Gy	1/58 (2%)
				8-10 Gy	1/58 (2%)
				10-12 Gy	0/67 (0%)
				>12 Gy	2/69 (3%)

Gy, respectively. Conversely, Pollock et al [43] observed no cases of RION in 62 patients with non-functioning pituitary adenomas receiving a median D_{max} of 9.5 + 1.7 Gy to the optic apparatus during single-fraction SRS, using a 12Gy D_{max} as the dose constraint for the optic apparatus. From a study of 50 patients with benign base-of-skull tumors treated with single-fraction SRS and a median follow-up of 40 months, Leber et al [44] estimated a 0, 27 and 78% risk of RION for D_{max} <10, 10 to <15, and ≥15 Gy, respectively. No data for dose-volume and RION were available for the hypofractionated stereotactic radiotherapy (4-8Gy/fraction.) [7]

Per the QUANTEC paper, the above studies suggest that the incidence of RION is rare for D_{max} <8 Gy, increases in the range of 8-12 Gy Dmax and becomes >10% when D_{max} exceeds 12 Gy. Though iso-effect curves for RION are presented over a range of 2-12 Gy/fraction using various radiobiologic models, the authors emphasize that there is no data in the hypofractionated range and caution that the curves should not be used to predict toxicity in HFSRT. [7]

AUDITORY APPARATUS

Damage to the auditory apparatus, leading to sensorineural hearing loss (SNHL), is frequently reported following single-fraction SRS and HFSRT of vestibular schwannomas [8]. SNHL following conventionally fractionated radiotherapy is typically measured by a decrease in the bone conduction threshold at 0.5-4kHz, the primary range for human speech, using pure-tone audiometry (PTA). While the technique is well-established and standardized, a broad range of specific audiometric parameters are used to characterize SNHL, including the frequency (range) used for testing, the threshold chosen for a clinically significant change in the bone conduction threshold (10-20 dB), the control/standard used for comparison [8]. In SRS or HFSRT, hearing status is more commonly evaluated using the Gardner-Robertson scale which is based on both PTA and speech discrimination. Hearing loss after SRS/HFSRT may be characterized by changes in Gardner-Robertson hearing grade, retention of serviceable hearing (i.e., functional hearing with the aid of hearing aid) or any measurable hearing. In addition, the length of follow-up will influence reported hearing loss, as deficits may develop more rapidly following single-fraction SRS than HFSRT, and hearing loss increases over time in both situations.

Both the acoustic nerve and cochlea are small structures, and the dose gradient at the latter structure is often quite steep. Moreover, the acoustic nerve anatomy is distorted by the tumor, significantly increasing its apparent diameter. Thus, the dose to these structures is typically characterized by an average or maximum dose, rather than a dose-volume distribution. In many studies, the primary dose metric was the dose to the acoustic neuroma, rather than the normal tissue structures *per se*, which is not unreasonable as the dose to the tumor appears to be correlated with the dose received by the acoustic nerve [45].

Table 3 summarizes the reported incidence of hearing loss for single-fraction SRS and FSRT in the treatment of vestibular schwannomas [46-56]. The range of hearing loss reported is broad, in part due to the variation in the definition of hearing preservation and the length of follow-up. Nonetheless, several studies suggest that there is a relationship between the volume/length of acoustic nerve irradiated and/or the dose to the nerve and cochlea with hearing loss. In a study of 82 patients treated to a marginal dose of 12 Gy in single-fraction SRS, Massager et al [57] found that increased intracanalicular tumor volume (<100 vs. ≥100mm^3) and volume averaged intracanalicular dose were significant predictors of increased hearing loss. Pollock et al reported that hearing preservation was more likely when tumors <3 cm vs. >3 cm diameter were treated with single-fraction SRS[58].

Niranjan et al [59] found that the dose extending extending beyond the intracanalicular tumor volume and the prescription dose were the most important factors adversely affecting hearing. In that study, serviceable hearing was preserved in 100 % of patients treated with a marginal tumor dose of ≤14Gy in single-fraction SRS versus 20% in those receiving >14Gy. Similarly, Kondziolka and Lunsford et al reported significantly improved hearing preservation rates when the marginal dose was reduced from 16-20 to 12-14 Gy [52, 53].

Several studies suggest that the rate of hearing preservation is improved with fractionated stereotactic radiotherapy versus single-fraction SRS [46, 47, 60]. However, there is an issue of selection bias in that patients are frequently selected for fractionated treatment because their hearing is good. Meijer et al [54] found no significant difference in hearing preservation in acoustic neuroma patients treated with 4-5 fractions of 5Gy HFSRT vs. 10-12.5 Gy single-fraction SRS (61 vs. 75%), though trigeminal nerve preservation was significantly higher with HFSRT (98 vs. 92%.)

To minimize hearing loss while maintaining adequate tumor control, the QUANTEC authors recommend a marginal dose of 12-14Gy for single-fractions SRS [8, 61]. Though data for hypofractionated regimens is quite limited, the authors speculated that a total dose of 21-30 Gy, presumably delivered in three 7Gy, five 5Gy or ten 3Gy fractions, would provide an acceptable balance of hearing preservation and tumor control [8].

Table 3. Summary of published reports of hearing loss in patients receiving stereotactic radiosurgery of vestibular schwannomas.

Reference	Technique: number of patients	Treatment dose, Gy	Mean/Median follow-up, months (range)	Tumor control, %	Rate of hearing preservation, %
Hirsch , 1988 [48]	SRS: 126	18–25	56	86	26
Noren, 1993 [52]	SRS: 254 (NF2:61)	18–20 10–15	(12–204)	Unilateral: 94 NF2: 84	22 (Moderate vs. severe hearing loss: 55 vs 23%)
Foote, 1995 [47]	SRS: 36	16–20	(2.5–36)	100	42 +/- 17 at 2 yr
Flickinger , 1996 [46]	SRS: 273 (CT vs MRI planned: 118 vs 155)	12–20		CT: 44 MR: 32	CT: 39 MRI : 68
Kondziolka, 1998 [49]	SRS: 162	12–20 Mean: 16.6	(6-102) (60% > 60)	94	47–51
Lunsford , 1998 [50]	SRS: 402	Earlier in the series: 17 Later in the series: 12-14	36	93	Earlier in the series: 39 Later in the series: 68
Flickinger, 2001 [45]	SRS:190	11–18 Median:13	30 (Max: 80 mo)	91 at 5 yr	74
Andrews, 2001[43]	SRS: 64 (NF2: 5) FSRT: 46 (NF2: 10)	SRS:12 FSRT: 50 (2Gy/fx)	SRS: 30+/-17 SRT: 30+/-24	SRS: 98 SRT: 97	SRS: 33 SRT:81
Williams, 2002 [53]	HFSRT: 125	Tumors <3cm: 25/5 fxs Tumors ≥ 3cm: 30/10 fxs	22 (12-68)	100	64
Meijer, 2003 [51]	SRS:12 HFSRT: 25	SRS: 10-12 HFSRT: 20-25	25 (12–61)	–	HP: 91

SRS = Stereotactic radiosurgery; MRI = Magnetic resonance imagine based planning; CT = Computed tomography based planning, NF2 = Neurofibromatosis type 2; FSRT= conventionally fractionated stereotactic radiotherapy; H-FSRT = hypofractionated stereotactic radiotherapy

SPINAL CORD

Metastatic disease to the spine is a frequent indication for spinal radiotherapy, with an estimated 40% of all cancer patients ultimately developing vertebral body metastases[62].

Though rare, spinal cord injury, i.e., myelopathy, from radiation therapy can be severe, resulting in pain, parathesias, sensory deficits, paralysis, Brown-Sequard syndrome and bowel/bladder incontinence [63]. Radiation myelopathy should be reported using CTCAE v4.0 definitions for a grade 2 or higher myelitis [25]. Thus, asymptomatic changes in the cord detected radiographically or mild symptoms such as Babinski's sign or L'Hermitte syndrome are sub-acute transient symptoms and recover gradually with the use of steroid. Long-

term radiation myelopathy typically occurs between 6-36 months following completion of radiotherapy

The spinal cord consists of bundles of motor and sensory tracts, surrounded by the thecal sac, which is, in turn, encased by the spinal canal [64]. While the cord proper extends from the base of skull through the top of the lumbar spine, individual nerves continue down the spinal canal to the level of the pelvis. The cord and epidural disease are typically well-visualized on T2-weighted MRI [65] and the osseous spine accurately demarcated on CT scan. In evaluating spinal cord toxicity as a function of dose, it is essential to determine the volume of "cord" defined in the particular study, as the cord proper is segmented in some studies, the thecal sac and its contents in others and occasionally the entire spinal canal [66, 67].

Published reports [68-76] of radiation myelopathy from radiosurgery to the spine are summarized in Table 4. These studies include *de novo* radiosurgery alone, re-irradiation alone and combination of the two (mixed series.) Of the exactly 1400 cases of spinal radiosurgery presented in the published literature, there are only 12 reported instances of radiation-induced myelopathy for a crude rate of 0.8%. Since the survival is generally short for most of these patients, this is likely an under-estimate of the true rate of injury. Given the small number of cases of radiation-induced myelopathy, as well as the variation in the dosimetric parameters reported, it is impossible to construct a meaningful curve for the risk of myelopathy as a function of cord dose in spinal radiosurgery. In fact, most of the cases of myelopathy involved cord doses well within the range of doses *not* associated with myelopathy.

While it is tempting to use the curve for radiation-induced myelopathy versus 2Gy-equivalent dose derived by Schultheiss [77], these data were derived from patients treated primarily with conventionally fractionated, full-thickness cord irradiation. It is not clear if this data can be used to estimate toxicity rates at higher doses per fraction delivered only to the surface of the cord. Applying the Schultheiss data to the setting of spinal radiosurgery almost certainly overestimates the toxicity risk. For example, using the α/β ratio of 0.87Gy estimated from the data, the model yields an estimated risk of myelopathy of 0.8, 13.6, 50 and 73% for 12, 13, 13.7 and 14Gy delivered in a single fraction. In contrast, Ryu et al [72] found only one case of myelopathy in 86 patients treated with single-fraction spine radiosurgery at a mean cord D_{max} of 12.2Gy (+/- 2.5Gy standard deviations) and no cases in the subset of 39 lesions prescribed 18Gy and treated to a mean cord D_{max} of 13.8 Gy. Note that Medin et al's study of single-fraction irradiation of the swine spinal cord shows a steep dose response curve with a median effective D_{max} of 20Gy [78].

For irradiation of the osseous spine via single-fraction with SRS or HFSRT, a maximum cord dose of 13 Gy in a single fraction or 20 Gy in 3 fractions appears associated with a <1% risk of injury. At the same time, this risk is non-zero with radiosurgery and Sahgal et al recommend a *de novo* single-fraction maximum point dose to the thecal sac of 10Gy to avoid myelopathy [79]. RTOG protocol 0631, a study underway of radiosurgery in vertebral body metastases, specifies a cord D10 and D0.35cc of 10Gy and D_{max} of 14Gy for the involved spine. Establishing a viable model of dose/volume/outcome for spinal cord toxicity will require more data be collected; including detailed data on entire cohorts of patients treated with radiosurgery, not just those with myelopathy. Recommended dosimetric parameters to be collected might include parameters such as D_{max}, D1, D10, D50, D0.1cc, D0.35cc and D1cc and the volume of the involved segment of the spinal cord, as well as the prescribed total dose and dose fraction, the spinal level(s) involved, the portion of the vertebral body irradiated, the irradiation technique and patient clinical characteristics/demographics.

ISSUES & RECOMMENDATIONS FOR FUTURE STUDIES

1. Additional information regarding the shape and location of the dose-response curve for both tumor and normal tissue, are needed to help guide dose selection. The utility of models to "correct/consider" fraction size needs to be defined. For example, the applicability of the linear-quadratic model at high doses per fraction is controversial [80-85].
2. The mechanisms of tissue damage at high doses per fraction are not well understood. An understanding of the mechanism of injury might facilitate the generation and validation of a dose-response model. In particular, understanding the dose-response of the vascular endothelium and neuronal tissue, and the mechanisms underlying the observed changes, might be useful. For example, identification of a threshold dose for changes in the vascular endothelium [86] in normal neuronal tissues, and in tumors, may have significant implications for radiosurgery treatment and planning.
3. Rates of normal tissue toxicity are low in the practice of radiosurgery and it is unclear that sufficient numbers of cases will be available to model normal tissue complications. As suggested by Jackson et al [87], the radiosurgical community needs to develop a data pooling culture in which treatment and outcome data from multiple institutions can be shared,

Table 4. Summary of published reports of spinal cord doses and myelopathy in patients receiving spinal stereotactic radiosurgery or hypofractionated stereotactic radiotherapy.

Reference	Cases of Myelopathy/ Total Patients	Total Dose (Gy)	Dose/ fraction (Gy)	Dose to cord (Gy)	BED to Cord (Gy3)	Proportion of Patients Previously Irradiated to Involved Segment of Spine
Gibbs, 2009 [71]	6/1075	12.5-25	5-25	D_{max}: 3–28	Range: 24-121Gy3	>55%
		25	12.5	D_{max}: 26.2	D_{max}: 141	
		20	12.5	D_{max}: 29.9	D_{max}: 81	
		21	10.5	D_{max}: 19.2	D_{max}: 46	
		24	8	D_{max}: 13.9	D_{max}: 129	
		20	10	D_{max}: 10	D_{max}: 33	
		20	20	D_{max}: 8.5	D_{max}: 43	
Ryu, 2007 [74]	1/86*	<10-18	<10-18	Mean + s.d. D_{max}:12.2±2.5 D10:8.6±2.1 Maximum D_{max}:19.2 D10:13	Mean + s.d. D_{max}:62±4.6 D10:33±3.6 Maximum D_{max}:142 D10:69	0%
		18**	18	Mean + s.d. D_{max}:13.8±2.2 D10: 9.8±1.5	Mean + s.d. D_{max}: 77±3.8 D10: 42±2.3	
		16	16	D_{max}:14.8 D1: 13.0 D10: 9.6	D_{max}:88 D1:69 D10: 40	
Gwak, 2005 [72]	2/9	21-44	3-5	Median D_{max}:32.9 D25:11.0 Range D_{max}:11-37 D25: 1.2-24	Median D_{max}:106 D25:21 Range D_{max}:19-172 D25: 1-88	33%
		30	10	D_{max}: 35.2 D25: 15.5	D_{max}:172 D25: 42	
		33	11	D_{max}: 32.9 D25: 24.0	153 88	
Benzil, 2004 [68]	3/31	Median: 10 100 12 20	Median:5 50 12 5	Median: 6.0	12	Unknown
Sahgal, 2007 [76]	0/38	24	8	Median $D_{0.1cc}$: 10.5 D_{1cc}: 7.4	Median $D_{0.1cc}$: 23 D_{1cc}: 14	62%

Reference	Cases of Myelopathy/ Total Patients	Total Dose (Gy)	Dose/ fraction (Gy)	Dose to cord (Gy)	BED to Cord (Gy3)	Proportion of Patients Previously Irradiated to Involved Segment of Spine
Sahgal, 2007 [75]	0/16	21	7	Median D_{max}:20.9 D_{1cc}: 13.8 Range D_{max}:4.3-23 D_{1cc}: 2.8-19	Median D_{1cc}:22 Range D_{1cc}: 6-54	6%
Chang, 2008 [69]	0/63	30 pts:30 33 pts:27	30 pts: 6 33 pts: 9	30 pts: <10 33 pts:<9	30 pts: <16.7 33 pts: <18	56%
Gerzsten, 2009 [70]	0/50	19	19	Mean D_{max}:10 Range D_{max}: 6.5-13	Mean D_{max}: 21 Range D_{max}: 11-32	96%
Nelson, 2009 [73]	0/32	Median:18	Median: 7	Mean + s.d. D_{max}:14.4±2.3 D10:11.5±2.1 Maximum D_{max}:19.2 D10:15.2	Mean + s.d. D_{max}:46.0±13.2 D10:31.2±8.1 Maximum D_{max}:78.3 D10:46.5	58%

All patients within that institutional series are shown in normal font; myelopathy cases shown in bold italics.

*Patients surviving at least 1 year.

**Results for subset of 39 lesions treated at Henry Ford Hospital with a single 18Gy fraction.

† For the Benzil data (51), the cord dose was calculated assuming that the total dose was delivered in two fractions. While the cord dose for the patients developing myelopathy were not given in the paper, the total BED to the tumor for the 3 patients experiencing myelopathy was 53.3, 60 and ~167 Gy_3 versus <50Gy_3 for patients without myelopathy.

combined and analyzed, such that ample numbers of patients with and without toxicity can be studied to generate models. For such pooled data to be useful, a uniform and consistent method to report dose-volume-outcome data are needed.

4. Similarly, additional data on the impact of location on the dose-volume-outcome data are needed. Any pooled registry of clinical data should include detailed information regarding location.
5. If such pooled clinical data are not practical/feasible/useful, pre-clinical models might be needed to establish the mechanisms of normal tissue toxicity and determine the dose-response curve over a broad range of dose and fractionations. Even if this were done, clinical data would still be required to validate, at least to some degree, these data in human patients.
6. Understanding the underlying mechanisms and translating this knowledge into improved patient outcomes will require contributions from radiobiologists, molecular biologists, geneticists, radiation physicists, epidemiologists and clinicians [3].
7. As noted in the QUANTEC papers, the data on CNS toxicity in hypofractionated regimens using 4-8Gy per fraction is sparse. Two to five fractions of radiosurgery are often used in place of a single fraction with the intent of avoiding radiation-induced toxicity [65, 71, 73]. It would be valuable to have a validated model that permits dose effects to be extrapolated and interpolated, along the lines of iso-effect curves, as a function of biologically equivalent doses.
8. The efficacy of a radiosurgical treatment is as important as normal toxicity and these key issues are inextricably linked. All clinical studies of normal tissue toxicity in the CNS should report survival time, patterns of failure and symptom relief in addition to the detailed toxicity and adverse events. Clinicians and patients constantly require such information in order to select the most appropriate treatment. Clearly, one could avoid radiation-induced damage by selecting

a very low dose of radiation but this could severely compromise tumor kill, defeating the central purpose of radiation therapy.

9. Whether radiosurgery is employed to treat lesion in the CNS with curative or palliative intent, maintaining quality of life and/or neurocognition is always a key objective. In many cases, preservation of function and quality of life are the critical decision points in electing a stereotactic treatment.

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