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RADIATION
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Dose-Response Modeling of the Visual Pathway Tolerance to Single-Fraction and Hypofractionated Stereotactic Radiosurgery

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Patients with tumors adjacent to the optic nerves and chiasm are frequently not candidates for single-fraction stereotactic radiosurgery (SRS) due to concern for radiation-induced optic neuropathy. However, these patients have been successfully treated with hypofractionated SRS over 2-5 days, though dose constraints have not yet been well defined. We reviewed the literature on optic tolerance to radiation and constructed a dose-response model for visual pathway tolerance to SRS delivered in 1-5 fractions. We analyzed optic nerve and chiasm dose-volume histogram (DVH) data from perioptic tumors, defined as those within 3 mm of the optic nerves or chiasm, treated with SRS from 2000-2013 at our institution. Tumors with subsequent local progression were excluded from the primary analysis of vision outcome. A total of 262 evaluable cases (26 with malignant and 236 with benign tumors) with visual field and clinical outcomes were analyzed. Median patient follow-up was 37 months (range: 2-142 months). The median number of fractions was 3 (1 fraction $n = 47$, 2 fraction $n = 28$, 3 fraction $n = 111$, 4 fraction $n = 10$, and 5 fraction $n = 66$); doses were converted to 3-fraction equivalent doses with the linear quadratic model using $\alpha/\beta = 2$ Gy prior to modeling. Optic structure dose parameters analyzed included D_{min}, D_{median}, D_{mean}, D_{max}, $V_{30\ Gy}$, $V_{25\ Gy}$, $V_{20\ Gy}$, $V_{15\ Gy}$, $V_{10\ Gy}$, $V_{5\ Gy}$, $D_{50\%}$, $D_{10\%}$, $D_{5\%}$, $D_{1\%}$, $D_{1\ cc}$, $D_{0.50\ cc}$, $D_{0.25\ cc}$, $D_{0.20\ cc}$, $D_{0.10\ cc}$, $D_{0.05\ cc}$, $D_{0.03\ cc}$. From the plan DVHs, a maximum-likelihood parameter fitting of the probit dose-response model was performed using DVH Evaluator software. The 68% CIs, corresponding to one standard deviation, were calculated using the profile likelihood method. Of the 262 analyzed, 2 (0.8%) patients experienced common terminology criteria for adverse events grade 4 vision loss in one eye, defined as vision of 20/200 or worse in the affected eye. One of these patients had received 2 previous courses of radiotherapy to the optic structures. Both cases were meningiomas treated with 25 Gy in 5 fractions, with a 3-fraction equivalent optic nerve D_{max} of 19.2 and 22.2 Gy. Fitting these data to a probit dose-response model enabled risk estimates to be made for these previously unvalidated optic pathway constraints: the D_{max} limits of 12 Gy in 1 fraction from QUANTEC, 19.5 Gy in 3 fractions from Timmerman 2008, and

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Conflict of interest: none.
Presented in part at the Radiosurgery Society SRS/SBRT Annual Meeting, May 2014.

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http://dx.doi.org/10.1016/j.semradonc.2015.11.008

25 Gy in 5 fractions from AAPM Task Group 101 all had less than 1% risk. In 262 patients with perioptic tumors treated with SRS, we found a risk of optic complications of less than 1%. These data support previously unvalidated estimates as safe guidelines, which may in fact underestimate the tolerance of the optic structures, particularly in patients without prior radiation. Further investigation would refine the estimated normal tissue complication probability for SRS near the optic apparatus.
Semin Radiat Oncol 26:97-104

Stereotactic radiosurgery (SRS) is a noninvasive, highly accurate form of radiation therapy that is increasingly used to treat benign and malignant intracranial tumors with high rates of local control. Recent large studies of patients treated with SRS for pituitary adenomas and meningiomas have shown long-term disease control of over 95% with reduced toxicity as compared to traditional external beam radiation therapy (EBRT).[1,2] However, patients with tumors located near the optic nerves or optic chiasm (anterior optic apparatus) have been frequently excluded from SRS owing to concerns for visual toxicity. For tumors within 3 mm of the optic structures ("perioptic tumors"), single-fraction SRS risks vision loss either from radiation-induced optic neuropathy (RION) if the optic apparatus dose is too high, or from tumor progression if the tumor dose is too low to yield control.[3,4] Historically, the SRS maximum dose (D_{max}) limit to the optic pathway has been cited as 8 Gy in a single fraction. For single-fraction doses necessary to control benign tumors (13-16 Gy), a risk of blindness as high as 27% has been reported.[5] Given these potential risks of single-fraction SRS ("SRS"), we have typically treated these perioptic tumors with hypofractionated SRS ("fSRS") over 2-5 days, although evidence-based dose constraints for fSRS have not yet been reported. Here we summarize the literature on dose constraints for the optic structures and report our institutional experience with over 250 patients treated with single-fraction and hypofractionated SRS for perioptic tumors.

Optic Structure Tolerance to Radiation

Optic apparatus dose constraints have been best defined for conventionally fractionated EBRT. The Emami data for EBRT dose causing a 5% risk of toxicity at 5 years (TD 5/5) for the chiasm and optic nerves is 50 Gy, and the 50% risk tolerance dose (TD 50/5) is 65 Gy.[6] Of note, these estimates are for whole organ irradiation, and reports suggest they may be conservative, particularly in the setting of partial-organ dose. More recently, QUANTEC data estimates the risk of toxicity for optic nerve or chiasm maximum point dose (D_{max}) of <55 Gy at $<3\%$, for 55-60 Gy of 3%-7%, and for >60 Gy of $>7\%$-20%.[7] Among 131 patients treated with EBRT at the University of Florida, no RION occurred at maximum doses at or below 59 Gy. The 15-year risk of RION was 11% with doses above 60 Gy with dose fractions of less than 1.9 Gy, and 47% with doses above 60 Gy when fraction size was greater than or equal to 1.9 Gy.[8] Other studies provide normal tissue complication probability (NTCP) calculations for optic structures, including a report of 39 patients treated for advanced paranasal sinus tumors, of which 13 patients were treated without optic nerve or chiasm sparing. Of these 13 patients, 3 patients experienced moderate or severe vision loss, and all 3 with vision loss received maximum dose to the optic apparatus of at least 64 Gy.[9] Although hyperfractionation may reduce the risk of vision injury with EBRT, maximum dose to the optic apparatus best correlates with optic neuropathy.[10]

Single-Fraction SRS for Perioptic Tumors

Early Studies

Early studies of RION after SRS supported strict dose constraints for the optic structures. Among 62 patients treated with single-fraction SRS for cavernous sinus meningiomas, 17 who received an optic apparatus D_{max} of >8 Gy developed visual complications; a single-fraction optic apparatus limit of 8 Gy was proposed.[11] Another early report described 4 patients with RION after an SRS *D*max ranging from 7-14 Gy.[12] Leber et al[5] reported no cases of RION for a single-fraction dose of less than 10 Gy, but they reported a risk of 27% for 10-15 Gy and 78% for >15 Gy. Given these early reported complications, initial single-fraction SRS dose constraints for the optic apparatus were conservative at a D_{max} of less than 8 Gy.

Dose Escalation

Despite an early recommended optic apparatus D_{max} of 8 Gy, multiple groups subsequently reported favorable vision outcomes with higher single-fraction doses. At the University of Maryland, 20 patients received an average D_{max} of 9 Gy, with none experiencing RION with serial visual field testing.[13] In a report from Norway of 100 patients treated for cavernous sinus meningiomas, 1 patient, with a visual pathway D_{max} of 8.6 Gy, experienced RION, consistent with a 1% risk.[14] Mayo Clinic reported on 88 patients treated with SRS for skull base meningiomas, with no RION at a median D_{max} of 10 Gy (range: 1-16 Gy).[15] These investigators later reported a rate of 1.1% for patients receiving up to 12 Gy to the optic apparatus.[16] This series was later updated with a reported risk of RION of $<1\%$ at a maximum dose of <12 Gy.[17] In this