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CLINICAL INVESTIGATION **Central Nervous System Tumor**

NORMAL TISSUE COMPLICATION PROBABILITY ESTIMATION BY THE LYMAN-KUTCHER-BURMAN METHOD DOES NOT ACCURATELY PREDICT SPINAL CORD TOLERANCE TO STEREOTACTIC RADIOSURGERY

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Purpose: To determine whether normal tissue complication probability (NTCP) analyses of the human spinal cord by use of the Lyman-Kutcher-Burman (LKB) model, supplemented by linear–quadratic modeling to account for the effect of fractionation, predict the risk of myelopathy from stereotactic radiosurgery (SRS).

Methods and Materials: From November 2001 to July 2008, 24 spinal hemangioblastomas in 17 patients were treated with SRS. Of the tumors, 17 received 1 fraction with a median dose of 20 Gy (range, 18–30 Gy) and 7 received 20 to 25 Gy in 2 or 3 sessions, with cord maximum doses of 22.7 Gy (range, 17.8–30.9 Gy) and 22.0 Gy (range, 20.2–26.6 Gy), respectively. By use of conventional values for α/β, volume parameter n, 50% complication probability dose TD_{50}, and inverse slope parameter m, a computationally simplified implementation of the LKB model was used to calculate the biologically equivalent uniform dose and NTCP for each treatment. Exploratory calculations were performed with alternate values of α/β and n.

Results: In this study 1 case (4%) of myelopathy occurred. The LKB model using radiobiological parameters from Emami and the logistic model with parameters from Schultheiss overestimated complication rates, predicting 13 complications (54%) and 18 complications (75%), respectively. An increase in the volume parameter (n), to assume greater parallel organization, improved the predictive value of the models. Maximum-likelihood LKB fitting of α/β and n yielded better predictions (0.7 complications), with $n = 0.023$ and $\alpha/\beta = 17.8$ Gy.

Conclusions: The spinal cord tolerance to the dosimetry of SRS is higher than predicted by the LKB model using any set of accepted parameters. Only a high α/β value in the LKB model and only a large volume effect in the logistic model with Schultheiss data could explain the low number of complications observed. This finding emphasizes that radiobiological models traditionally used to estimate spinal cord NTCP may not apply to the dosimetry of SRS. Further research with additional NTCP models is needed. © 2012 Elsevier Inc.

Hemangioblastoma, Spinal, SBRT, Radiosurgery, Spinal cord tolerance, NTCP.

INTRODUCTION

Spinal cord myelopathy is among the most feared radiotherapy complications. The risk of radiation myelopathy after conventionally fractionated radiotherapy is relatively well-established (1–5). However, spinal cord tolerance to the small-volume, high dose–per–fraction, heterogeneous dosimetry encountered in stereotactic radiosurgery (SRS) remains poorly understood. Although many spinal radiosurgical series have reported the safe and effective treatment of a small volume of spinal cord to high doses, the true tolerance of the cord is not well-established (6–13). Radiation myelopathy after SRS has been reported in only a handful of cases (11, 14), further impeding robust dosimetric predictive modeling. To allow for safe dose escalation, better understanding of the human spinal cord dose–volume tolerance for SRS is needed.

Normal tissue complication probability (NTCP) models quantitatively predict the risk of normal tissue complications based on radiation dose received and volume irradiated. The Lyman probit model allows estimation of complication probability from uniform partial-volume irradiation (15). The Kutcher-Burman reduction algorithm allows for reduction of nonuniform, complex dose distributions to a partial-volume uniform irradiation at a reference dose (16, 17) or, alternatively, to an effective dose to the entire volume that

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Conflict of interest: John R. Adler is currently employed by Varian Medical, whose business includes the manufacture of equipment used for therapeutic radiation. Steven D. Chang is a shareholder in Accuray, the manufacturer of the CyberKnife. Iris C. Gibbs has served on the Clinical Advisory Board and received honoraria for lectures from Accuray.

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would give the same NTCP (18). This formula for the effective dose was referred to as the equivalent uniform dose (EUD) by Niemierko (19). The application of the Kutcher-Burman reduction algorithm to the Lyman model (Lyman-Kutcher-Burman [LKB] model) is one of the most widely used NTCP estimation methods. To facilitate the use of the LKB model for treatment planning, a simplification of the LKB method was previously derived (20); this simplified formula has been shown to calculate normal tissue effects equivalently to the LKB model and was used for the LKB calculations presented here.

Although the LKB model has been shown to successfully predict complication rates for a variety of organs, including the rectum (21–26), liver (27), parotid gland (28–31), duodenum (32), and lung (31, 33), from nonuniform, partial-volume irradiation, it is not known how well this widely used model can predict the NTCP for spinal cord from the high-dose, small-volume radiation dosimetry encountered in SRS. We recently reported a detailed SRS dose–volume histogram (DVH) analysis for a series of patients with spinal cord hemangioblastoma (34), a relatively radioresistant, benign tumor. These patients received maximum point doses greatly exceeding published cord limits, albeit to a small median treatment volume; therefore this group represents an ideal cohort for NTCP modeling studies that explore the limits of spinal cord radiation tolerance. We have used the widely cited spinal cord radiobiological parameters of Emami *et al.* (3) and Schultheiss (5), together with the application of the linear–quadratic model for the effect of fractionation (35), to evaluate whether the LKB model may effectively estimate the complication probability of spinal SRS. To our knowledge, this is the first human study that attempts to evaluate high-dose, small-volume dosimetry of spinal SRS using NTCP modeling.

METHODS AND MATERIALS

Patient and tumor characteristics

Between July 1995 and June 2008, 31 pial-based spinal cord hemangioblastomas in 19 patients were treated with robotic SRS at Stanford University Medical Center (Stanford, CA). Treatment plans for 5 lesions generated on an older planning system were not fully retrievable for purposes of EUD calculation, and 1 patient with 2 treated lesions was lost to follow-up immediately after treatment; the remaining 17 patients with 24 lesions were analyzed. Tumors were situated within the cervical ($n = 12$), thoracic ($n = 11$), or lumbar/conus ($n = 1$) spinal cord. The median patient age at treatment was 29 years (range, 20–61 years). Seventeen tumors were treated with single-fraction SRS, with a median target dose of 20 Gy (range, 18–30 Gy), whereas three tumors received a 2-fraction regimen with a median dose of 22 Gy (range, 20–25 Gy) and four tumors were treated in 3 fractions with a target dose of 21 Gy. The overall median tumor volume was 150 mm^3 (range, 58–2,494 mm^3); the median tumor volume among single- and multiple-fraction treatments was 97 mm^3 (range, 58–2,494 mm^3) and 356 mm^3 (range, 95–2,363 mm^3), respectively. The spinal cord maximum dose (D_{max}) was 22.7 Gy (range, 17.8–30.9 Gy), 22.0 Gy (range, 21.3–26.6 Gy), and 21.3 Gy (range, 20.2–25.4 Gy) for single-fraction, 2-fraction, and 3-fraction regimens, respectively.

By use of methods described previously (34), multiple-fraction treatment doses were converted to a single-fraction biologically equivalent dose by the linear–quadratic (LQ) model and, for comparison purposes, the linear quadratic–linear model/universal survival curve, which hybridizes the LQ model with the multitarget model as described by Park *et al.* (36). A transition dose between the LQ model and multitarget model of 6.2 Gy was assumed, and α/β of 3 Gy was used. Patient and treatment characteristics, including comparison of calculated LQ and linear quadratic–linear median dose and range for fractionated treatments, are outlined in Table 1.

Treatment planning

The CyberKnife image-guided robotic radiosurgery system (Accuray, Sunnyvale, CA) was used for all treatments. Patient immobilization and treatment parameters have been described previously in detail (9). After immobilization, contrast-enhanced 1.25-mm-thick computed tomography (CT) scans and axial 2.0-mm-thick stereotactic magnetic resonance (MR) images were obtained through the region of interest. The CT and MR image sets were then fused on the treatment planning workstation, and the target

Table 1. Patient and treatment characteristics

	Data
Sex	
Male	9
Female	8
Age [median (range)] (y)	29 (20–61)
Genetic status	
VHL	12
Sporadic	5
Spinal level	
Cervical	12
Thoracic	11
Lumbar	1
Tumor volume [median (range)] (mm^3)	150 (58–2,494)
1 Session	97 (58–2,494)
2 Sessions	156 (95–221)
3 Sessions	716 (356–2,363)
Prescribed dose [median (range)] (Gy)	
1 Session	20 (18–30)
2 Sessions	22 (20–25)
3 Sessions	21 (21–21)
Prescription isodose line [median (range)] (%)	77 (68–86)
Modified conformity index [median (range)]	1.47 (1.08–2.60)
Spinal cord D_{max} [median (range)] (Gy)	
1 Session	22.7 (17.8–30.9)
2 Sessions	22.0 (21.3–26.6)
SF-BED (LQ model)	16.1 (15.6–19.4)
SF-BED (LQ-L model)	19.5 (18.8–24.1)
3 Sessions	21.3 (20.2–25.4)
SF-BED (LQ model)	13.2 (12.6–15.6)
SF-BED (LQ-L model)	16.3 (15.2–20.4)
Spinal cord V_{10} [median (range)] (mm^3)	
1 Session	454 (226–2,543)
2 Sessions	711 (114–1,216)
3 Sessions	926 (780–1,240)
Spinal cord D_{500} [median (range)] (Gy)	
1 Session	9.5 (5.3–22.5)
2 Sessions	12.8 (2.9–15.0)
3 Sessions	13.2 (12.3–14.1)

Abbreviations: VHL = von Hippel–Lindau disease; D_{max} = maximum dose; SF-BED = single-fraction biologically equivalent dose; LQ = linear–quadratic; LQ-L = linear quadratic–linear; V_{10} = volume receiving 10 Gy; D_{500} = dose (in gray) received by 500 mm^3.