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RADIATION DOSE–VOLUME EFFECTS OF OPTIC NERVES AND CHIASM

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Publications relating radiation toxicity of the optic nerves and chiasm to quantitative dose and dose–volume measures were reviewed. Few studies have adequate data for dose–volume outcome modeling. The risk of toxicity increased markedly at doses >60 Gy at ≈1.8 Gy/fraction and at >12 Gy for single-fraction radiosurgery. The evidence is strong that radiation tolerance is increased with a reduction in the dose per fraction. Models of threshold tolerance were examined. © 2010 Elsevier Inc.

Optic, Nerve, Chiasm, Tolerance, Radiotherapy.

1. CLINICAL SIGNIFICANCE

The therapeutic dose levels for tumors in the central nervous system and head-and-neck area are often constrained by the radiation tolerance of the optic apparatus. Visual impairment from radiation-induced optic neuropathy (RION) is uncommon but disabling (1, 2). It usually presents with painless rapid visual loss. Vasculature injury has been suggested as a significant contributor to RION (3, 4). Treatment of radiotherapy (RT)-associated visual loss is limited.

2. ENDPOINTS

Visual impairment is typically defined according to the visual acuity (3, 5–8) and is typically defined as 20/100 vision or less, meaning that the patient can see at 20 feet no more than a normal person can see at 100 feet. Furthermore, impairment is often described by the size/extent of the ''visual fields'' (how much of the potentially visible region can be visualized). For instance, patients often lose vision of one-half or a quadrant of the visual field owing to injury of a part of the optic nerves/chiasm. The interval between RT and the development of visual symptoms is generally ≤3 years (mode, 1–1.5; median, 2.5) (2, 9).

Optic nerve injury typically results in monocular visual loss, except if it occurs very close to the optic chiasm, where fibers looping up from the contralateral medial eye/retina can be affected. Injury to the entire chiasm can cause bilateral vision loss. Temporary injury limited to the inferior central optic chiasm from pituitary adenoma results in bilateral upper outer quadrant visual field impairment. The loss of a proximal optic tract causes loss of the same half of the visual field in each eye. Because the optic tracts spread out on their way toward the occipital cortex, injuries along the way typically result in small visual field cuts.

Uncertainties exist in scoring the toxicity. Acuity problems can result from cataracts, dry eye or radiation retinopathy (usually distinguishable by examination). Vascular insufficiency to the retina, optic nerves, tracts, or occipital lobes can also cause visual impairments, particularly visual field deficits. Because patients often undergo RT to many of these areas concurrently, it can be challenging to know how to accurately ascribe the clinical events.

Lesions anterior to the chiasm will affect the ipsilateral eye, lesions of the chiasm will affect the bilateral temporal visual fields, and lesions posterior to the chiasm will affect visual fields in both eyes.

3. CHALLENGES DEFINING VOLUMES

The optic nerves progress from the posterior aspect of the center of the globe roughly through the center of the orbit, bracketed by the rectus muscles. They angle up through the optic canals just medial to the anterior clinoid process of the lesser wings of the sphenoid bone. The axonal bundles of the left and right optic nerves, divide at the optic chiasm.

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The medial fibers cross to the contralateral optic tract, and the lateral fibers continue on the ipsilateral tract. The optic chiasm forms an X shape at this junction. Typically, it is just superior to the sella turcica, with the nerves crossing just anterior to the pituitary stalk. It is bracketed laterally by the internal carotid arteries and is inferior to the third ventricle (10–12). With conventional computed tomography or magnetic resonance imaging, the optic tracts are visible for only 1–2 cm posterior to the optic chiasm before the fibers spread and appear to blend into the rest of the brain parenchyma.

The optic nerve is thin, usually 2–5 mm thick (10). Depending on the orientation of the scan plane relative to the brain, the optic nerve and chiasm can appear on multiple images. Computed tomography-magnetic resonance imaging (T_1- and T_2-weighted imaging/fast fluid-attenuated inversion recovery imaging) is recommended for better definition. Continuous axial images at ≤3 mm spacing increase the resolution of the optic apparatus over the entire course. It is essential to contour the optic apparatus in continuity, because gaps in the structures (*e.g.,* where the optic nerves pass through the optic canal) will result in exclusion of the dose from the missing volume for that structure's dose–volume histogram.

4. REVIEW OF DOSE–VOLUME DATA

Complication data for RT-induced optic nerve and chiasm injury have been reported for several external beam RT delivery systems, including fractionated photons, stereotactic radiosurgery (SRS), protons (with or without photons), and carbon ions. Selected studies are summarized in Tables 1 and 2. The average follow-up was 42 and 50 months for studies with and without an incidence of RION, respectively.

Multiple fraction therapy

The maximum dose (Dmax) to the optic structures is often the only dosimetric data reported. Emami *et al.* (13) did not report the partial volume tolerance data for the optic nerve and chiasm. For whole organ tolerance, Emami *et al.* (13) listed the doses corresponding to 5% probability of blindness within 5 years of treatment and the 50% probability within 5 years as 50 and 65 Gy, respectively.

The data for the incidence of toxicity with conventional fractionation are summarized in Fig. 1. A probabilistic component clearly exists, because some patients receiving greater doses did not sustain complications. A steep increase in the incidence might exist past 60 Gy. None of the patients (<70y) in the study by Parsons *et al.* (4) with a Dmax <59 Gy developed RION. In the study by Martel *et al.* (14), the average maximum chiasm and nerve dose was 53.7 Gy (range, 28–70) and 56.8 Gy (range, 0–80.5) for patients without RION. The optic nerves had received a Dmax of ≥64 Gy with 25% of the volume receiving >60 Gy for patients with moderate to severe complications. Jiang *et al.* (15) reported no incidence of ipsilateral RION for a dose <56 Gy and a <5% incidence at 10 years for a dose <60 Gy at ≤2.5 Gy/fraction.

The range of low-risk total doses is reflected in the planning constraints reported. Hoppe *et al.* (16) and Martel *et al.* (14) constrained the Dmax to <54 and <60 Gy, respectively. Daly *et al.* (17) constrained the dose to the hottest 1% of the volume to 54 and 45 Gy for the nerves and chiasm, respectively.

Tolerance might be lower in patients with pituitary tumors. Complications at doses as low as 46 Gy at 1.8 Gy/fraction have been reported (7, 18, 19). Mackley *et al.* (18) and van den Bergh *et al.* (7) constrained the optic structure Dmax to 46 and 45 Gy, respectively. The RION latency was shorter in patients with pituitary tumors. The average latency was 10.5 and 31 months (range, 5–168) in patients with pituitary targets and nonpituitary targets, respectively (18, 19).

Evidence has shown that the mean dose is greater for patients with complications vs. those without (14) and the maximum doses are similar for both groups. This might indicate that a volume effect exists. However, dose–volume data to support this are scarce in the published reports. There is some indication that keeping 5–30% of the optic nerve to less than ≈50–60 Gy might reduce the incidence of complications (14, 20, 21).

The risk of nerve injury appears to be related to the fraction size. Parsons *et al.* (4) reported 15-year actuarial rates of RION for total doses of 60 to <70 Gy of 50% vs. 11% at ≥1.9- vs. <1.9-Gy dose/fraction, respectively. No patients treated twice daily with 1.2 Gy/fraction developed RION. At greater total doses, 70–83 Gy, the incidence was 33% vs. 11% for ≥1.9 vs. <1.9 Gy/fraction and 12% for 1.2-Gy twice-daily fractions. Bhandare *et al.* (20) noted similar reductions in RION rates for once- vs. twice-daily fractionations.

The proton results have been consistent with the photon results. Note, that the proton doses are presented as Cobalt Gray Equivalent (CGE), reflecting the greater biologic effect owing to the greater linear energy transfer of particles compared with photons. Widely accepted proton dosimetry standards were developed later than those for photons (22–24), and some studies have reflected a revision of the dose estimates according to these changes (25). Many proton patients were also treated with photons.

Most proton series have reported a very low incidence of RION. Those reporting cases of RION, noted a threshold in the range of 55–60 CGE, consistent with that of photons. As with photons, many patients with doses within this range or greater have not developed RION. Wenkel *et al.* (25), Noel *et al.* (26), Weber *et al.* (27), and Nishimura *et al.* (28) reported using a Dmax constraint to the optic structures of 54, 55, 56, and 60 CGE, respectively. More aggressive fractionation regimens (~3 CGE/fraction) with greater linear energy transfer, carbon ions, reported 54 CGE as a planning constraint (29).

Single fraction therapy

Dose–volume analyses with radiosurgery are challenging owing to the small volumes irradiated and rapid dose

Table 1. Selected studies documenting dose to optic structures *without* radiation-induced optic neuropathy

Investigator(ref)/ #Patients	Disease/technique	Prescription dose (range)/fraction (range)	Dmax	Mean/median dose
Daly (17)/36	Paranasal sinus, nasal cavity/photon IMRT	70 (63–72) Gy CTV 1.8 Gy/fx GTV 2.12 Gy/fx	Chiasm 52.3 ± 5.1 Gy Nerve 59.1 ± 7.7 Gy	Chiasm 39.5 ± 4.2 Gy Nerve 48.1 ± 3.7 Gy
Hoppe (21)/85	Paranasal sinus, nasal cavity/photon mixed	63 (50–70) Gy (1.8–2.0) Gy/fx	Chiasm 52 (4–105) Gy Nerve 54 (4–105) Gy	Chiasm 45 (5–51) Gy Nerve 35 (6–81) Gy
Weber (27)/29	Chordoma, chondrosarcoma/proton	C: 74 (67–74) CGE (1.8–2.0) CGE/fx CS:68(64–74) CGE (1.8–2.0) CGE/fx	Chiasm 58.1 (12.2–68.6) CGE Nerve 51.7 (9.0 –74.9) CGE	Chiasm 47.0 (3.9–60.7) CGE Nerve 16.5 (0.6–60.2) CGE
Nishimura (28)/14	Olfactory neuroblastoma/proton	65 CGE 2.5 CGE/fx	67.7 (35.1–68.9) CGE	27.3 (6.5–53.3) CGE
Lee (47)/11	Craniopharyngioma/CyberKnife	25 (18–38) Gy 5 (3.8–6.7) Gy/fx	< 5 Gy/fx	NR
Pollock (32)/62	Nonfunctioning pituitary adenoma/gamma knife	16.3 (11–20) Gy Single fraction	9.5 Gy ± 1.7 (5.0–12.6) Gy	NR

Abbreviations: Dmax = maximum dose; IMRT = intensity-modulated radiotherapy; CTV = clinical target volume; GTV = gross tumor volume; fx = fraction; CGE = Cobalt Gray Equivalent; NR = not reported; RION = radiation-induced optic neuropathy.

Average reported mean follow-up was 38 months (range, 15–60) for all studies not reporting RION.

Some of data were estimated from text, tables, and figures of the published articles.

gradients. Image segmentation uncertainties and distinctions between the mean dose vs. Dmax, could be particularly relevant for SRS. Tishler *et al.* (30) reviewed optic nerve injury from the early radiosurgery experience. They proposed 8 Gy as a limit for optic tolerance from their analysis, which cited the lowest dose for optic neuropathy as 9.7 Gy. Stafford *et al.* (31) reported that optic neuropathy occurred in 4 of 215 patients receiving a median dose of 10 Gy to the optic chiasm, with chiasm/optic nerve Dmax of 0.4–16 Gy. The risk of RION was estimated at 1.7%, 1.8%, 0%, and 6.9% for a Dmax of <8, 8–10, 10–12, and >12 Gy, respectively. Of the 4 patients, 3 had undergone previous external beam RT with doses in the range of 45–58.8 Gy. Pollock *et al.* (32) observed no cases of RION in 62 patients undergoing gamma knife SRS for nonfunctioning pituitary adenomas. The median Dmax to the optic apparatus was 9.5 ± 1.7 Gy. They reported using <12 Gy as an optic structure dose constraint. Leber *et al.* (33) analyzed optic neuropathy risks in 50 patients 24–60 months (median follow-up, 40 months) after gamma knife SRS for benign skull base tumors. They reported optic neuropathy risks of 0% with <10 Gy, 27% with 10 to <15 Gy, and 78% with ≥15 Gy, respectively.

5. FACTORS AFFECTING RISK

Parsons *et al.* (4) reported an increased risk of RION with increasing age. None of the 38 patients in the 20–50-year range developed RION, even though the reported optic nerve doses were >60 Gy for 58% and >70 Gy for 26% of patients. In contrast, RION was noted in older patients. For patients with doses >60 Gy, the incidence was 26% vs. 56% for the 50–70 vs. >70-year age groups. Similarly, Bhandare *et al.* (20) noted RION in 0%, 4%, 13%, and 14% of patients aged <20, 20–50, 51–70, and >70 years, respectively.

Data on other clinical factors such as chemotherapy, diabetes mellitus, and hypertension have been inconsistent. Minimal data are available on re-irradiation of the optic apparatus and the effect of the interval between courses on RT tolerance. Flickinger *et al.* (34) found that 1 of 10 patients studied after repeat irradiation developed RION (they had received an initial 40 Gy, with a 7.5-year interval, and then received 46 Gy; both at 2 Gy/fraction).

6. MATHEMATICAL/BIOLOGIC MODELS

The original Lyman-Kutcher-Burman normal tissue complication probability volumetric modeling parameters were estimated (35) as TD50= 65 Gy, n = 0.25, and m = 0.14. The dose–response data from Jiang *et al.* (15) (≈1.5–2.2 Gy/fraction) suggested TD50 ≈72–75 Gy. Martel *et al.* (14) and Brizel *et al.* (36) estimated TD50 at 72 and 70 Gy, respectively. The Parsons' dose response extrapolated TD50 to >70 Gy.

Isoeffect models have been used to estimate the threshold Dmax values. In linear quadratic modeling, the α/β can be very small. Jiang *et al.* (15) estimated the α/β at 1.6 for the optic nerves, but the lower 95% confidence interval value was −7. For the optic chiasm, they found an α/β of <0. Flickinger *et al.* (37) also found an α/β of <0 in their modeling. The inadequacies of the linear-quadratic model for SRS have recently been discussed by Kirkpatrick *et al.* (38). Alternative biologically effective dose models that incorporate the number of fractions (Optic Ret) or number of fractions and overall treatment time (Neuret) have been explored. Flickinger *et al.* (39) examined complications vs. the normalized total dose (NTD) calculated from the Neuret formula (NTD 1.8 [Neuret]). This formulation is designed to represent the equivalent dose delivered in 1.8-Gy fractions, 5 d/wk. They found the actuarial risk of optic neuropathy was

Table 2. Selected studies documenting incidence of radiation induced optic neuropathy

Investigator(ref)/#Patients	Disease/technique	Prescribed treatment dose (range), dose/fraction (range)	Incidence of RION	Dose detail for group*
Aristizabal *et al.* (19)/122[†]	Pituitary adenoma/ conventional ^{60}Co	<40 to >46 Gy <1.8 to >2.2 Gy/fx	0/7 2/99 2/16	<2 Gy/fx 2–2.2 Gy/fx > 2.2 Gy/fx
Mackley *et al.* (18)/34	Pituitary adenoma/photon IMRT	45.9 Gy (45–49.3) 1.7 Gy/fx(1.7–2.0)	1/34[‡]	49.3 Gy[§§]
Flickinger *et al.* (39)/21	Craniopharyngioma/photon non-IMRT	57.9 Gy (51.3–70) 1.83 Gy/fx (1.61–2.76)	2/21[‡]	> 61.5 Gy[§§]
Pigeaud-Klessens *et al.* (48)/56	Mixed sites/photon non-IMRT	61.8 Gy (84–25)	6/56[‡§] Nerve	64.3 Gy (59–65)[§§] 69 Gy Nerve 60 Gy Chiasm
Martel *et al.* (14)/20	Paranasal sinus/photon non-IMRT	50.4–70.2 Gy 1.8 Gy/fx	1/20[‡] Chiasm 6/20[‡] Nerve 0/2[¶] 1/4[¶] 0/2[¶] 2/10[¶]	59.5 Gy[§§] 63.1 Gy (47.5–75.5)[§§] Mean 55.2 Gy (38.3–72.9) 50 to <55 Gy 55 to < 60 Gy 60 to < 65 Gy 65 to < 80 Gy
Jiang *et al.* (15)/219	Paranasal sinus/photon non-IMRT	NR	3% (0–9) Nerve (1/39[|]) 34% (8–53) Nerve (20/59[|]) 4% (0–9) Chiasm (4/110[|]) 13% (2–24) Chiasm (9/66[|])	50–60 Gy, ∼2.1 Gy/fx, 5-y incidence (95% CI) 61–78 Gy, ∼2.2 Gy/fx, 5-y incidence (95% CI) 50–60 Gy, ∼2.1 Gy/fx, 5-y incidence (95% CI) 61–76 Gy, ∼2.2 Gy/fx , 5-y incidence (95% CI)
Parsons *et al.* (4)/131	Head-and-neck cancer/ photon, non-IMRT	55 to >75 Gy 1.2–2.6 Gy/fx	0/21 5/7 1/16 1/15 6/73	55 to <65 Gy, < 1.9 Gy/fx 55 to <65 Gy, ≥ 1.9 Gy/fx 55 to <60 Gy, <70 y 60 to <65 Gy, <70 y 65 to >75 Gy, <70 y
Goldsmith *et al.* (40)/49	Meningioma/photon, non-IMRT	53.6 Gy (45–59.4) 1.0–1.8 Gy/fx	1/49[‡]	Optic Ret = 8.9 Gy[§§]
Bhandare *et al.* (20),[#]/273	Nasopharynx, paranasal sinus, nasal cavity/photon, non-IMRT	<50 Gy to >70 Gy ∼1.8 or 1.1–1.2 Gy/fx twice daily**	3/27 16/90 1/14 4/69	50 to <60 Gy, ∼1.8 Gy/fx 60 to >70 Gy, ∼1.8 Gy/fx 50 to <60 Gy, 1.1–1,2 Gy/fx twice daily 60 to >70 Gy 1.1–1.2 Gy/fx twice daily
Hoppe *et al.* (16)/39	Paranasal sinus, nasal cavity/photon mixed	BED 70 Gy (48–72)	1/39[‡]	>77 Gy[§§]
Noel *et al.* (26)/45	Base of skull/photon, non-IMRT + proton	67 CGE (60–70) 1.8–2.0 CGE/fx	1/45 Chiasm	≤58 CGE[§§]
Wenkel *et al.* (25)/46	Meningioma/photon, non-IMRT + proton	59 CGE (53.1–74.1) 1.8–2.13 CGE/fx	3/46[‡] 1/46[‡]	56.4–62 CGE[§§] 63 CGE[§§]
Schulz-Ertner *et al.* (29)/96	Base of skull, chordoma/carbon ion	60 CGE (60–70) 3–3.5 CGE/fx	3/96[‡] Chiasm 1/96[‡]	60 CGE[§§] 54 CGE[§§]
Tishler *et al.* (30)/62	Meningioma (n = 44), mixed histologic type/ Gamma Knife (n = 33), linear accelerator (n = 29)	10–40 Gy[††] Single fraction	0/35 1/2 3/15	<8 Gy 8–10 Gy >10 Gy

(*Continued*)

Table 2. Selected studies documenting incidence of radiation induced optic neuropathy (*Continued*)

Investigator(ref)/#Patients	Disease/technique	Prescribed treatment dose (range), dose/fraction (range)	Incidence of RION	Dose detail for group*
Leber *et al*. (33)/45	Base of skull, mixed histologic features/Gamma Knife	14.3 Gy (8–25) Single fraction	0% (0/31 eyes[|]) 26.7% (6/22 eyes[|]) 77.8% (10/13 eyes[|])	<10 Gy 10 to <15 Gy ≥15 Gy
Stafford *et al*. (31)/215	Meningioma (n = 122), pituitary adenoma (n = 86), craniopharyngioma (n = 7)/Gamma Knife, previous photon (n = 23)	18 Gy (12–30)[‡‡] Single fraction	1/58 1/58 0/67 2/29	<8 Gy 8–10 Gy 10–12 Gy >12 Gy

Abbreviations as in Table 1.

Data estimated from tables, figures, and text reported in studies, because exact incidence data not always provided; 1 patient in study by Parson *et al*. (4) with event in 55–60-Gy range was treated to 59 Gy; 1 event in study by Martel *et al*. (14) in 55–60-Gy range received 59.5 Gy.

* Estimated Dmax unless otherwise noted.

[†] In report by Aristizabal *et al*. (19), 88 (72%) of 122 received >40 Gy (26 patients >46 Gy); most patients received 2–2.2 Gy/fx, 16 received >2.2 Gy/fx, and only 4 received <1.8 Gy/fx.

[‡] Subgroup dose analysis not performed, documents dose characteristics for observed RION.

[§] In report by Pigeaud-Klessens *et al*. (48), 3 patients with isolated retinopathy not included in numerator; mixed tumor sites included nose, pharynx, nasopharynx, and sinus.

[¶] Re-analysis, by us, of moderate to severe complication data presented in figures of original report; 2 patients received <50 Gy.

[|] Author provided actuarial estimate of percentage incidence. Fractional value was estimated by us based on data provided in the paper.

[#] Dose to nerves was specified as minimum delivered to one-third of optic nerve, dose to chiasm was specified as mean.

** In report by Bhandare *et al*. (20), 109 patients received ≤1.8 Gy/fx and 63 received >1.8 Gy/fx; 101 patients were treated with twice-daily fractions at 1.1–1.2 Gy/fx.

[††] Estimated ''maximum cavernous sinus dose range,'' rather than prescription doses, as in other studies.

[‡‡] In report by Stafford *et al*. (31), 3 of 4 patients (2 at <10 Gy, 1 at >12 Gy) with complications had been treated with previous conventional fractionated photons to 45–58.8 Gy.

[§§] Detail is for all patients in study, rather than for subgroup analysis of narrow, defined, dose range. Incidence for this dose detail may differ from ratio in incidence column.

30% for patients receiving a NTD >60 Gy at 1.8 Gy/fraction. Goldsmith *et al*. (40) found Optic Ret >8.9 Gy was significant in predicting RION. Shrieve (41) supported the use of Optic Ret = 8.9 Gy = total dose/(number of fractions)$^{0.53}$ model as a guide for selecting the Dmax values in a hypofractionation regimen.

Figure 2 summarizes the data relating the total dose and dose per fraction and the models. For fractionations >2 Gy/fraction, the ''tolerance doses'' were estimated to be greater with the linear-quadratic model than with the NTD or Optic Ret. Optic Ret provided the most conservative estimates of the Dmax and had the advantage of being easy to calculate in clinical practice. The NTD model was more consistent with the threshold values. The available data are insufficient for the range >2.0 Gy/fraction to judge the accuracy of the NTD or Optic Ret curves or to define an empirical curve for guidance. Figure 2 demonstrates the disagreement among the models and the significant lack of published data, particularly in the range used for hypofractionation protocols.

7. SPECIAL SITUATIONS

Data implicating the total dose and fraction size as the two most important treatment-related risk factors for optic nerve/chiasm injury are strong. Most have been derived from studies that used either conventional fractionation or single-fraction techniques. Minimal (or no) data have been derived from patients receiving hypofractionated schedules; thus, care should be taken in that setting. Furthermore, volume dependence is not well understood. Many of the studies that provided good statistical information on RION were performed in an era before the routine use of computed tomography-based planning, dose–volume histogram analysis, and steep dose gradients across structures. Because the different portions of the optic nerves/chiasm carry nerve fibers associated with particular parts of the visual field, it is logical to assume that these nerves have a ''parallel architecture'' in the very-small-volume range (<1–3 mm). For treatment with rapid dose gradients, one would expect to observe injury to a part of the nerve, with a resultant visual field defect, rather than necessarily a large field defect. The latter might occur if the injury was mediated by a more global process (*e.g.,* a vascular insult causing a more general nerve injury). With the high radiation doses and uniformly sharp gradients used in radiosurgery and intensity-modulated RT, proper training in accurately delineating the optic system is critical for limiting complications without limiting tumor control.

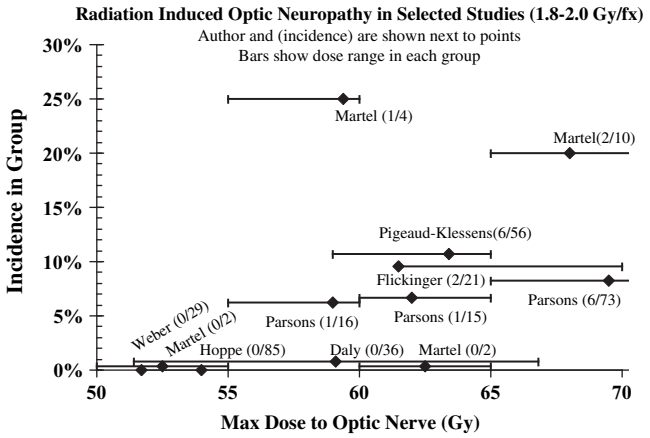

Fig. 1. Selected data from Tables 1 and 2 used to compare incidence of radiation-induced optic neuropathy (RION) vs. maximum dose (Dmax) to optic nerves. Selected studies generally used fraction sizes with range of 1.8–2.0 Gy, assessed the dose to the nerve directly from their best estimate of dose distribution in the structure (*i.e.,* not as a partial volume average), did not include pituitary lesions (lower tolerance), and selected patient age <70 years (if segregated). Bars illustrate range of doses for groups characterized by incidence values. Points offset from 0% to ≤1% were shifted to clearly show range bars. For points displayed at 0%, available range information was outside 50–70 Gy. Threshold for RION appears to be 55–60 Gy. However, range bars illustrate treatment in 60–65 Gy range for some studies without RION. Data estimated from tables, figures, and text reported in the studies, because exact incidence data were not always provided. The 1 patient in the study by Parsons *et al.* (4) with an event in the 55–60-Gy range was treated to 59 Gy. The 1 patients with an event in the study by Martel *et al.* (14) in the 55–60-Gy range received 59.5 Gy.

''Overcontouring'' the structures to add an implicit buffer will lead to significant errors in dose estimates.

8. RECOMMENDED DOSE–VOLUME LIMITS

From the dosimetric data and predictive model results discussed previously (''Review of Dose–Volume Data,'' ''Factors Affecting Risk,'' and ''Mathematical/Biologic Models''), some general guidelines for treatment planning can be given. The dose limits need to be considered in the clinical context. In some settings, it might be reasonable to accept greater risks.

The Emami estimate of 5% probability of blindness within 5 years of treatment for a dose of 50 Gy appears inaccurate. From the present data review, 50 Gy is closer to a ''near zero'' incidence. The incidence of RION was unusual for a Dmax <55 Gy, particularly for fraction sizes <2 Gy. The risk increases (3–7%) in the region of 55–60 Gy and becomes more substantial (>7–20%) for doses >60 Gy when fractionations of 1.8–2.0 Gy are used. The patients with RION treated in the 55–60 Gy range were typically treated to doses in the very high end of that range (*i.e.,* 59 Gy). For particles, most investigators found that the incidence of RION was low for a Dmax <54 CGE. One exception to this range was for pituitary tumors, in which investigators used a constrained Dmax of <46 Gy for 1.8 Gy/fraction.

For single-fraction SRS, the studies have indicated the incidence of RION is rare for a Dmax <8 Gy, increases in the range of 8–12 Gy, and becomes >10% in the range of 12–15 Gy. Unlike the fractionated series, most of these data were derived from the same treatment planning/delivery system (Gamma Knife). This might or might not affect the dose estimates using other systems. Consistent agreement has been reached on the low risk of RION for a Dmax of ≤10 Gy, and one major study indicated a low risk with a Dmax of ≤12 Gy.

9. FUTURE TOXICITY STUDIES

Multi-institutional studies of RION incidence for plans using rapid dose gradients of intensity-modulated RT fields and dose–volume histogram analysis of nerve and chiasm are needed to examine the volumetric dose response.

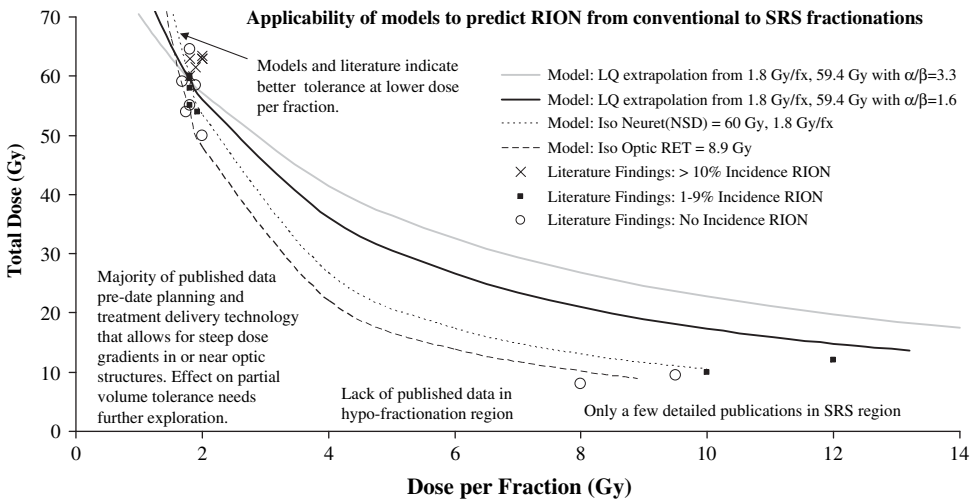

Fig. 2. Isoeffect linear-quadratic model extrapolations and alternative biologically effective threshold models (curves) compared with reported maximum optic nerve/chiasm doses detailing incidence of radiation-induced optic neuropathy (RION) (symbols) for full range of dose per fraction. Linear-quadratic model was unreliable for extrapolating from fractionated (1.8–2.0-Gy/fraction) dose range to single-fraction range. Detailed data needed for low (<1.8 Gy) and hypofractionated regions to better define organ response.

A more uniform approach to defining RION that explicitly addresses the differences between changes in acuity vs. visual fields and the role of gadolinium-enhanced magnetic resonance imaging for diagnosis of RION (7, 8) is needed.

Routinely providing statistical data on the total dose and the dose per fraction seen by the optic structures would improve our understanding of the interdependence of the dose per fraction and the threshold doses.

Routinely noting the types and dosages of concurrent chemotherapy agents would improve our understanding of their effect on the incidence of toxicity.

Studies of anti-angiogenic agents, such as bevacizumab, as a potential treatment of radiation-induced damage to the optic apparatus (42, 43) are needed.

Improving consistency within and among institutions in defining the optic nerves and chiasm is important for an accurate determination of the dose thresholds and the dose–volume effects.

10. TOXICITY SCORING

Several formalized systems are available for scoring visual impairment. The Common Terminology Criteria for Adverse Events, versions 3.0 (44) and 4.0, as well as Common Toxicity Criteria, version 2.0 (45) are available from the Website of the National Cancer Institute Cancer Therapy Evaluation Program (available from: www.ctep.cancer.gov). Other systems frequently used include the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (46) and the Late Effects of Normal Tissues-Subjective, Objective, Management and Analytic scoring system (6). Visual impairment can be fairly well scored using the latter system, which addresses both objective and subjective findings. Patients suspected of having an injury should be evaluated to assess for contributing factors that might affect the vision and to assist with care and visual correction.

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