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Single and Multi-fraction Stereotactic Radiosurgery Dose Tolerances of the Optic Pathways

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Abstract

Purpose/Objective(s)—Dosimetric and clinical predictors of radiation-induced optic nerve/chiasm neuropathy (RION), after single-fraction stereotactic radiosurgery (SRS) or hypofractionated (2–5 fraction) radiosurgery (fSRS), were analyzed from pooled data that were extracted from published reports (PubMed indexed from 1990 to Jun-2015). This study was undertaken as part of the American Association of Physicists in Medicine Working Group on Stereotactic Body Radiotherapy, investigating normal tissue complication probability (NTCP) after hypofractionated radiation.

Materials/Methods—Eligible studies described dose delivered to optic nerve/chiasm and provided crude or actuarial toxicity risks, with visual endpoints (i.e. loss of visual acuity, alterations in visual fields, and/or blindness/complete vision loss). Studies of patients with optic nerve sheath tumors, optic nerve gliomas or ocular/uveal melanoma were excluded in order to

obviate direct tumor effects on visual outcomes, as were studies not specifying causes of vision loss (i.e. tumor progression vs. RION).

Results—Thirty-four studies (1,578 patients) were analyzed. Histologies included pituitary adenoma, cavernous sinus meningioma, craniopharyngioma and malignant skull base tumors. Prior resection (76% of patients) did not correlate with RION risk (p=0.66). Prior irradiation (6% of patients) was associated with a crude 10-fold increased RION risk vs. no prior radiotherapy. In patients with no prior radiotherapy receiving SRS/fSRS in 1 to 5-fractions, optic apparatus maximum point doses resulting in <1% RION risks include 10 Gy in 1 fraction, 20 Gy in 3 fractions and 25 Gy in 5 fractions. Omitting multi-fraction data (and thereby eliminating uncertainties associated with dose conversions), a single-fraction dose of 10 Gy was associated with a 1% RION risk. Insufficient details precluded modeling of NTCP risks after prior radiotherapy.

Conclusions—Optic apparatus NTCP and tolerance doses after single- and multi-fraction stereotactic radiosurgery are presented. Additional standardized dosimetric and toxicity reporting is needed to facilitate future pooled analyses and better define RION NTCP following SRS/fSRS.

SUMMARY:

Data were pooled from published reports; from this data, dosimetric and clinical predictors of radiation-induced optic nerve/chiasm injury (RION) after stereotactic radiosurgery in 1 to 5 fractions were analyzed. RION risks are low (<1%) in the modern era with optic apparatus maximum point doses <10 Gy in 1 fraction, 20 Gy in 3 fractions and 25 Gy in 5 fractions (in patients without prior radiotherapy). More standardized dosimetric and toxicity reporting is needed to facilitate future pooled analyses and better define RION NTCP.

1. CLINICAL SIGNIFICANCE

The optic nerve and optic chiasm transmit visual sensory information to the visual cortex. Radiation injury to the optic apparatus can cause diminished visual acuity, visual field deficits or vision loss, generally occurring within 3 years after radiation [20,48,77]. After single-fraction radiosurgery (SRS) or hypofractionated (2–5 fraction) radiosurgery (fSRS), radiation-induced optic neuropathy (RION) is relatively uncommon (~1–2% in studies published in the 2000s) owing to clinician's diligence in maintaining acceptable dose exposure to these critical structures. The accurate patient alignment coupled with sharp dose gradients of stereotactic techniques enables the optic apparatus dose exposure to be minimized. Tumors compressing the optic structures may themselves cause visual symptoms; such lesions may be better treated with surgical resection and/or conventionally fractionated radiotherapy. Peri-optic lesions that are within a few millimeters of the optic apparatus may be amenable to fSRS/SRS, although understanding the risk of optic nerve and chiasm injury is critical in making this determination.

2. ENDPOINTS

Injury to the optic nerve, optic chiasm, optic tracts or occipital cortex can result in visual symptoms. With conventionally fractionated radiotherapy, optic nerve toxicity has been attributed to ischemia-related vascular injury resulting in optic atrophy, and/or injury to

neuronal elements [60,77]. Injury to the glial cells and/or demyelination may also play a role in RION. With SRS/fSRS, the extent to which these processes contribute to RION is not well-characterized. While visual complications can also result from radiation injury to the lens, retina, or lacrimal glands, there are insufficient data on post-SRS/fSRS injury to these structures, as they are generally not in close proximity to most targets treated with SRS/fSRS. Post-SRS/fSRS injury to the occipital cortex may affect visual fields, though such visual loss is more relevant to an analysis of brain tolerance. Thus, this review will focus on RION.

Various endpoints can be used to evaluate visual impairment, including visual acuity, alterations in visual fields, and blindness/complete vision loss (unilateral or bilateral). Visual acuity endpoints can be quantified by the extent of decline or by decline below a threshold. Visual field testing is objective, but difficult to quantify in simple measures. Optic neuropathy can also be based upon objective fundoscopic findings. The Radiation Therapy Oncology Group /European Organization for Research and Treatment of Cancer, Late Effects in Normal Tissue/Subjective, Objective, Management, Analytic (RTOG/EORTC LENT SOMA) scale published in 1995 graded objective RION relative to the extent of optic nerve pallor observed on fundoscopic examination and symptomatic visual field loss, while symptomatic vision loss (not specific to RION) incorporated visual field loss and effect of vision loss on daily activities (Table 1) [2]. The Common Terminology Criteria for Adverse Events (CTCAE) version 3 [74] uses a generic toxicity scoring system (i.e. effect on daily activities) for optic nerve toxicity, while CTCAE version 4 [3] grades optic nerve toxicity based upon visual acuity and does not incorporate visual field loss (Table 1). In the papers included in this review, various endpoints and/or scoring systems were used (as described in Online Table 2), with most describing a decline in visual acuity or new/worsening visual field deficit as RION, and with some studies specifically using CTCAE criteria. In the studies that included patients with pre-treatment visual symptoms (e.g. from nerve compression), worsening of symptoms not attributable to tumor progression were typically scored as RION.

The toxicity scoring system used in any given analysis likely impacts the extent of the reported outcomes. For example, Leber et al. used a relatively broad definition of RION and reported the highest rate (23%) of events after SRS, with a median maximum optic apparatus doses of ~15 Gy. RION was reported as a decline in visual acuity, new or worsened visual field defect or increased latency of visual evoked potentials (VEP) [42]. The latter measure is unique to this study, and raises concern about over-reporting RION relative to other studies. However, the authors describe that altered VEPs represented the first sign of RION, and “thereafter, various degrees of visual field deficits became apparent, mostly combined with decreased visual acuity” [42]. It is unclear if any patient had altered VEP without change in visual acuity or visual field testing. In 5 patients, pre-existing visual deficits improved after SRS despite persistent abnormal VEPs after SRS; however, the authors do not specify if RION was scored in these patients. Nevertheless, the relatively high maximum optic apparatus doses (up to 24 Gy) in this study may account for the high rate of RION.

Toxicity reporting is dependent on the rigor and frequency of assessments (described in Online Table 2). The different endpoints used in different studies represent a limitation of these analyses. Studies that did not specifically describe toxicity endpoints and/or type and frequency of assessments used to assess visual function, were seemingly reporting subjective symptoms (i.e. what patients might describe at follow-up visits). Notably, more objective measures of altered visual acuity or visual fields might not be associated with symptoms severe enough for patients to report and therefore may be under-reported in these studies, thereby under-representing the frequency of RION.

3. CHALLENGES DEFINING VOLUMES

The optic apparatus includes the optic nerves (extending from the posterior globes to the chiasm), chiasm, and optic tracts (extending posteriorly from the chiasm into the cortex); the meninges of the optic nerves and chiasm cannot be readily distinguished with computerized tomography (CT) or magnetic resonance imaging (MRI). The optic nerves consist of intraocular, intraorbital, intracanicular, intracranial (from the optic foramen) and prechiasmatic components [18,50]. The optic chiasm is situated where the optic nerves converge at midline [18,50], superior to the sella turcica, behind the tubercle of the sella turcica, medially to the internal carotid arteries, and inferior to the 3rd ventricle [48,51,66]. In clinical practice, there is variability in how the optic apparatus is contoured; such heterogeneity could impact reported dosimetric tolerances.[65]

The optic nerves, chiasm and proximal tracts can be segmented independently or in concert. The delineations between optic nerves and chiasm and between the chiasm and optic tracts are not clearly visualized on MRI. The anterior-posterior extent of the chiasm is variable [51], and thus consistent delineation between these optic apparatus components is challenging. The European Society for Radiotherapy & Oncology Advisory Committee on Radiation Oncology Practice (ESTRO-ACROP) suggest, “for consistency” that “the anterior and posterior ‘limbs’ should extend 5 mm to include the start of the optic nerves anteriorly and optic tracts posteriorly” [57]. They also recommend that the optic nerve originate from the back of the globes, entering into the skull anterior and inferior to the anterior clinoid process. Both the QUANTEC authors and ESTRO-ACROP practice guidelines emphasize the need to have no gaps between the optic nerves and chiasm [48,57].

The optic apparatus is on the order of several millimeters in cranial-cephalad direction [48,50,51], necessitating thin slice CT and/or MRI to adequately visualize and contour. CT facilitates differentiating bone from nerve and tumor. Coronal images are particularly helpful in defining the superior/inferior extent of the optic apparatus. Tumor abutting or compressing the optic apparatus can make delineating the optic apparatus difficult. Potential sources of heterogeneity and error in published visual toxicity dose metrics include variability of expertise in segmenting the small optic apparatus volume, variability in image quality and scan slice thickness, and the rapid dose fall off with highly-conformal techniques.

4. REVIEW OF OUTCOMES DATA

As part of the American Association of Physicists in Medicine (AAPM) Working Group on Stereotactic Body Radiotherapy (WGSBRT), data were pooled from published reports to analyze dosimetric and clinical predictors of RION after SRS/fSRS. While different nomenclature has been used to describe multi-fraction SRS, the abbreviation fSRS is used in this manuscript, reflecting the 2006 (and re-affirmed in 2009) position statement from American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons, and the American Society for Radiation Oncology (ASTRO) defining intracranial radiosurgery as 5 or fewer fractions [1].

PubMed searches were performed for reports published from 1990 through June 2015 (the search criteria are detailed in the Online Appendix). Studies included in the analyses [4,6,8,10,13,16,19,24,27–29,31–34,38–40,42,44,49,53–56,58,61–63,69–71,73,75,76,78] reported visual endpoints after SRS/fSRS, as well as information about dose to the optic apparatus (also described as optic nerve, chiasm and/or anterior visual pathway), The optic apparatus dose must have been reported in patients (if any) who developed RION and in the study population (either explicitly reported, or able to be estimated). Studies of RION after conventionally-fractionated or >5-fraction hypofractionated stereotactic radiotherapy were omitted (unless a subset of 1–5 fraction SRS/fSRS patients were analyzed separately). Studies reporting visual outcomes for treatment of ocular/uveal melanoma were excluded as many of these patients have pre-existing visual deficits and are at risk for vision loss unrelated to optic apparatus injury (i.e. retina, lacrimal gland, lens). Similarly, data from patients with primary tumors involving the optic nerve (e.g. optic gliomas and nerve sheath tumors) or orbits were omitted. As progressive growth of peri-optic tumors can cause optic nerve dysfunction [68], studies that did not differentiate vision loss from tumor progression from vision loss without tumor progression were excluded. Case reports and series that lacked the detail needed to extract the necessary data were excluded.

Maximum point dose

Published studies have primarily used maximum point dose to the entire optic apparatus as the preferred dose metric in assessing RION risks, with point dose generally indicative of dose to a small volume (i.e. <0.035 cc as recommended by the AAPM TG101 report [7]). Maximum point dose (subsequently referred to here as “maximum dose”) seems logical (and simple) to use since RION can occur from focal injury to any part along the optic apparatus’ pathway. However, maximum dose can be planning system dependent, and more modern planning systems may offer more robust metrics (discussed in Section 10) that may prove advantageous in future studies.

The Mayo Clinic’s published experience represents the largest patient cohort studied for RION after SRS [40,53,62,63,71], with some overlap of patients between studies (i.e. some patients analyzed in more than one study) [40,62,71]. Their two most recent studies [40,63] were restricted to patients with no prior radiotherapy. Among >300 patients treated with SRS with no prior radiotherapy [40,63], in which the median maximum dose to the optic apparatus was 9.2 Gy in one study [63] and 10 Gy in another [40], 1 RION event occurred after a maximum dose of 12.8 Gy, suggesting a low risk of RION after optic apparatus

maximum doses <12 Gy. A ~1% to 1.5% rate of visual dysfunction was reported in three large (n=217, 199 and 137 patients) modern series [11,12,43], not included in these analyses since they did not report optic apparatus maximum dose in patients (n=2 in each study) with RION. The QUANTEC literature review found that the incidence of RION was negligible for SRS maximum doses to the optic structures below 8 Gy, and rising to 10% for maximum doses in the 12–15 Gy range [48]. Maximum doses of <8 Gy have been adopted by some institutions, and are considered safe [35].

While optic apparatus maximum doses >14–15 Gy are risky [41,42,53,73], a Japanese study reported no RION in 5 selected patients, followed for >3 years after receiving maximum optical apparatus doses of 14.2–15.2 Gy. In these patients, the optic apparatus volume receiving 10, 12, and 14 Gy or more was (on average) 25.5%, 12.5% and 5.7% respectively [37]. In another study, a patient developed a RION event after a slightly lower optic apparatus dose-volume exposure: 39.5% received 7.8 Gy and 0.93% received 14.8 Gy [29].

Two studies of 3–5 fraction fSRS (with 86–87% receiving 5-fraction fSRS in both studies) were published after our June 2015 cut-off. One reported optic nerve/chiasm maximum doses ranging from 2.4–32.0 Gy; with strict adherence to tolerance doses (which were not specified) no visual toxicity was reported [64]. In another study, worsening vision occurred in 10 of 143 patients after optic nerve/chiasm maximum doses ranging from 2.5–34.0 Gy (range of 4.0–32.0 Gy among those with worsening vision) [46]. There was no significant correlation between worsening vision and total or fractional maximum optic nerve or chiasm doses, though these maximum doses were not reported for the 7 patients with RION vs. 3 with worsening vision from progressive disease.

Dose-volume metrics

Maximum dose may not be the ideal metric. It is possible that there is some volume dependence and/or regional variation of susceptibility within and along the optic apparatus. Because the optic apparatus is small, data correlating RION risks with dose-volume metrics are limited. Several studies have reported that, given similar maximum doses, the mean dose to visual pathway structures was greater for patients who developed complications than for those who did not [17,36,47]. A recent Mayo Clinic study of 133 patients (266 “sides,” i.e. right and left) with parasellar tumors, none of whom developed RION after SRS, noted that the ipsilateral optic apparatus maximum dose exceeded 8, 10 and 12 Gy in 65%, 35% and 11% sides, respectively. For sides exceeding these maximum doses, the median volumes of optic apparatus receiving >8 Gy, 10 Gy, and 12 Gy are fairly small (15.8, 1.6, and 0.1 mm^3, respectively). The authors reported that the dose falls to 4–6 Gy within a “few” millimeters outside the prescription isodose line [63]. In one study, 3 of 47 patients with peri-optic meningomas developed visual changes (including diplopia) after SRS, but none classified as RION [6]. There was no association between optic apparatus maximum dose or volume receiving greater than 8 Gy or 10 Gy and visual toxicity risk. The understanding of potential correlations of RION risk with optic apparatus dose-volume metrics is currently incomplete.

5. FACTORS AFFECTING OUTCOMES

Radiation-related vision loss is multifactorial. RION might be exacerbated by comorbid conditions (i.e. vasculopathies, hypertension, diabetes) [15], although the current published data do not adequately address which clinico-pathologic factors may influence risks. It is also conceivable that tumor histology may impact risks, due to tumor microenvironment or anatomic location; these data are similarly lacking. Although prior surgical resection may contribute to RION [41], the likelihood of undergoing resection and the type of surgical resection are a reflection of tumor histology. For example, most patients treated with SRS/fSRS for pituitary adenomas had undergone prior trans-sphenoidal resection (Online Table 1). For meningiomas (particularly of the cavernous sinus), surgical resection is less commonly performed, and generally entails open craniotomy. In a study of 215 patients with meningioma, pituitary adenoma or craniopharyngioma, there was a non-statistically significant trend suggesting that prior surgical resection might increase the risk of RION ($p=0.19$; all 4 events occurred among the 141 patients who had undergone prior resection) [71]. Additionally prior radiotherapy was associated with significantly increased risks ($p=0.004$) of RION; 3 RION patients received prior 45.0–58.8 Gy external beam radiation (of whom one also received prior SRS with a maximum dose of 9 Gy to the optic nerve), and an additional 20 patients received prior external beam radiation with no subsequent RION.

Improved radiosurgery techniques over time might have led to reduced toxicity risks [2]. For example, the historic use of older planning software, planning with CT alone (versus CT with MRI co-registration), or use of MRI for planning without CT-MRI co-registration (i.e. overlaying isodose distribution on axial MR images) may have resulted in suboptimal dosimetry, and inaccurate calculation of RION risks, as described by Stafford et al. [71]. Most studies described whether or not MRI was used for planning (as described in Online Table 1); in older studies, MRI was often used “if needed,” for “some patients” or after a planning system upgrade, and not specifically analyzed as a potentially confounding variable.

Variations (and perhaps inaccuracies) in dose calculations [71], and other clinical factors, might influence observed outcomes and risks. For example, doses reported from different planning systems, or different versions of the same planning system, may vary, perhaps in the order of 10% [23], due to differences in dose calculation methods and grid sizes. Patients in different studies were treated with varying immobilization techniques and image-guidance capabilities (and thus with potential differences in the association between ‘planned’ and ‘delivered’ doses). Because of the multitude of technologic variables potentially affecting reported dose, year of SRS/fSRS treatment was chosen as a surrogate for technologic advancement as described below.

Pre-treatment visual symptoms and/or nerve compression/injury may affect the risk of injury, and the reported rate of injury. Interestingly, animal data suggests that, for a given SRS dose, optic nerves compressed by a balloon have a higher risk of RION [14]. In some studies, visual function in some patients improved after SRS/fSRS (Online Table 2). Most studies did not differentiate toxicity outcomes based upon pre-existing visual deficits. A

pretreatment visual deficit did not correlate with a greater or lesser risk of RION in one study that analyzed this potential effect [42].

6. MATHEMATICAL/BIOLOGICAL MODELS

Online Table 3 summarizes the visual toxicity events reported in the studies analyzed. Figure 1 summarizes the data, depicting a plot of crude risk of RION as a function of median maximum dose to the optical apparatus, computed as a single-fraction equivalent dose with alpha-beta ratio (α/β) of 1.6 Gy (from Jiang et al.) [36]. Figure 1A shows studies with all patients completing treatment prior to 1997 and Figure 1B shows more recent studies (as discussed below). Figure 1B (panel B) also shows the maximum optic apparatus doses associated with each reported RION event.

For the analysis of the impact of technology on the event rate, four of the six earliest studies had RION rates in excess of 5% among patients with no prior radiotherapy, but only one of the subsequent studies (with only 5 SRS patients) [29] had complication rates that high. Based on this observation and by examining the dates of accrual of each manuscript, studies were divided into those in which all patient accrual/treatment was complete prior to 1997 vs. those in which some or all patients were treated during or after 1997 (i.e. to represent a shift to more modern planning and delivery technologies). Admittedly, this segregation is somewhat arbitrary, and chosen to segregate those early studies with excessive rates of RION. Notably, the Leber et al. study [42], that employed the VEP endpoint, accrued patients from 1992–1994 and was therefore not used in the 1997+ model. The apparent lower rates of RION in the later cohort (Table 2) might be attributable to better technologies and/or a greater awareness of, and diligence in minimizing, RION risks in more recent decades. There was no significant effect of treatment delivery system on RION risk (Table 2). Among all studies, the median rate of resection was 76% (range: 0–100%) with no significant correlation with RION rate (p=0.66).

Among the studies that included some or all patients treated during or after 1997 (1997+ studies), accounting for patients analyzed in more than one study (Online Table 1 footnotes), the overall crude rate of RION with no prior radiation is <1% (9 of 1224), with no significant differences between SRS (9 of 959) and fSRS (1 of 265) (p=0.7, Fisher Exact test). The crude rate of RION with no prior radiation was 8.5% from studies in which all patients were treated before 1997 (first 6 rows in Online Tables). Omitting the study that included altered VEP as a criteria for RION (since altered VEP is perhaps too-sensitive of a measure of clinically-relevant injury), the crude rate was 3.6% and significantly greater than the <1% rate in the 1997+ studies (p=0.002, Fisher Exact test). Within the twenty-eight 1997+ studies, the crude rate of RION was 11% (7 of 61) among patients with radiation prior to SRS/fSRS, vs. <1% (9 of 1224) in those without prior radiotherapy (p<0.00001, Fisher Exact test).

Figure 2 shows the actuarial plot of the incidence of RION risk probability using the Kaplan-Meier method with time-to-toxicity for all studies and 1997+ studies among patients with no prior radiotherapy. The data in Figure 2 are stratified by optic apparatus maximum dose <12 Gy or ≥12 Gy single-fraction ($EQD2_{1.6}$=45.3 Gy). Lower RION risks are seen

after optic apparatus maximum doses of <12 Gy versus ≥12 Gy. Among cases with a ≥12 Gy maximum dose, RION risk probabilities are lower in the more modern 1997+ studies. It was not feasible to separately analyze patients with prior radiotherapy due to the limited number of patients, events, and details.

A dose response analysis was conducted using the probit NTCP model [45] as a function of the maximum dose delivered to the optical apparatus, using incidence rates with no prior radiotherapy, from 1997+ studies (Figure 3):

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-u^2}{2}} du$$

$$t = \frac{D - TD50}{m \cdot TD50}, \quad m = \frac{1}{\gamma_{50}\sqrt{2\pi}}$$

The responses were adjusted to sampling errors according to their binomial confidence limits using an inverse variance weighting approach (solid line). Confidence intervals were calculated using Agresti's approximation [5]. The dose resulting in 50% complication risk (TD50) was estimated to be $EQD2_{1.6}$=157.3 Gy (95% CI: 157.2–157.4) and gradient γ_{50} = 1.31 (95% CI: 1.30–1.32). The modeled tolerance doses for a 1%, 2% and 5% NTCP, in $EQD2_{1.6}$, and 1-, 3- and 5- fraction equivalent doses are summarized in Table 3. Common 1, 3 and 5 fraction regimens result in estimated NTCP risks of 0.4%, 1.1% and 1.0% after optic apparatus doses of 10 Gy in 1 fraction, 21 Gy in 3 fractions and 25 Gy in 5 fractions, respectively.

It is possible that uncertainties associated with the linear-quadratic conversion may under- or overestimate the calculated normal tissue $EQD2_{1.6}$ and/or single-fraction equivalent dose from 2–5 fraction fSRS regimens. The uncertainties in the value of α/β used for the optic apparatus can also affect calculated risks. For example, using an α/β value of 2.0 Gy instead of 1.6 Gy in the model lowers the estimated 1% NTCP doses to 11.4 Gy (from 12.1 Gy) in 1 fraction, 18.6 Gy (from 20.0 Gy) in 3 fractions and 23 Gy (from 25.0 Gy) in 5 fractions. To negate potential errors in equivalent dose conversion, an NTCP model was generated that omitted fSRS studies and used physical dose (Figure 3B). The predicted incidences are slightly higher, thus resulting in more conservative dose tolerances after SRS (Table 3, section B).

NTCP models omitting 2 events described as asymptomatic visual field loss in one paper [75], resulted in less conservative dose tolerances for symptomatic RION (data not shown). Asymptomatic visual field loss may be un/under-reported in other studies, albeit many describe routine visual field testing (Online Table 2). We favor the NTCP models incorporating all reported RION events because asymptomatic visual field loss does indeed reflect radiation-induced injury, which may be minimized by patient reporting and/or represent an exceptional circumstance in not being symptomatic.

It is noteworthy that, with a dose of 50 Gy in conventional fractionation ($EQD2_{1.6}$ =50 Gy), the estimated incidence of RION is “near zero” and increases to >3% beyond 55 Gy [1], which represents ~1–2% risk in our models (Table 3).

Parameters for Modeling:

While the NTCP risks from our model (Figure 3) seem reasonable for the commonly accepted safe dose-fractionation schemes, it must be recognized that:

- There are uncertainties in the data used for the NTCP curves, reflected in the error bars and confidence bands in Figure 3.
- There are uncertainties in the α/β value of 1.6 Gy used for equivalent dose calculations [36,48], although this uncertainty was negated in the NTCP models restricted to single-fraction SRS (Table 3B and Figure 3B). With such low incidence of RION events, accurate determination of α/β was not feasible in our analyses.
- The biological validity of the EQD2/BED conversions are uncertain [59], particularly when applied to NTCP [21,22] after the high fractional doses with SRS/fSRS [21].
- There are limited data in the higher dose range (i.e. single-fraction >13 Gy, $EQD2_{1.6}$>52 Gy).
- RION events reportedly occur as late as >6–7 years after SRS/fSRS (Online Table 3, Figure 2), which is longer than the median follow-up time (Online Table 3) of most studies, raising the possibility of the NTCP model underestimating risks.
- Our NTCP calculations do not account for the magnitude of toxicity, raising the possibility that there are differences in the extent of injuries occurring at lower doses.
- The NTCP model does not take into account variations in the definition and contouring of the optic apparatus between practitioners, nor differences in the resolution and accuracy of imaging
- The NTCP model is based upon studies which used a variety of treatment planning and delivery methods.
- The NTCP model did not account for maximum ‘point volume’ (described below in section 10), as these data were not available from published studies.

7. SPECIAL SITUATIONS

Re-irradiation:

Based on our pooled analysis, patients with prior radiotherapy appear to be at a greater risk of RION after SRS/fSRS (Figure 1B), with a >10-fold increase in crude rate. However, more accurate determination of the magnitude of the increased risk from prior radiotherapy is limited by the small number of reported events and the multitude of variables affecting

RION risk. Details such as the impact of prior dose(s)/dose fractionation, time interval between radiation courses, and age at time of initial radiotherapy are unknown. The studies reporting RION events after prior radiotherapy did not separately report the range and median optic apparatus maximum dose among those who did versus did not undergo prior radiotherapy. Notably, all RION events after prior radiotherapy occurred after SRS doses ≤9 Gy, and all were reported in 1997+ studies. Presumably, few patients received SRS doses in excess of 10 Gy to the optic apparatus after prior radiotherapy. The use of fractionation with SRS can facilitate delivery of single-fraction equivalent optic apparatus maximum doses >10 Gy in the re-irradiation setting [49], but the data are sparse and caution is advisable. Given the large number of patients that are seen for consideration of radiosurgery who have had prior radiation, these are important issues and should be addressed in future studies.

Surgical resection:

While prior resection was not significant for RION in our analyses, one can speculate that surgical manipulation of the optic apparatus (perhaps causing microvascular devascularization) would increase susceptibility to RION, with the critical variable not being a simple binary variable (yes/no) of prior surgery but rather whether or not there was any prior surgical injury (occult or symptomatic) to the optic apparatus. Other possible prognostic factors would include the number of prior surgeries, surgery for compressing lesions and types of resection(s).

Pediatric patients:

Our analyses did not specifically address RION risks in the pediatric population due to insufficient data.

8. RECOMMENDED DOSE/VOLUME OBJECTIVES

Dose Limits:

Recognizing the limitations in NTCP modeling (discussed above), an optic apparatus maximum dose limit associated with a clinically reasonable (for most patients) RION risk among patients with no prior radiotherapy is no more than: 10 Gy in 1 fraction, 20 Gy in 3 fractions, and 25 Gy in 5 fractions. These values represent doses calculated for 1% NTCP risks (Table 3A and 3B), and are similar to recommendations from the AAPM TG101 report [7] and others [25,52,72]. The TG101 report suggested maximum point (defined as 0.035 cc or less) doses of less than 10 Gy in 1 fraction, 17.4 Gy in 3 fractions, and 25 Gy in 5 fractions. For a 0.2 cc threshold volume, the TG101 report suggested thresholds of less than 8 Gy in 1 fraction, 15.3 Gy in 3 fractions and 23 Gy in 5 fractions [7]. A recent study of 262 patients treated at Stanford University also found less than 1% toxicity risk with optic apparatus maximum point doses of 10 Gy in 1 fraction, 20 Gy in 3 fractions and 25 Gy in 5 fractions [30]. This study, which was not included in our model since the manuscript was not yet published at the time of our analysis, serves as an independent confirmation of our risk estimates.

For patients with prior radiotherapy, our data were too limited to model NTCP risks, and therefore we make no dose recommendations. The RION risks after prior radiotherapy are

likely affected by prior dose and fractionation, as well as duration between radiotherapy courses. Not accounting for these factors, this review suggests a crude ~10-fold increase RION risk after prior radiotherapy, with all RION events occurring after SRS maximum doses ≤9 Gy. Thus, for patients with prior radiotherapy, a >10% RION risk is anticipated after 10 Gy in 1 fraction, 20 Gy in 3 fractions, and 25 Gy in 5 fractions, albeit not accounting for dose-time factors. Clinicians considering SRS/fSRS for re-irradiation of peri-optic tumors should appropriately consent patients for such an increased risk.

When making treatment decisions of peri-optic lesions, the risks of not treating or under-treating the target(s) are weighed against RION risks (which can be negligible, but never zero after radiotherapeutic doses to the optic apparatus). For benign disease, NTCP risks should be minimized, and in some situations (such as tumor compressing or surrounding the optic apparatus) conventionally fractionated radiation may be the best approach to maximize therapeutic dose while minimizing potentially toxic dose exposure.

9. FUTURE STUDIES

Given the historical basis for limiting the optic apparatus dose to < 8–12 Gy in 1 fraction, and the reluctance of radiation oncologists to escalate the dose beyond these levels, future prospective studies to better understand RION risks from SRS are unlikely. More long-term data are needed from those institutions that were earlier adopters of fSRS, as this approach seems safe and feasible for tumors closely approaching the optic apparatus. The impact of prior surgery and prior radiotherapy on RION risks needs to be better characterized, particularly with respect to surgical manipulation of the nerve, prior radiotherapy dose, and time course between prior treatments and SRS/fSRS. There is also a poor understanding of the effect (if any) of dose on duration to onset of RION symptoms. While it is fortunate that RION is relatively uncommon, the limited number of events may preclude the possibility of accurately modeling dose-response relationships. The collaborative ASTRO and AANS SRS registry [67] may facilitate such analyses.

10. REPORTING STANDARDS

To date, all of the RION data come from descriptive studies reporting maximum doses to the optic apparatus. It is noteworthy that these maximum doses are derived from the calculated radiation plan. Putting the aforementioned dosimetric uncertainties aside, a steep dose gradient coupled with positional uncertainties (i.e. uncertainties related to image slice thickness and voxel size, image co-registration, patient set-up, isocenter accuracy), albeit small with stereotactic radiation, may underestimate the maximum dose resulting in toxicity. In other words, RION risks may reflect the calculated maximum dose in conjunction with the likelihood of a positional error in a direction resulting in a higher-than-calculated maximum dose. The reverse situation (in which a positional error results in a lower maximum normal tissue dose than suggested by the radiation plan) can also occur. Generally, setup uncertainties are on the order of 1+ mm, and in high dose-gradient regions, this may make a difference of several Gy in the delivered maximum dose.

Delineating an optic apparatus-planning organ at risk volume (PRV, e.g. with a volumetric expansion ~1–2 mm) might better reflect the ‘potential 3-dimensional space’ occupied by the nerves. Dose characteristics to such an expanded volume (not considered in any of the analyzed reports) might be interesting to consider in future dose-volume outcome studies. Likely, some practitioners are overly generous in delineating the optic apparatus in an effort to minimize the likelihood of RION. Regardless of how the optic apparatus avoidance structure is defined, accurate and reproducible delineation is critical (as described in section 3).

Notably, the calculated ‘point’ doses represent a dose to a volume, and not to a mathematic point which has no size. The point dose will be affected by: (1) the grid size [26,47] used by the algorithm that generates the dose volume histogram, and (2) the discrete ‘point’ volume (voxel or small volume) that is used. The AAPM TG101 recommended ‘point volume’ of 0.035 cc is volume-equivalent to a ~3.3 mm cube or ~4 mm diameter sphere (albeit the dose to this volume would be complex-shaped); perhaps for small structures, such as the optic apparatus, doses to smaller volumes should also be considered.

Symptomatic patients should undergo baseline (prior to SRS/fSRS) visual field testing and visual acuity assessment. Similar testing should be offered to patients who develop new or worsening visual symptoms, and RION should be scored using standardized toxicity criteria. The CTCAE version 4 quantifies diminished visual acuity, but does not specifically address visual field deficits. Conversely, the objective RTOG/EORTC LENT SOMA scale for “optic nerve” addresses visual field defects, but not visual acuity, although there is a separate RTOG/EORTC LENT SOMA objective grading scale for “visual acuity” (not shown in Table 1). Thus, we suggest that patients with RION be scored on 2 separate scales: either (1) CTCAE version 4 and RTOG/EORTC LENT SOMA scales, or (2) RTOG/EORTC LENT SOMA scales for “optic nerve” and “visual acuity”. While double scoring of toxicity can be cumbersome, since clinical toxicity is not very common this is a reasonable approach that will not require too much effort.

Standardized reporting for SRS is needed, and reportedly forthcoming [9]. Ideally the details should be reported per treatment for all patients whether they had toxicity or not, so the denominator of all cases would be known. With respect to RION reporting, we propose recording and reporting the following information:

- Details of prior radiotherapy
  - Dose to optic apparatus
  - Fractionation
  - Time interval prior to SRS/fSRS
- Details of prior surgery/ies
  - Surgical technique
  - Time interval prior to SRS/fSRS
- Details of tumor/target

  - Tumor type/histology
  - Tumor contact with or compression of optic apparatus
- Baseline visual function
  - Visual acuity
  - Visual field deficits
- Description of how optic apparatus was delineated
  - MRI sequence(s)
  - CT and MR image slice thickness
  - Use of CT-MRI co-registration (a notably important factor after resection, as post-operative changes can potentially affect normal anatomy)
  - Distal extent of optic tracts - measured from center of chiasm
  - PRV margin (if any)
  - Volume of optic apparatus
- Description of how optic apparatus was compartmentalized
  - i.e. was one optic apparatus delineated or were the optic nerves, chiasm and tracts delineated separately (and in what criteria were used to delineate these components). We recommend the approach described in ESTRO-ACROP consensus guidelines [57] as described in section 3.
- Treatment planning parameters *
  - Planning software (with version)
  - Dose calculation algorithms
  - Dose calculation grid size
- Methods of treatment set-up and positional verification
  - systematic assessment of uncertainties in the treatment process
- Optic apparatus dose metrics and/or DVH *
  - Maximum point dose
    - ‘point volume’ (AAPM TG101 [7] recommends 0.035 cc)
  - “Small-volume” (i.e. 0.2 cc) maximum dose
  - Mean dose
- Duration and frequency of follow-up

*The dose gradient across the optic apparatus may be relevant to RION risk, although difficult to characterize in a consistent manner. For example, target prescriptions to the 50% isodose line (common with gamma knife) vs 80% (common with LINAC) would likely lead to different dose gradients across neighboring normal tissues.

- Control of tumor
- Post-radiotherapy visual assessment
  - Timing of assessment (from SRS/fSRS)
  - Subjective scoring of vision (i.e. Functional Assessment of Cancer Therapy (FACT) questionnaires)
  - Visual acuity
  - Visual field testing
- RION toxicity grade
  - CTC-AE version 4
  - RTOG LENT-SOMA
  - Timing of onset of RION (from SRS/fSRS)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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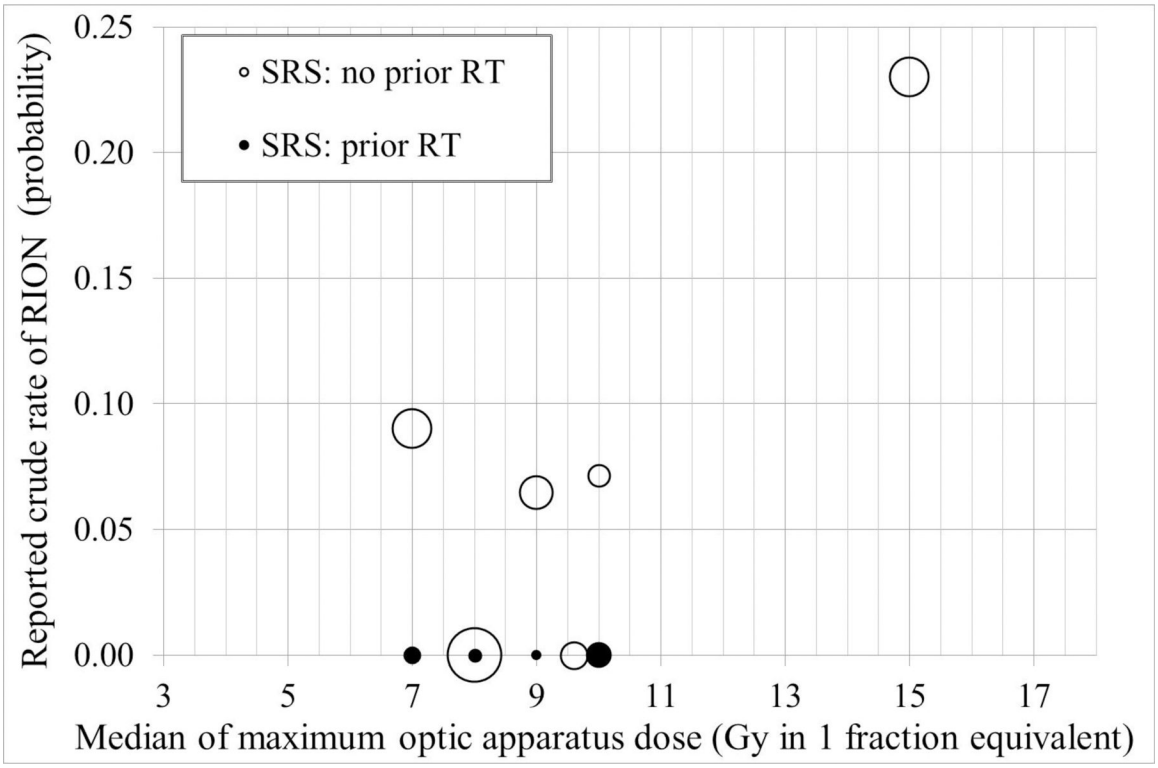
A



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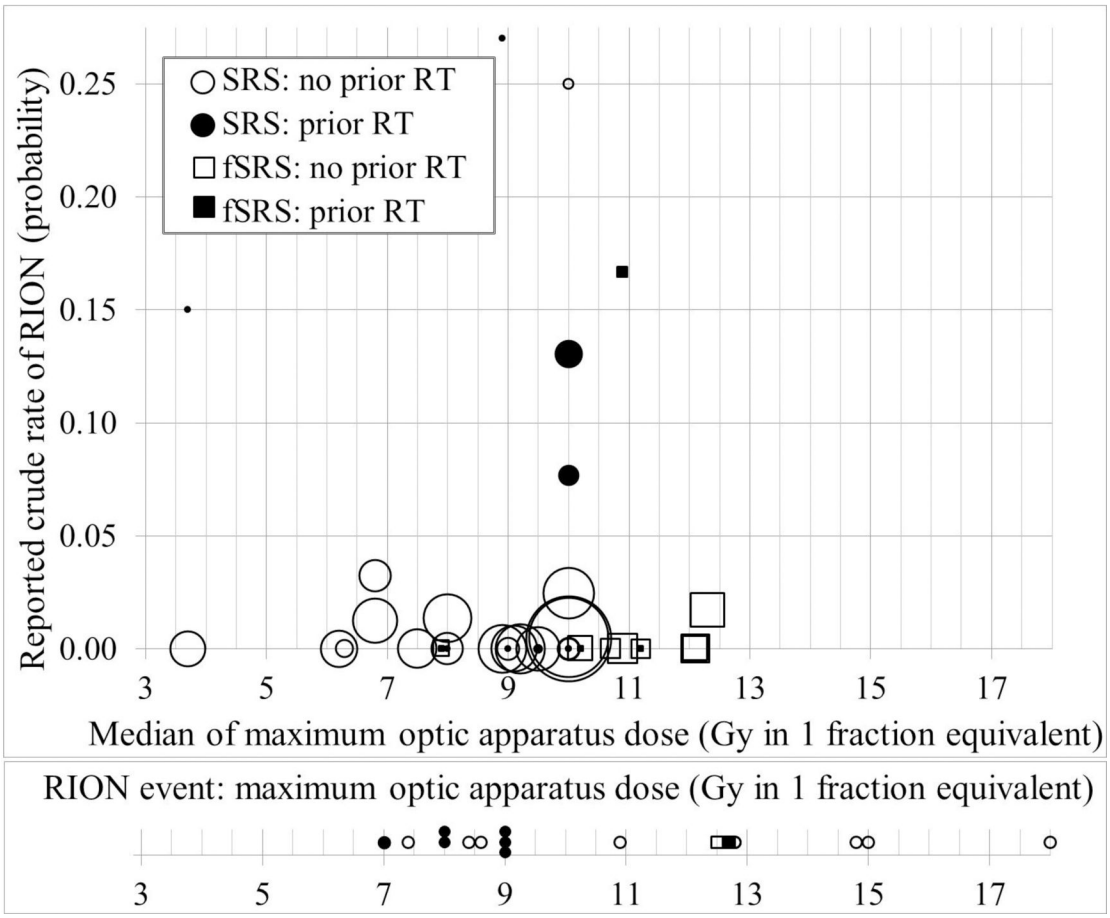


Figure 1.

Summary of radiation-induced optic neuropathy (RION) data. The reported crude rate of RION is plotted (as a probability) is plotted against the reported optic nerve/chiasm median maximum dose for studies with all patients completing treatment prior to 1997 (A); and for studies where some or all patients were treated during or after 1997 (B). The size of each data point reflects the number of patients analyzed (not a reflection of the error or uncertainty of data). In panel B, also shown below the x-axis are the maximum doses resulting in RION; each data point (square or round as described below) represents 1 event. Patients who had received no prior radiotherapy (hollow shapes) are shown separately from patients who had received prior radiotherapy (solid shapes), as are patients treated with single-fraction radiosurgery (SRS; circles) and patients treated with 2–5 fraction radiosurgery (fSRS; squares).

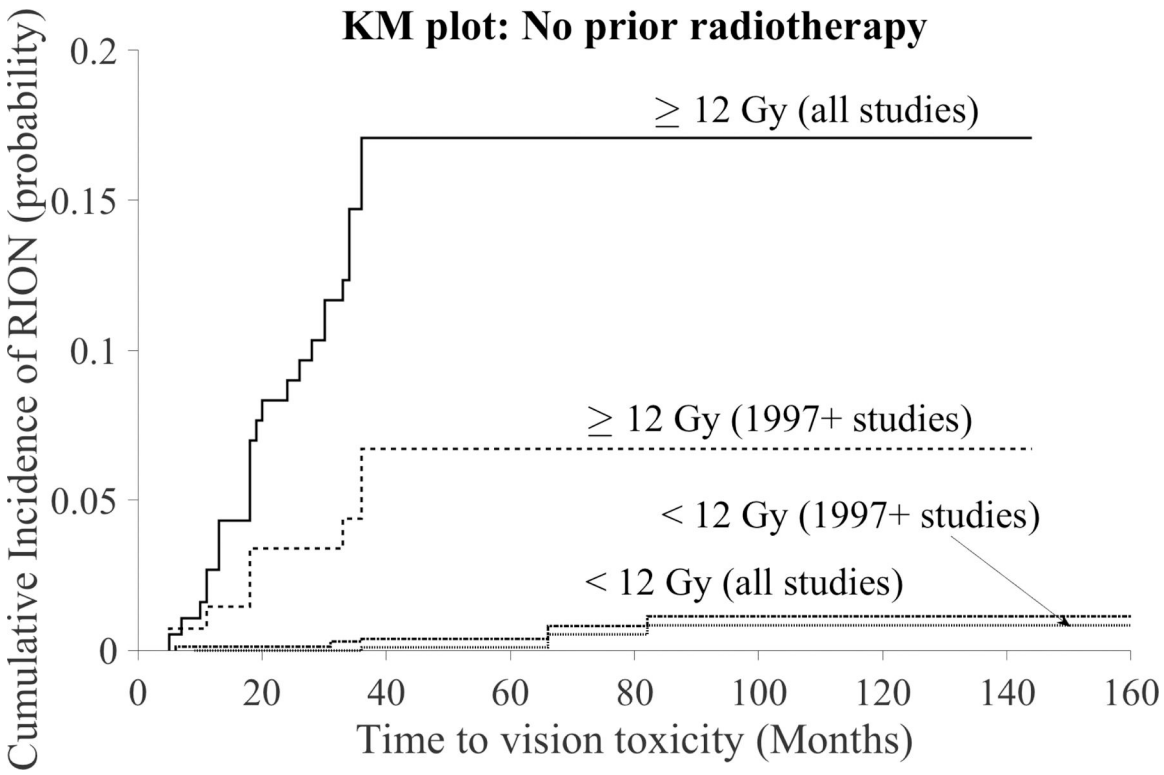
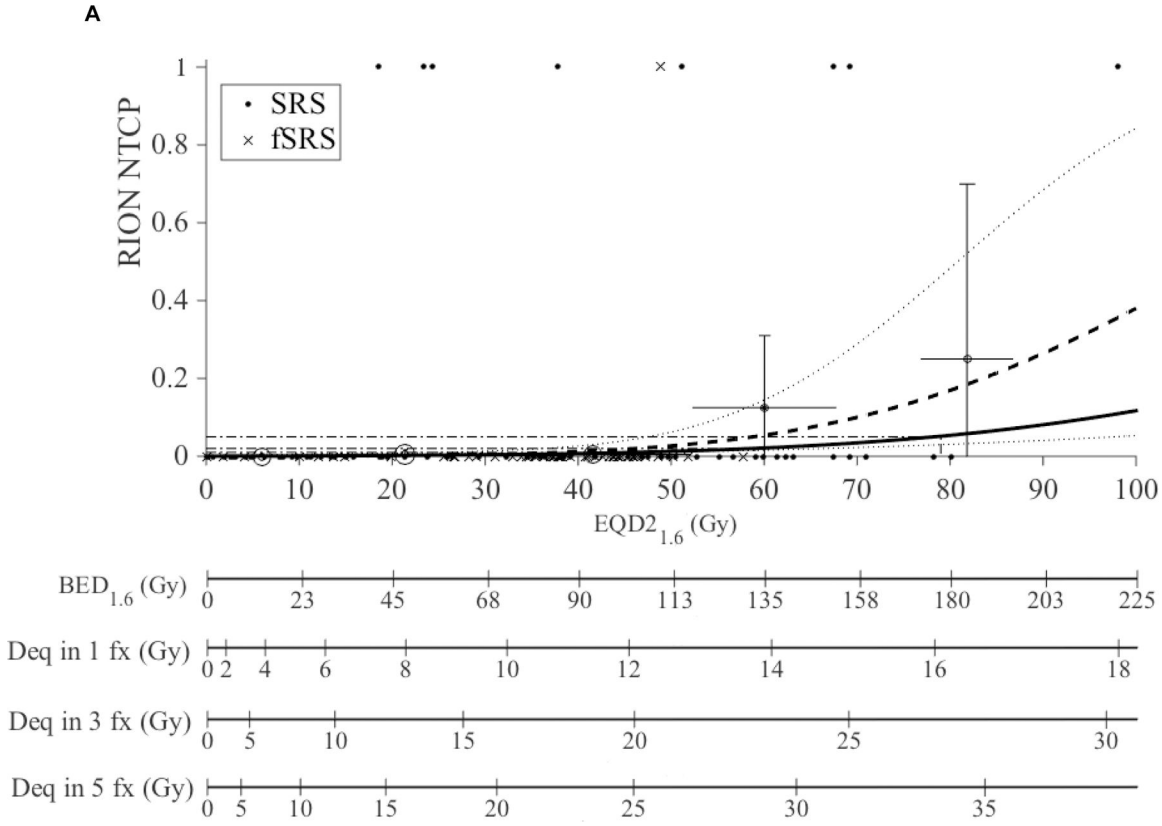


Figure 2.

Kaplan-Meier (KM) analysis of the cumulative probabilities of RION among patients with no prior radiotherapy. KM analyses used follow-up data when available and median optic apparatus maximum dose, with events scored at the time of occurrence, and at the doses which events occurred. When no detailed actuarial data was available, the timings of all complications in the cohort were assigned as the median length of follow-up." (Online Table 3). Separate KM curves are shown for optic apparatus maximum single-fraction equivalent doses of <12 Gy and ≥12 Gy ($EQD2_{1.6}$=45.3 Gy, depicted as "12 Gy" in figure), grouped by inclusion of all studies or only studies which included some or all patients treated during or after 1997 (1997+ studies).



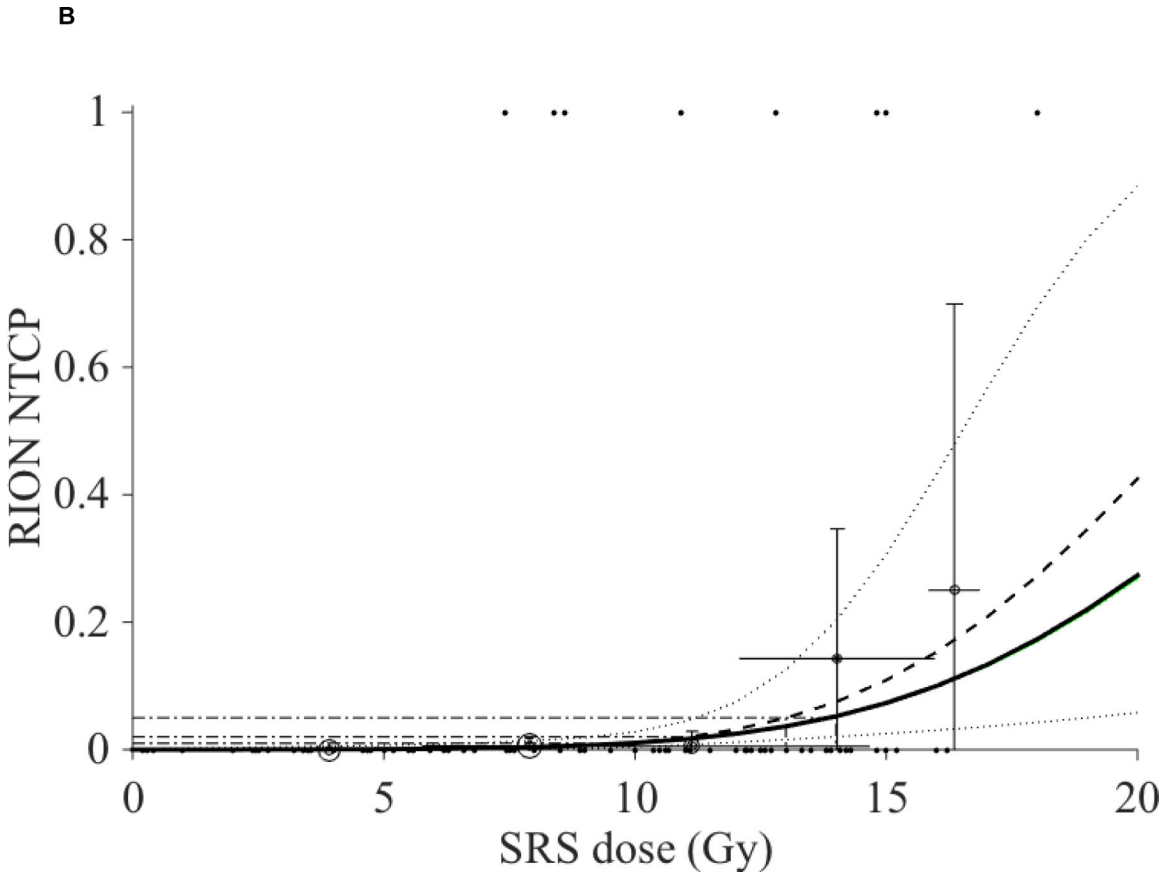


Figure 3.

Results of the model fit to the available data from the 1997+ studies (those including some or all patients treated during or after 1997), and with no prior radiotherapy. Dose-response for radiation-induced optic neuropathy estimated using the probit model. (A) Patients treated with single-fraction stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiosurgery (fSRS). (B) Only patients treated with a single-fraction stereotactic radiosurgery (SRS). Maximum optic apparatus doses resulting in RION in individual patients were identified in all studies that reported RION events (Figure 1 and Online Table 3). For patients not developing RION, maximum doses were extracted in the most granular groupings possible (i.e. individual patients vs. patients grouped by maximum dose vs. median/mean of the maximum dose for the entire study cohort). This data was binned into 5 dose groups, with NTCP calculated for each binned group, and are depicted as the 5 data points with associated error bars. Confidence intervals for the NTCP curve were calculated using Agresti's approximation.

While the maximum doses were reported for all of the cases with complications, the doses reported for most of the cases without complications were only provided as medians or quartiles. To deal with this uncertainty, two methods of calculating a dose response were used. The inverse variance weighting method groups patients together and weights these data points by patient numbers in each group. This loses resolution in dose for the complications. The maximum likelihood approach method weights the response using individual patient data when available. However, when a dataset only provides the median

dose of the non-complications cases, but the spread of non-complications cases includes higher doses in the vicinity of the complications cases, the maximum likelihood algorithm has no way to account for this. Consequently the complications may be overemphasized and a more conservative dose response results. The dashed (more superior) curve depicts direct likelihood fitting; dotted lines show the 95% confidence band reflecting the uncertainty in the data. The solid (more inferior) curve depicts the adjusted model, using effective inverse variance weighting.

For illustrative purposes, the maximum doses resulting in RION events are shown as 100% NTCP points, while the points at 0% NTCP points reflect those patients who did not experience RION. The plot shows the 1%, 2% and 5% NTCP risks (from the model adjusted for using effective inverse variance weighting). In (A) these 1%, 2% and 5% NTCP risks are shown as a function of biologically effective dose ($EQD2_{1.6}$; equivalent dose at 2 Gy/fraction assuming α/β=1.6 Gy), the corresponding biologically equivalent dose ($BED_{1.6}$), and 1, 3, 5 fractions (Fx) equivalent doses (Deq; also computed assuming α/β=1.6 Gy).

Table 1

Scoring systems for optic nerve and optic chiasm toxicity

Scoring system	Criteria
RTOG/EORTC LENT SOMA subjective (vision)	
Grade 0	None
Grade 1	Indistinct color vision
Grade 2	Blurred vision, loss of color vision
Grade 3	Severe loss of vision, symptomatic visual field defect with decrease in central vision, some ability to perform ADL
Grade 4	Blind, inability to perform ADL
RTOG/EORTC LENT SOMA objective (optic nerve)	
Grade 0	None
Grade 1	Afferent pupillary defect with normal-appearing nerve
Grade 2	<1/4 pallor with asymptomatic visual field defect
Grade 3	>1/4 pallor or central scotoma
Grade 4	Profound optic atrophy, complete blindness
CTCAE version 3 (cranial nerve II neuropathy)	
Grade 0	None
Grade 1	Asymptomatic, detected on examination/testing only
Grade 2	Symptomatic, not interfering with ADL.
Grade 3	Symptomatic, interfering with ADL
Grade 4	Life-threatening; disabling
CTCAE version 4 (optic nerve disorder)	
Grade 0	None
Grade 1	Asymptomatic; clinical or diagnostic observations only
Grade 2	Limiting vision of the affected eye (20/40 or better)
Grade 3	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)
Grade 4	Blindness (20/200 or worse) in the affected eye *

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organization for Research and Treatment of Cancer; LENT = Late Effects in Normal Tissue; RTOG = Radiation Therapy Oncology Group; SOMA = Subjective, Objective, Management, Analytic.

* Proposed for version 5: Best corrected visual acuity of 20/200 or worse in the affected eye.

Table 2

Analysis of accrual year and technology confounding effects on event rate

Factor	All patients			Patients with no prior radiation therapy		
	Number	Rate (%)	*P*	Number	Rate (%)*	*P*
Year (accrual ends)						
<1997	293	8.33 ± 5.15	.023	259	9.07±5.05	.019
≥1997	1285	1.53 ± 0.78		1224	1.47± 0.96	
Radiosurgery planning/delivery system*						
L1NAC	96	6.67 ± 6.67		90	8.33 ± 8.33	
Gamma Knife	1315	2.54 ± 1.44	.42	1234	2.54 ± 1.46	.31
Cyber Knife	167	0.74 ± 0.46		160	0.34 ± 0.34	
Radiosurgery planning/delivery system (for year of accrual of ≥1997 only)*						
L1NAC	68	6.67 ± 6.67		66	8.33 ± 8.33	
Gamma Knife	1050	0.89 ± 0.31	.97	998	0.63 ± 0.27	.79
Cyber Knife	167	0.74 ± 0.46		160	0.34 ± 0.34	

Abbreviation: LINAC = linear accelerator.

*High standard errors reflect small patient numbers.

Table 3

Calculated NTCP risk of radiation-induced optic nerve/chiasm toxicity after SKS/fSKS with no prior radiation therapy

NTCP model	$EQD2_{1.6}$ (Gy)	1-Fraction SRS (Gy)	3-Fraction fSRS (Gy)	5-Fraction fSRS (Gy)
NTCP model including all studies				
1% risk	46.0	12.1	20.0	25.1
2% risk	59.1	13.8	23.0	28.9
5% risk	79.0	16.1	26.9	33.9
NTCP model including only single-fraction SRS studies				
1% risk	32.2	10.0	-	-
2% risk	39.2	11.1	-	-
5% risk	60.7	14.0	-	-

Abbreviations: $EQD2_{1.6}$ = equivalent dose at 2 Gy/fraction assuming α/β = 1.6 Gy; fSRS = hypofractionated stereotactic radiosurgery; NTCP = normal tissue complication probability; SRS = single-fraction stereotactic radiosurgery.