Response of the Normal Eye to High Dose Radiotherapy

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Radiation therapy of tumors near the eye or optic nerves often requires incidental irradiation of these structures, even when they are not clinically involved by tumor. Depending on the radiation treatment volume and dose required, radiation injury to the lens, lacrimal apparatus, retina, or optic nerve may result. The time to expression and severity of injury are dose-dependent. This paper reviews the results of 157 patients who were followed for a minimum of 3 years after radiotherapy for primary extracranial tumors at the University of Florida, in which the lacrimal gland, lens, retina, and/or optic nerve(s) received irradiation. This review shows that, after treatment at approximately 1.8 to 2.0 Gy per fraction, the incidence of severe dry-eye syndrome, retinopathy, and optic neuropathy appears to increase steeply after doses of 40, 50, and 60 Gy, respectively. [ONCOLOGY 10(6):837-852, 1996]

Introduction

Although primary tumors of the eye (eg, melanoma, retinoblastoma) and optic nerve (eg, glioma) are rare, tumors that involve tissues adjacent to these structures are relatively common. Because many of these tumors are best treated with radiation therapy, the visual apparatus frequently receives incidental irradiation. Tumors for which irradiation usually is employed include those of the nasal cavity and paranasal sinuses, nasopharynx, orbit (eg, lymphomas), and central nervous system (eg, pituitary), as well as advanced cancer of the eyelid and periorbital skin.

The manner in which radiation oncologists report ocular complications differs from the way in which such complications are reported in the surgical literature. Characteristically, radiation damage that leads to a marked reduction in visual acuity (typically after a latent interval of 1 to 3 years) has been scored by radiation oncologists as a "severe complication." In contrast, surgical sacrifice of the orbital contents (with immediate visual loss) has been regarded as an unfortunate by-product of complete tumor removal and not as a complication per se.
When tumors of the paranasal sinuses are irradiated, varying portions of the eye fall within the treatment fields, depending on the degree to which the orbit is invaded. When orbital invasion is extensive, all of the orbital contents are irradiated, including the eyeball and all of the lacrimal tissue.[1] If the administered dose is high, as is the case when a carcinoma is treated, a dry eye results; visual loss usually occurs within 6 to 10 months after treatment, due to degeneration of the anterior segment of the eye, with resultant corneal ulceration and opacification and possible endophthalmitis. Lower doses, as are used in the treatment of lymphomas, result in only mild symptoms of a dry eye and cataract formation, usually a correctable form of visual loss.
If orbital invasion is limited, so that most of the lacrimal tissue can be spared high-dose irradiation,[1,2] severe dry-eye problems do not occur, even when high doses are administered. If the dose to the eyeball itself is high, however, visual loss due to posterior segment degeneration (radiation retinopathy) may occur, usually after a 2- to 3-year latency period. If low total doses are used, patients usually remain asymptomatic in the follow-up period with regard to dry-eye complaints and retinal problems but are still at risk for cataract formation if the lens was irradiated.
Even when the orbial invasion has not occurred, it is often necessary to include a portion of the contiguous orbit and the medial one-fourth to one-third of the eyeball in the irradiation field[1] because of the anatomic configuration of the sinuses and because of possible subclinical disease extensions through the thin bony walls that separate the sinuses from the orbit. Although visual loss secondary to eyeball injury is rare in this setting, there is still a risk of blindness due to optic nerve injury, usually after a 1- to 6-year latency period; the magnitude of risk depends on the daily fraction size and total dose administered.
Patients who are to undergo high-dose eye or optic nerve irradiation should be evaluated before treatment by an ophthalmologist knowledgeable about radiation complications. Most potential visual

complications can be anticipated during the treatment planning stage, and patients should understand these risks. Follow-up should be continued in the post-treatment period on a regularly scheduled basis of prophylaxis, not just when indicated by specific problems. Frequently, a number of ophthalmologic problems occur simultaneously (eg, dry-eye symptoms, cataracts, radiation retinopathy, and glaucoma), which makes assessment confusing and management difficult.
Before undertaking any specific treatment, the ophthalmologist should correlate the treatment details with the radiation therapist, because some pitfalls may be avoided by good communication. For example, if high-dose irradiation has been administered to the eyeball, cataract formation will almost certainly be accompanied by the development of radiation retinopathy. Unless measures have been taken to manage the radiation retinopathy, removal of the cataract may increase the incidence of neovascular glaucoma. Also, anterior-segment disease should be treated early and aggressively to avoid corneal complications. Even when vision is lost, vigorous attempts to save the eye are worthwhile for cosmetic reasons.
Between October 1964 and May 1989, 157 patients underwent radiotherapy at the University of Florida, Gainesville, for primary extracranial tumors that required irradiation of the eyes or optic nerves. All patients were followed for a minimum of 3 years. In this article, we will explore the various ophthalmologic complications that may occur in patients undergoing radiation therapy at these sites, based on our own experience, as well as a review of the literature.

Severe Dry-Eye Syndrome

When the orbit is extensively invaded by carcinoma, high-dose irradiation of the entire orbit is necessary, and generally results in severe dry-eye syndrome. Patients develop a red, painful, scratchy eye (foreign-body sensation) and photophobia. The drying effects of wind are particularly bothersome. Severe problems may produce corneal epithelial breakdown, ulceration with bacterial infection, vascularization, opacification, or perforation. Some patients develop iritis in association with corneal ulceration. Symblepharon (scarring of the conjunctival tissue) or phthisis bulbi (shrinking of the globe) are observed occasionally.
Most patients who develop severe dry-eye syndrome become severely symptomatic within 1 month after completion of irradiation. Corneal opacification and vascularization are often pronounced within 9 to 10 months after therapy is completed.
Various treatments have been administered in an attempt to control symptoms of severe dry-eye syndrome, including artificial tears, lubricating ointments, bandage contact lens, conjunctival flaps, or tarsorrhaphy. Topical steroids are occasionally used for iritis. Topical and/or systemic antibiotics are prescribed for treatment of corneal ulcers. Retrobulbar alcohol injections may be used in a uninfected painful eye. Many patients eventually require enucleation or evisceration because of endophthalmitis with pain and perforation of the globe.

University of Florida Data

At the University of Florida, 33 patients with extracranial head and neck tumors received irradiation of an entire orbit. Most patients were treated with cobalt-60. The dose to the lacrimal apparatus was calculated at a depth of 1 cm from the anterior skin surface, the approximate depth of the major lacrimal gland. The end point of the study was severe dry-eye syndrome sufficient to produce visual loss secondary to corneal opacification, ulceration, or vascularization.
Follow-up in 13 patients who did not develop severe dry-eye complications ranged from 3 to 20 years (mean, 7.3 years; median, 4 years). Sixteen patients received 45 Gy or less and 17 patients received 57 Gy or more. There are no data in the mid-range of doses (45.01 to 56.99 Gy). All 17 patients who received doses of 57 Gy or more developed severe dry-eye syndrome, as compared with 3 (19%) of 16 patients who received 45 Gy or less.

Data From the Literature

There are limited data in the literature on the probability of dry-eye complications according to dose. Consideration of the data from Parsons et al [3], Morita and Kawake [4], Bessell et al [5], and Letschert et al[6] reveals that the exact clinical end points of the various studies were not always clearly defined and probably differ somewhat from study to study. The sigmoid dose-response curve that has been constructed should be considered a first approximation, and more data are needed, particularly along the steep portion of the curve. The probability of complications appears to increase steeply at doses above 40 Gy.

Radiation Retinopathy

When the lacrimal apparatus is shielded from high-dose irradiation, permanent visual loss secondary

to degeneration of the anterior segment of the eye usually is preventable; there is still a risk of radiation injury to the retina, however.

Radiation retinopathy presents a clinical picture similar to that seen in diabetic retinopathy. Retinal injury after high-dose irradiation usually is not expressed clinically for 1½ to 3 years after irradiation, during which time visual acuity often remains normal. Subsequent deterioration is often thought to occur because of progressive obliteration of small retinal vessels, resulting in retinal ischemia, edema, microaneurysm formation, capillary dilatation, hemorrhage, and retinal or nerve head neovascularization.[2,7,8] Retinal ischemia and resultant hypoxia result in the development of a vasoproliferative factor, which is presumed to lead to retinal and optic nerve head neovascularization.

Some patients with radiation retinopathy develop vasoproliferation on the anterior surface of the iris, and into the angle of the eye (rubeosis iridis). Anterior-segment neovascularization is postulated to have the same cause as posterior-segment neovascularization; namely, vasoproliferative factor. New blood vessels usually appear first at the pupillary margin, then progress to the angles, resulting in peripheral anterior synechiae and neovascular glaucoma, which is secondary to angle closure.[2]

University of Florida Data

At our institution, 68 retinas in 64 patients were exposed to therapeutic irradiation by techniques that did not produce severe dry-eye complications (ie, corneal injury) but did place the retina at risk of injury. Radiation retinopathy developed in 27 eyes in 26 patients, resulting in visual acuity of 20/200 or worse. The mean and median times to the onset of symptoms attributable to retinal ischemia were 2.8 and 2.5 years, respectively. Of the 27 affected eyes, 14 developed rubeosis iridis and/or neovascular glaucoma.

Radiation retinopathy was not observed at doses below 45 Gy but increased steadily in incidence at doses 45 Gy or less. At doses between 45 and 55 Gy, there was an increased risk of injury among patients who received doses per fraction of 1.9 Gy or greater ($P = .09$). There was also a trend toward an increased risk of radiation retinopathy among patients who were also treated with chemotherapy (in the 45- to 51-Gy range of radiation, retinopathy occurred in 2/2 patients who received chemotherapy vs 4/10 who did not; $P = .23$). The lowest dose associated with retinopathy was 45 Gy delivered to a diabetic patient by twice-daily fractionation. The data did not suggest an increased risk of radiation retinopathy with increasing age.

Data From the Literature

Our data suggest the importance of total dose as well as dose per fraction, and add support to a small body of literature suggesting that patients who have diabetes mellitus or who receive chemotherapy are at increased risk of retinal injury [9-15]. Limited data suggest that panretinal laser photocoagulation may help prevent complications of neovascularization.

Based on data for 68 retinas in 64 patients, follow-up in 41 eyes in which radiation retinopathy did not develop was 3 to 26 years (mean, 9 years; median, 8 years).[16] Data from Petersen et al [17], Bessell et al [5], Letschert et al [6], Chan and Shukovsky [13], and Parsons et al [16] were used to construct a sigmoid dose-response curve.[16]. As illustrated by this curve, the risk of radiation retinopathy increases steeply at doses above 50 Gy.

Radiation Optic Neuropathy

Two types of optic neuropathy may be seen after irradiation: anterior ischemic optic neuropathy and retrobulbar ischemic optic neuropathy. Both types are believed to be caused by vascular occlusive disease, with an interruption of blood supply to either the nerve head or the retrobulbar portion of the nerve, respectively. Patients with preexisting small-vessel occlusive disease are at increased risk for this complication.

Ophthalmoscopic findings in anterior ischemic optic neuropathy include disc pallor and edema with splinter hemorrhages on or adjacent to the disc. Ophthalmoscopic findings in retrobulbar ischemic optic neuropathy shortly after the onset of symptoms are either normal or reveal pallor of only one sector of the disc. Eventually, both the anterior and retrobulbar types lead to a picture consistent with optic atrophy.

University of Florida Data

At the University of Florida, 215 optic nerves in 131 patients received fractionated external-beam irradiation during the treatment of primary extracranial head and neck tumors. The clinical end point was visual acuity of 20/100 or worse as a result of optic nerve injury.

Anterior ischemic optic neuropathy developed in five nerves (at mean and median times of 32 and 30 months, respectively, and a range of 2 to 4 years). Retrobulbar optic neuropathy developed in 12

nerves (at mean and median times of 47 and 28 months, respectively, and a range of 1 to 14 years). No injuries were observed in 106 optic nerves that received a total dose of < 59 Gy. Among nerves that received doses of 60 Gy or more, the dose per fraction was more important than the total dose in producing optic neuropathy. The 15-year actuarial risk of optic neuropathy after doses of 60 Gy or more was 11% when treatment was administered in fraction sizes of < 1.9 Gy, as compared with 47% when given in fraction sizes of 1.9 Gy or less. The data also suggest an increased risk of optic nerve injury with increasing age.

In another time-dose scatter distribution of optic nerve dose vs the number of fractions to produce optic neuropathy, data on 215 optic nerves in 131 patients were plotted.[18] The length of follow-up of uninjured nerves was 3 to 21 years (mean, 8.1 years; median, 7.0 years). Of the 17 optic nerve injuries, 11 (65%) were evident by 3 years.

Data From the Literature

Most cases of optic neuropathy after modest-dose (42.5 to 50 Gy) irradiation reported in the literature occurred after treatment of pituitary tumors; in many of the reported patients, treatment was administered at doses per fraction of 2.5 Gy or greater [19-22]. The occurrence of optic neuropathy after doses as low as 45 to 50 Gy administered in fractions of 1.67 to 2 Gy seems to be a problem unique to patients with pituitary tumors [19,23-26], and likely is a reflection of preexisting optic nerve and chiasm compression and vascular compromise secondary to mass effect and possibly surgery.

Chemotherapy may sensitize the optic nerve to radiation injury. There are several reports of optic neuropathy occurring after irradiation to doses ranging from 40 to 49 Gy administered at 2 Gy or less per fraction when irradiation was administered concurrently or sequentially with chemotherapy [27-29].

A dose-response curve at 10 years for patients who received treatment at 2 Gy or less per fraction,[18] including data from Goldsmith et al,[30] showed dose ranges and incidences of neuropathy as follows: 25 to 34.99 Gy, none of 6 eyes; 35 to 44.99 Gy, none of 14 eyes; 45 to 54.99 Gy, none of 11 eyes; 55 to 64.99 Gy, 3 (25%) of 12 eyes; and 65 to 74.99 Gy, 9 (35%) of 26 eyes. Dose data from the University of California, San Francisco are recorded as the mean dose (54 Gy). The incidence appears to increase steeply above 60 Gy.

As there is no effective treatment for radiation-induced optic neuropathy, efforts should be directed at prevention. This can be achieved by minimizing the total dose, paying attention to the dose per fraction to the nerve, and using reduced-field techniques where appropriate to limit the volume of tissue that receives high-dose irradiation.

Conclusions

After conventionally fractionated (1.8 to 2.0 Gy/fraction) external-beam irradiation, the incidence of severe dry-eye syndrome, retinopathy, and optic neuropathy appears to increase steeply after doses of 40, 50, and 60 Gy, respectively.

References:

1. Parsons JT, Mendenhall WM, Bova FJ, et al: Head and neck cancer, in Levitt SH, Khan FM, Potish RA (eds): Levitt and Tapley's Technological Basis of Radiation Therapy: Practical Clinical Applications, 2nd Ed, pp 203-231. Philadelphia, Lea & Febiger, 1992.
2. Parsons JT, Fitzgerald CR, Hood CI et al: The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 9:609-622, 1983.
3. Parsons JT, Bova FJ, Fitzgerald CR et al: Severe dry-eye syndrome following external beam irradiation. Int J Radiat Oncol Biol Phys 30(4):775-780, 1994.
4. Morita K, Kawake Y: Late effects on the eye of conformation radiotherapy for carcinoma of the paranasal sinuses and nasal cavity. Radiology 130:227-232, 1979.
5. Bessell EM, Henck JM, Whitelocke RAF, et al: Ocular morbidity after radiotherapy of orbital and conjunctival lymphoma. Eye 1:90-96, 1987.
6. Letschert JGJ, González González D, Oskam J, et al: Results of radiotherapy in patients with Stage I orbital non-Hodgkins lymphoma. Radiother Oncol 22:36-44, 1991.
7. Parsons JT, Bova FJ, Fitzgerald CR, et al: Tolerance of the visual apparatus to conventional therapeutic irradiation, in Gutin PH, Leibel SA, Sheline GE (eds): Radiation Injury to the Nervous System, pp 283-302. New York, Raven Press, 1991.
8. Parsons JT: The effect of radiation on normal tissues of the head and neck, in Million RR, Cassisi NJ

(eds): Management of Head and Neck Cancer: A Multidisciplinary Approach, 2nd Ed, pp 245-289. Philadelphia, JB Lippincott, 1994.
9. Viebahn M, Barricks ME, Osterloh MD: Synergism between diabetic and radiation retinopathy: Case report and review. Br J Ophthalmol 75:629-632, 1991.
10. Dhir SP, Joshi AV, Banerjee AK: Radiation retinopathy in diabetes mellitus. Acta Radiol Oncol 21:111-113, 1982.
11. Amoaku WMK, Archer DB: Cephalic radiation and retinal vasculopathy. Eye 4:195-203, 1990.
12. Brown GC, Shields JA, Sanborn G, et al: Radiation retinopathy. Ophthalmology 89:1494-1501, 1982.
13. Chan RC, Shukovsky LJ: Effects of irradiation on the eye. Radiology 120:673-675, 1976.
14. Lopez PF, Sternberg P Jr, Dabbs CK, et al: Bone marrow transplant retinopathy. Am J Ophthalmol 112:635-646, 1991.
15. Mewis L, Tang RA, Salmonsen PC: Radiation retinopathy after "safe" levels of irradiation. Invest Ophthalmol Vis Sci 22(suppl):222, 1982.
16. Parsons JT, Bova FJ, Fitzgerald CR, et al: Radiation retinopathy after external-beam irradiation: Analysis of time-dose factors. Int J Radiat Oncol Biol Phys 30:765-773, 1994.
17. Petersen IA, Kriss JP, McDougal IR, et al: Prognostic factors in the radiotherapy of Graves' ophthalmopathy. Int J Radiat Oncol Biol Phys 19:259-264, 1990.
18. Parsons JT, Bova FJ, Fitzgerald CR, et al: Radiation optic neuropathy after megavoltage external-beam irradiation: Analysis of time-dose factors. Int J Radiat Oncol Biol Phys 30:755-763, 1994.
19. Aristazabal S, Caldwell WL, Avila J: The relationship of time-dose fractionation factors to complications in the treatment of pituitary tumors by irradiation. Int J Radiat Oncol Biol Phys 2:667-673, 1977.
20. Atkinson AB, Allen IV, Gordon DS, et al: Progressive visual failure in acromegaly following external pituitary irradiation. Clin Endocrinol (Oxf) 10:469-479, 1979.
21. Hammer HM: Optic chiasmal radionecrosis. Trans Ophthalmol Soc UK 103:208-211, 1983.
22. Harris JR, Levene MB: Visual complications following irradiation for pituitary adenomas and craniopharyngiomas. Radiology 120:161-171, 1976.
23. Kline LB, Kim JY, Ceballos R: Radiation optic neuropathy. Ophthalmology 92:1118-1126; 1985.
24. McCollough WM, Marcus RB Jr, Rhoton AL Jr, et al: Long-term follow-up of radiotherapy for pituitary adenoma: The absence of late recurrence after 4500 cGy. Int J Radiat Oncol Biol Phys 21:607-614, 1991.
25. Roden D, Bosley TM, Fowble B, et al: Delayed radiation injury to the retrobulbar optic nerves and chiasm: Clinical syndrome and treatment with hyperbaric oxygen and corticosteroids. Ophthalmology 97:346-351, 1990.
26. Rush SC, Newall J: Pituitary adenoma: The efficacy of radiotherapy as the sole treatment. Int J Radiat Oncol Biol Phys 17:165-169, 1989.
27. Appen RE, Bosch A: Bilateral loss of vision following radiation therapy. Neuro-ophthalmol 3:97-102, 1983.
28. Fishman ML, Bean SC, Cogan DG: Optic atrophy following prophylactic chemotherapy and cranial radiation for acute lymphocytic leukemia. Am J Ophthalmol 82:571-576, 1976.
29. Wilson B, Perez GM, Kleinschmidt-Demasters BK: Sudden onset of blindness in patients treated with oral CCNU and low-dose cranial irradiation. Cancer 59:901-907; 1987.
30. Goldsmith BJ, Rosenthal SA, Wara WM, et al: Optic neuropathy after irradiation of meningioma. Radiology 185:71-76; 1992.