# Ocular Complications of Radiotherapy

# 11

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## Contents



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## 11.1 Introduction

Although radiotherapy is the standard treatment for most intraocular malignancies, various ocular complications may occur, including radiation-induced dry eye, cataract, secondary glaucoma from neovascularization of the iris, scleral necrosis, retinopathy, and optic neuropathy. In this chapter we review the ocular side effects of radiation administered from brachytherapy, proton beam radiotherapy, and external beam radiotherapy and their potential treatments. Particular emphasis will be placed on radiation retinopathy and optic neuropathy, the two most visually significant complications of radiotherapy.

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The ideal method to deliver radiation to malignant tissue is to reduce the dose to critical normal structures without decreasing dose to the tumor. Within the realm of brachytherapy, these methods can be broadly separated into two categories: low-penetrating brachytherapy isotopes and intraocular radiation blocking. The radioisotope iodine-125 was chosen for the Collaborative Ocular Melanoma Study because it emits relatively low-energy gamma ray photons and is readily commercially available [1]. Its low energy results in ease of shielding, which reduces dose to the patient outside the eye and protects medical personnel involved in the treatment. Theoretically, lower-energy gamma radiation results in lower penetration through the eye itself due to increased photoelectric interactions, which would lead to sparing of critical ocular structures. For that reason, the isotope palladium-103 with a steeper dose falloff in the eye than iodine-125 results in a modest decrease in predicted dose to critical structures [2, 3]. Although its use has been accepted by the American Brachytherapy Society [4], this isotope is not in wide use as its clinical benefit has not been demonstrated in controlled clinical trials.

In contrast to gamma radiation, which has an approximately exponential dose falloff, beta (electron) radiation is characterized by a much steeper dose falloff after the depth of maximum dose. The beta emitter ruthenium-106 has been in use for ocular melanoma for several decades, primarily in Europe. The rapid dose falloff indicates a theoretical benefit to critical structures displaced from the tumor and, however, also means that it can be safely used only with low-height tumors, up to about 5 mm [5]. Thus, in principle, ruthenium-106 therapy would be most suited to treatment of low-height tumors in the anterior portion of the eye [6].

As early as 1990, Finger et al. discussed the concept of intraocular radiation blocking [7]. Finger used a rabbit model to investigate attenuating radiation with intraocular iodinated contrast agent. Significant attenuation was obtained, but the technique was limited by the fact that the contrast agent exited too rapidly from the eye. More recently, our group demonstrated the use of silicone oil as an attenuating agent [8]. As with iodinated contrast agents, silicone oil works in this case because of the combination of an absorber with a significantly higher atomic number compared to water and a low-energy gamma radiation, leading to enhancement of the photoelectric effect. Our Monte Carlo simulation and experimental study found up to 55 % attenuation inside the human eye, relative to saline, was possible with the silicone oil. Clinical use of this technique is facilitated by the fact that vitrectomy with silicone oil endotamponade is an established surgical technique for treatment of non-oncologic ocular diseases.

## 11.2 Adnexa

### 11.2.1 Extraocular Muscles

Extraocular muscles are theoretically shielded from most of the iodine-125 radiation as only 0.1 % of radiation passes through a 0.5-mm-thick gold foil [1]. However, with the current plaque design, extraocular muscles may actually be exposed to a significant amount of laterally directed and uncollimated radiation. Kiratli et al. [9] compared biopsy specimens from radiation-exposed extraocular muscles with nonirradiated, extraocular muscles from enucleated controls and found that the radiation-exposed muscles had a focal decrease in muscular tissue with increased fibroblasts and collagen. Furthermore, on electron microscopy, a loss of sarcoplasmic reticulum with mitochondrial swelling was noted. The authors argued that the sarcoplasmic reticulum loss, vascular wall thickening, and focal muscle tissue loss suggested radiation injury rather than pure mechanical injury due to stretching and ischemia. Although these may simply represent nonspecific ultrastructural changes, they may affect extraocular muscle function.

### 11.2.2 Dose Relationship

Sener et al. [10] observed that 60 % of their patients (12/20) had ocular alignment and motility problems following plaque brachytherapy. However, only 10 % (2/20) of patients complained of diplopia. Dawson et al. 67 found that 1.7 % (16/929) of their patients developed persistent diplopia or strabismus following plaque brachytherapy during an 8-year follow-up. For 69 % (11/16) of these patients, the onset occurred within the first year. Whether these findings are attributable to radiation or simply mechanical injury from muscle manipulation, patients and physicians should be aware of this potential complication.

### 11.2.3 Treatment

Sener et al. [10] suggest using either prism correction or botulinum toxin A injections in the early postoperative period and recommend waiting at least 6 months before pursuing surgical correction of strabismus as radiation effects may be variable for some time.

In our experience, patients may require strabismus surgery in the long term to correct exotropia secondary to the loss of fixation in a poor seeing eye. We find it helpful to avoid use of an eye patch after brachytherapy in order to stimulate fixation to the greatest extent possible in the treated eye and encourage orthophoric alignment.

## 11.3 Periorbital Skin

### 11.3.1 Acute

Loss of eyelashes is one of the first and most common adverse effects to occur after radiotherapy, although they do usually grow back (Fig. 11.1). Erythema may occur within hours of radiotherapy [11]. Desquamation and scaling of the skin can follow lower-dose (10 Gy) radiation exposure, and more severe dermatitis occurs with higher doses (40 Gy) [12].

### 11.3.2 Late

Loss of eyelashes and eyebrows may be permanent [11, 12]. Other late sequelae of regular and high-dose radiotherapy (40 Gy or higher) to the eyelids include trichiasis, telangiectasia, hyperpigmentation, hyperkeratosis, entropion, ectropion, and punctal occlusion. Eyelid atrophy, necrosis, and frank ulceration are uncommon.

### 11.3.3 Management

Mild acute radiation effects can be relieved with the administration of topical corticosteroids, such as 1 % hydrocortisone. Late effects may be remedied by wound debridement, antibiotic therapy, and reconstructive surgery.

## 11.4 Conjunctiva

### 11.4.1 Acute

Conjunctivitis, chemosis, and a clear or purulent discharge may occur when radiotherapy doses of >5 Gy are used [11, 12].

### 11.4.2 Late

Effects of radiotherapy on the conjunctiva include telangiectasia, symblepharon, and sequelae of loss of goblet cells (keratinization and scarring). Doses of approximately 50 Gy lead to conjunctival scarring. Severe contracture occurs with doses of more than 60 Gy, and symblepharon is frequent with doses above 80–100 Gy [13].

### 11.4.3 Management

Topical corticosteroids are indicated for early conjunctivitis and chemosis. Artificial tears and ointment help replace the moisture lost due to damage to goblet cells and keratinization.

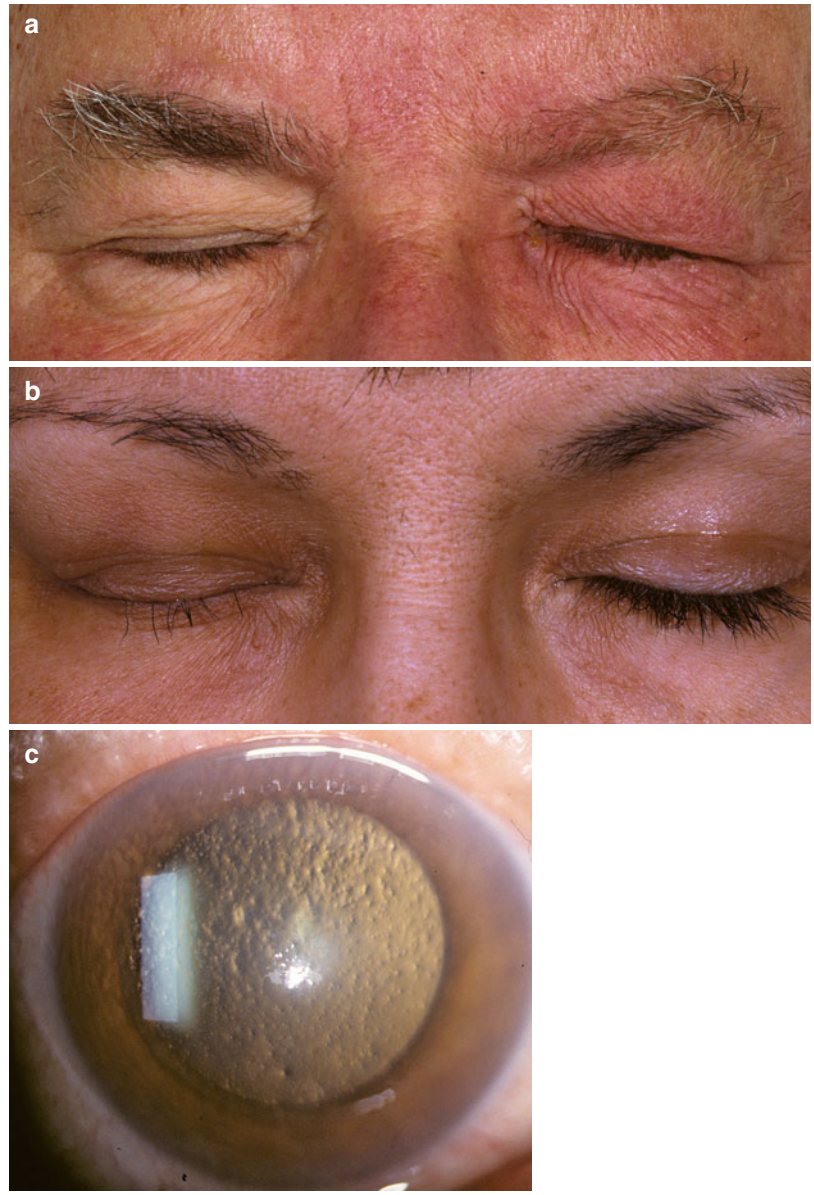


**Fig. 11.1** Acute complications of radiotherapy. (**a**) Radiation dermatitis. (**b**) Loss of eyelashes. (**c**) Punctate keratitis

## 11.5 Cornea

### 11.5.1 Radiation-Induced Dry Eye and Keratitis

Dry eye and keratitis are complications frequently seen after external beam radiotherapy for uveal metastases and proton beam radiotherapy for uveal melanoma, but are infrequent following brachytherapy (Fig. 11.1). An increase in conjunctival epithelial stratification and reduction in goblet cells contribute to dry eye [14]. Tear film instability and dysfunction may cause punctate epithelial erosions [15].

At our center, dry eye after iodine-125 brachytherapy is not more frequent than other procedures that involve alteration of the conjunctiva, such as scleral buckling. Dry eye was reported in 8.3 % of patients and occurs an average of 20.7 months after treatment with iodine-125

plaque [16]. In contrast, another study found that keratitis was present in 20.9 % of patients at 2 years after treatment, and this decreased to 2.8 % of patients by 5 years after treatment [17]. Few other studies reporting on iodine-125 brachytherapy describe this complication.

There is greater literature on developing dry eye after external beam radiation therapy and in particular its relationship to lacrimal gland dose. Parsons et al. reported on the University of Florida experience of patients treated with external beam radiation that included the entire orbit for head and neck cancers and found all patients developed dry eye who received doses ≥57 Gy, whereas 19 and 0 % did at doses of 30–45 Gy and <30 Gy, respectively [18]. The dose threshold for the lacrimal gland is different for fractionated stereotactic radiotherapy with one study that treated patients with 50 Gy in 5 fractions showing a median dose of 10 Gy/fraction resulting in a 50 % probability of dry eye syndrome, while a median dose of 7 Gy/fraction causing a 50 % risk of low Schirmer results [19]. Using a single fraction approach, dose to the lacrimal gland has also been shown to significantly correlated with Schirmer test values at 24 months when comparing the treated eye to the nontreated one [20]. Ultimately the dose to the lacrimal gland is an important factor in the development of a dry eye and efforts should be made to respect its tolerance as much as possible without compromising tumor coverage.

### 11.5.2 Treatment

Symptomatic treatment is recommended including topical lubricants and lacrimal punctal occlusion.

## 11.6 Scleral Necrosis

Scleral necrosis following plaque brachytherapy has been reported, often in association with postoperative brachytherapy. Petrovich et al. described the histologic appearance of enucleated eyes with choroidal melanoma that had been treated with plaque brachytherapy. Scleral atrophy was seen in 33 % of post-plaque eyes (Fig. 11.2) [21]. However, in the studies with iodine-125 brachytherapy, few reports mention scleral atrophy or necrosis as a complication. Stack et al. [22] documented that none of their 84 patients developed scleral necrosis after iodine-125 brachytherapy. Kaliki et al. recently reported a scleral necrosis rate of 1 % following iodine-125 brachytherapy with ciliary body location being the strongest risk factor. Observation was indicated in the majority of cases [23].

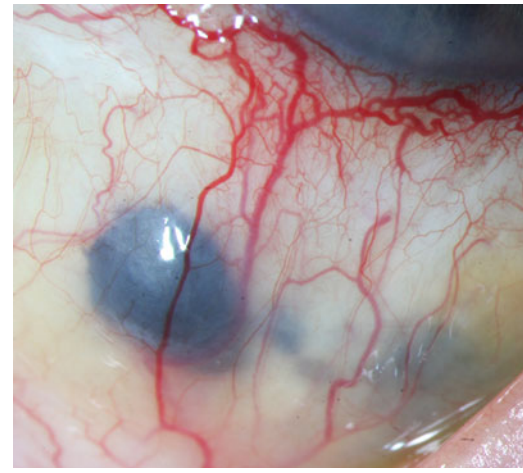

**Fig. 11.2** Scleral atrophy 10 months following plaque radiotherapy for a large ciliochoroidal melanoma

## 11.7 Iris

### 11.7.1 Radiation-Induced Iris Neovascularization and Neovascular Glaucoma

Though complications of the anterior segment occur frequently with external beam radiation, they also occur with plaque brachytherapy [24]. Ischemia associated with radiation retinopathy may result in iris neovascularization. This presents clinically as rubeosis iridis and neovascular glaucoma (Fig. 11.3). A careful examination of the iris and anterior chamber angle prior to pupillary dilation may detect early signs of neovascularization.

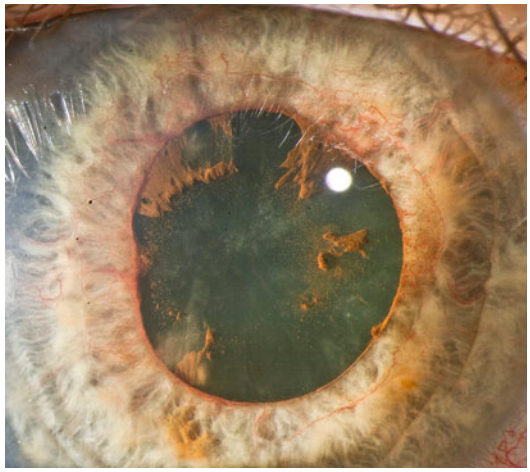

**Fig. 11.3** Neovascular glaucoma following radiation therapy

Rubeosis iridis following iodine-125 plaque brachytherapy is reported at rates of 4–23 %, occurring at a mean of 26.7 months. Neovascular glaucoma rates ranged from 2 to 45 %. Numerous factors may contribute to iris neovascularization. Studies using cobalt-60 and palladium-103 have associated increased neovascularization with an anterior tumor location [25, 26]. Increased tumor thickness is associated with higher rates as well as decreased time to the development of iris neovascularization and may be related to the elevated levels of tumor-related angiogenic factors [24, 27]. Recent data on a cohort of patients treated with stereotactic radiotherapy where six underwent enucleation for neovascular glaucoma and four because of tumor progression showed a lack of conclusive anterior segment changes attributable to radiation [28]. Mechanistically it is thought that proangiogenic factors released from radiation damage to endothelial cells diffuse through the vitreous to reach the anterior segment thereby promoting the formation of neovascularization on the iris and in the angle. This proposed mechanism is similar to other retinal vascular diseases like diabetic retinopathy [29].

### 11.7.2 Treatment

Currently, there are few studies supporting any specific treatment for radiation-induced neovascular glaucoma or rubeosis iridis (Chap. 16). Enucleation has traditionally been indicated for eyes with neovascular glaucoma in the setting of media opacity and poor vision. The rate of enucleation secondary to neovascular glaucoma after iodine-125 brachytherapy ranges from 1 to 12 % and indicates the difficulty in managing this complication. Although controversial, tube shunt procedure with vitrectomy and endolaser in eyes with good visual prognosis may also be considered. A report by Yeung et al. suggests that intravitreal bevacizumab may be used to treat neovascular glaucoma and salvage the eye following proton beam radiotherapy (Fig. 11.4) [30].

## 11.8 Lens

### 11.8.1 Clinical Features

Ionizing radiation is known to damage the lens equatorial fibers because of their high mitotic rate [31]. The compensatory mitosis occurs with disrupted organization and leads to deposition of Wedl cells at the posterior pole. The clinical appearance of a radiation cataract is of a small dot at the posterior pole of the lens and subsequently increases to a diameter of 1–2 mm [32]. The opaque region is comprised of scattered granules and vacuoles. As the cataract continues to develop, the center of the opacity clears, and the overall appearance is that of a doughnut with a total diameter of 3–4 mm. Radiation exposure may also lead to the development of cortical cataract or exacerbate existing nuclear sclerotic cataract [33].

### 11.8.2 Dose Relationship

The development of cataract is associated with a dose-dependent increase in radiation to the lens. In the largest study to date, the Collaborative Ocular Melanoma Study followed the incidence of cataract development in phakic patients over the first 5 years following iodine-125 brachytherapy [34]. The study found that 68 % (362/532) of study eyes developed vision-limiting cataract or underwent cataract surgery after iodine-125 brachytherapy

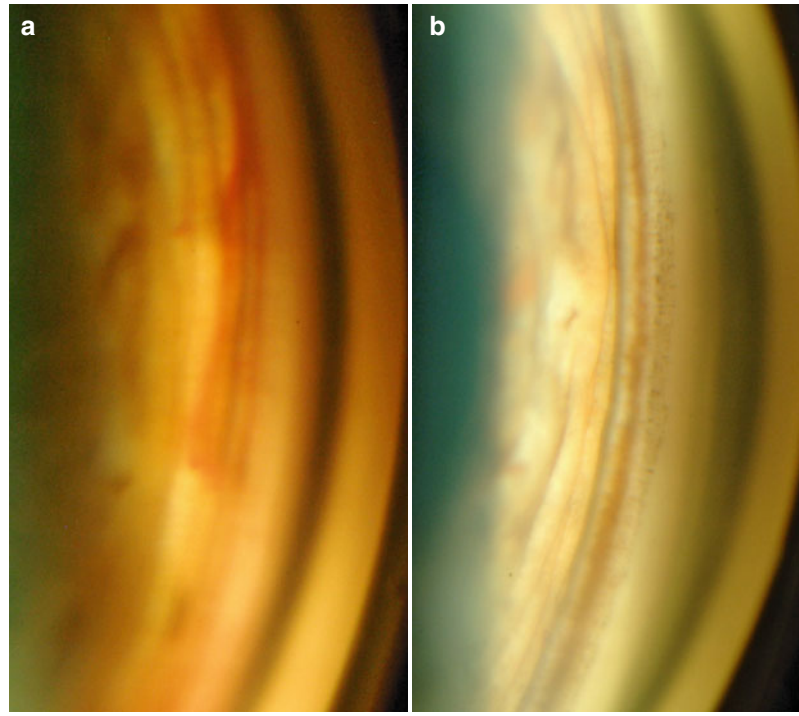


**Fig. 11.4** Gonio-photograph showing neovascularization and bleeding in the anterior chamber angle (**a**) Eight weeks after treatment with pan-retinal photocoagulation and intravitreal injection of bevacizumab (1.25 mg/0.05 ml). Note that the angle neovascularization and hyphema has resolved completely (**b**)

with a greater proportion developing cataract following higher doses to the lens. With a cumulative dose to the lens of 24 Gy or more, the 5-year cumulative incidence of cataract was 92 % compared with 65 % in those with less than 12 Gy.

The radiation dose to the lens is affected by both tumor size and location. Increasing tumor height has been shown to decrease the time to cataract development and a greater tumor diameter increases the risk of cataract [17, 24]. The location of the tumor is also important as treatment of an anterior tumor exposes the lens to more radiation. Fontanesi et al. [35] found that cataract developed earlier with anterior tumors (median 11 months posttreatment) compared with posterior tumors (median 26 months posttreatment) with a greater proportion of cataract occurring in eyes with anterior tumors. Data from patients treated with stereotactic radiation (10 Gy×5 fractions) also suggests a dose response relationship with cataract formation and dose to the lens and ciliary body with a median dose of 5 Gy/fraction causing a cataract in 50 % of cases and an overall rate of CTCAE version 3 grade 3 cataracts of 10 % [36].

### 11.8.3 Treatment

Radiation-induced cataract may be successfully treated with standard surgical techniques with improvement in vision (Chap. 15) [34]. Patients whose vision may fail to improve frequently have comorbidities, including radiation retinopathy, vitreous hemorrhage, retinal detachment, or optic neuropathy. We have found that eyes developing cataract following iodine-125 plaque brachytherapy tolerate standard phacoemulsification with lens implantation well.

## 11.9 Radiation Retinopathy

### 11.9.1 Clinical Features

Radiation retinopathy was first described in 1933 and includes microaneurysms, telangiectases, neovascularization, vitreous hemorrhage, hard exudates, cotton wool spots, and macular edema (Fig. 11.5). The pathogenesis of radiation reti-

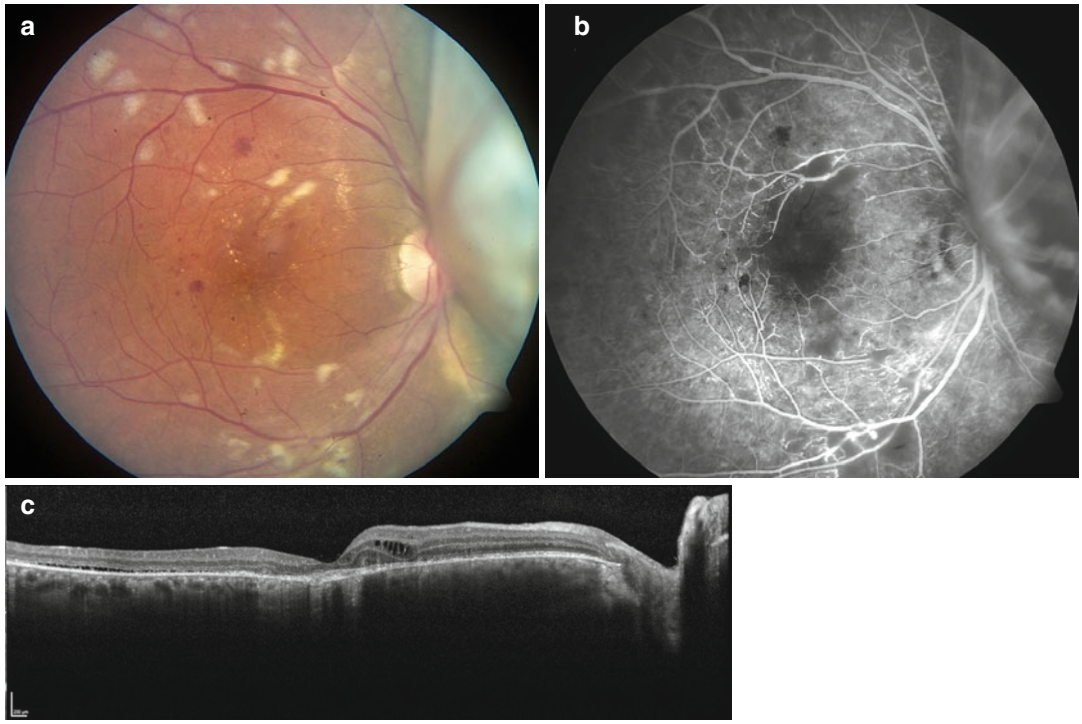


**Fig. 11.5** Characteristic ophthalmoscopic features of nonproliferative radiation retinopathy, such as cotton wool spots, telangiectasia, retinal hemorrhages, and macular edema following brachytherapy for choroidal melanoma (**a**). Retinal capillary nonperfusion in the macula and microaneurysms are most evident on the fluorescein angiography (**b**). Cystoid macular edema and foveal atrophy on the optical coherent tomograph (**c**)

nopathy begins after radiation exposure with the preferential loss of vascular endothelial cells and relative sparing of pericytes [11]. It has been hypothesized that the differential sensitivity between retinal endothelial cells and pericytes may be related to the direct exposure of the endothelial cells to high ambient oxygen and iron from blood that generates free radicals and damages cell membranes [37]. In acellular, poorly supported capillaries, microaneurysms emerge and telangiectatic-like channels appear, straddling regions of nonperfusion. Ultimately, the inner retinal ischemia leads to neovascularization, vitreous hemorrhage, tractional retinal detachment, and macular edema. On fluorescein angiography, the earliest changes that appear are focal capillary closure with neighboring areas of irregular capillary dilation and microaneurysms (Fig. 11.5).

### 11.9.2 Dose Relationship

The rate at which radiation-induced retinopathy and maculopathy develop ranges from 10 to 63 % and 13 to 52 %, respectively. The mean time to develop maculopathy was found to be 25.6 months after treatment [26]. The risk of radiation retinopathy and maculopathy after plaque therapy is related to radiation dose and factors affecting radiation dose, such as the height and location of tumor (Fig. 11.6). Higher radiation dose and tumors with thickness greater than 4 mm increase the risk for radiation maculopathy. Stack et al. [22] found a 63 % risk for radiation maculopathy if the dose to the macula exceeded 90 Gy. With the advent of ocular coherence tomography to evaluate the macular anatomy and wide-field angiography, which detect preclinical features of altered retinal

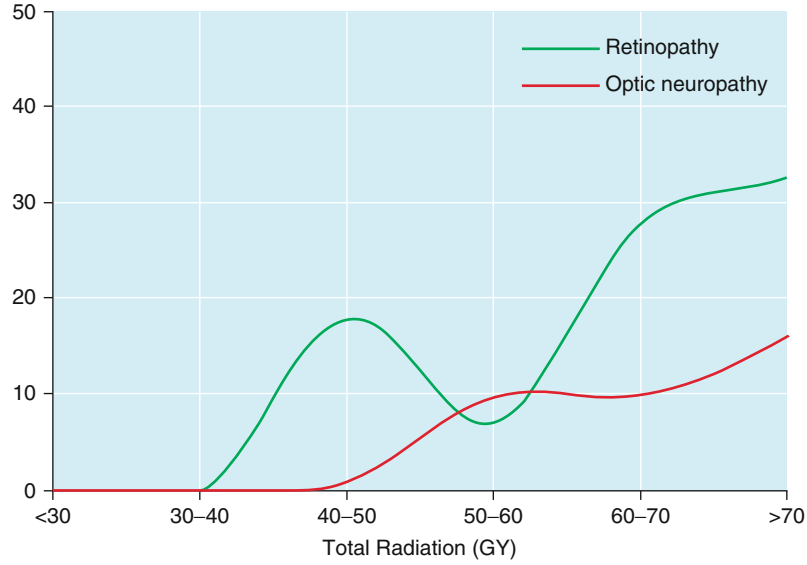


**Fig. 11.6** Total dose of radiation and risk of radiation retinopathy and radiation optic neuropathy (Modified with permission from Monroe et al. [51] and Bhandare et al. [52])

anatomy and function, radiation retinopathy is likely to occur in almost every patient treated with radiation over time.

### 11.9.3 Treatment

Numerous treatment modalities have been utilized in the management of radiation retinopathy and maculopathy. Recent studies and their results include intravitreal injections of triamcinolone and bevacizumab, laser photocoagulation, and hyperbaric oxygen treatment (Box 11.1).

**Box 11.1: Salient Features of Radiation Retinopathy**

- Total dose and fraction size of radiation are the key determinants
- Presence of diabetes and history of prior chemotherapy increases the risk and severity of radiation retinopathy
- Doses of less than 45 Gy (fractions size ≤2.0 Gy) are unlikely to cause significant retinopathy in the absence of coexisting host risk factors
- Insult to vascular endothelial cell is the underlying basis of radiation retinopathy
- Discrete foci of capillary nonperfusion (cotton wool spots) and telangiectasia are the earliest features
- The incidence peaks 2–3 years after radiation exposure
- At present, there is no effective treatment of radiation retinopathy

Intravitreal triamcinolone acetonide is used to treat macular edema secondary to other retinal vascular diseases. Although the mechanism is poorly understood, triamcinolone may help to restore a compromised inner blood–retinal barrier [38]. Triamcinolone acetonide is thought to modulate cytokines and regulate capillary permeability [39]. However, steroid-induced glaucoma necessitating topical therapy and or surgery may complicate this treatment modality.

Bevacizumab has been used to treat exudative age-related macular degeneration, diabetic retinopathy, and vein occlusion. Bevacizumab is a humanized monoclonal antibody to vascular

endothelial growth factor (VEGF), and blocking VEGF is thought to decrease vascular permeability and inhibit abnormal neovascularization [40]. Twenty-one patients with radiation retinopathy following palladium-103 brachytherapy were treated with intravitreal bevacizumab (1.25 mg/0.05 ml) every 6–12 weeks. After a mean follow-up of 7.8 months, 86 % (18/21) had stable or improved visual acuity, with 14 % (3/21) regaining 2 or more Snellen lines [38].

However, some studies utilizing bevacizumab suggest that the improvement is likely temporary [41]. It is our experience that intravitreal bevacizumab in patients with recent onset visual decrease secondary to radiation maculopathy have only a transient subjective response. However, vision usually returns to pre-injection treatment levels within a year. It is generally believed that the role of bevacizumab for radiation maculopathy is limited, as the initial damage has occurred at the time the radiation was delivered.

Laser photocoagulation has also been used to treat or prevent radiation retinopathy and macular edema. Pan-retinal laser photocoagulation has been shown to successfully treat proliferative radiation retinopathy, whereas focal photocoagulation has been used to treat or prevent macular edema with a more variable degree of vision improvement [42–44]. In 19 patients with radiation-induced macular edema, focal laser therapy led to resolution of edema in 26 % (5/19) at 6 months compared with 4 % (1/19) in the untreated group [42]. However, after 2 years, there was no significant difference in visual acuity between treated and untreated eyes.

### 11.9.4 Preventive Strategies

As the current experience with treating radiation damage of the retina remains disappointing, recent efforts to attenuate iodine-125 with vitreous substitutes at the time of treatment have been reported. Oliver et al. were the first to demonstrate an attenuating effect of silicone oil 1,000 centistokes, silicone oil 5,000 centistokes, perfluorocarbon, and heavy liquid against iodine-125 in cadaver eyes, in an in vitro model, and with Monte Carlo modeling. The effect of silicone oil 1,000 centistokes was the most robust at approximately 55 % when compared to vitreous [8]. Therefore, performing vitrectomy with silicone oil 1,000 centistokes at the time of iodine-125 plaque surgery may be a feasible method to reduce the exposure of healthy tissues to iodine-125 radiation and is currently being offered as a treatment option for uveal melanoma at some centers.

## 11.10 Radiation Optic Neuropathy

### 11.10.1 Clinical Features

Although poorly understood, ionizing radiation is believed to damage the optic nerve through injury to both glial and endothelial cells. Over time, these injured cells accumulate and lead to demyelination and neuronal degeneration. Damage to the vascular endothelial cells leads to vascular occlusion and necrosis. Pathology specimens show a decreased number of endothelial cells and endothelial cell-lined vessels as well as fibrosis of vessel walls, reactive gliosis, ischemic demyelination, and perivascular inflammation [45, 46]. The slow cellular turnover rate of endothelial and glial cells is consistent with the delayed onset of radiation-induced optic neuropathy [47].

Clinically, radiation-induced optic neuropathy may present with sudden, painless, monocular vision loss. Radiotherapy may lead to ischemic insult anterior to the lamina cribrosa, which causes swelling of the optic nerve head [48]. Other features of optic neuropathy may include disc swelling, peripapillary hard exudates, and hemorrhages (Fig. 11.7). Optic nerve head swelling eventually resolves resulting in a pale and featureless nerve associated with limited vision [49].

### 11.10.2 Dose Relationship

Important risk factors for developing postradiation optic neuropathy include close proximity of the tumor to the optic disc, greater dose to the optic disc, and large tumor size (Fig. 11.6) [33, 44, 45].

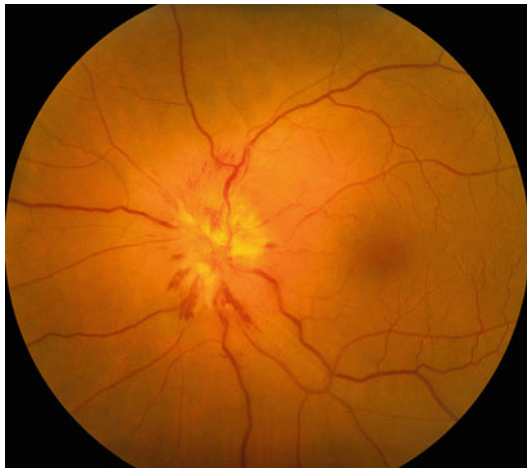

**Fig. 11.7** Typical appearance of radiation optic neuropathy. Note optic disc swelling with surrounding exudates and hemorrhages

### 11.10.3 Treatment

There are some reports of spontaneous improvement of anterior radiation-induced optic neuropathy. However, most cases progress to severe monocular vision loss and optic atrophy. Although there are studies examining treatment for optic neuropathy secondary to external beam radiation with bevacizumab, hyperbaric oxygen, corticosteroids, and pentoxifylline and vitamin E, few reports describe successful treatment for optic neuropathy after plaque brachytherapy.

Of all the complications associated with radiotherapy, optic neuropathy is the most devastating to visual function. It is our experience that most cases of severe visual loss following treatment are the results of this unavoidable and untreatable complication.

**Conclusions**

Although radiation therapy has become the treatment of choice for intraocular malignancies, there are numerous posttreatment complications of relevance to the ocular oncologist and referring ophthalmologist. Anterior segment pathology occurs in 4–23 % of treated patients with enucleation rates for neovascular glaucoma found to be as high as 12 % after treatment, perhaps greater in eyes undergoing proton beam radiation. Radiation-induced cataract develops in 8–83 % by 5 years post-radiation, and radiation retinopathy may occur in at least 10–63 % of treated eyes, if not more over time. Optic neuropathy has been reported in up to 16 % of patients. All of these complications affect overall visual acuity, and 26–62 % of treated eyes experience a loss of at least 2 Snellen lines. Although cataract surgery for radiation-induced cataract may be effective in improving visual acuity, other treatment modalities, such as intravitreal triamcinolone or bevacizumab injections, hyperbaric oxygen treatments, and laser photocoagulation, for radiation-induced retinopathy, maculopathy, and optic neuropathy appear to be far less effective. Ocular complications associated with radiotherapy are well known, and the incidence of reported complications is highly variable. Complications not only depend on tumor size and location but also may be related to radiation planning and surgical technique that may vary between treatment centers.

While radiation complications are difficult to compare between brachytherapy and stereotactic fractionated and single fraction therapy because of differences in fraction size, total dose, dose rate, and treatment volumes, it is clear that the risk of many complications increases above certain dose thresholds. Future efforts may be directed toward limiting the exposure to healthy tissue at the time that the radiation is delivered [50] such as has been demonstrated with silicone oil 1,000 centistokes placement at the time of brachytherapy [8].

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