

## Review Article

# Ophthalmic and adnexal complications of radiotherapy

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### ABSTRACT.

The role of radiotherapy in ophthalmic practice continues to grow. This growth has seen an expansion of indications for radiotherapy, a refinement of the modalities that can be used and a reduction in the ocular and adnexal complications that result from this form of therapy. The compendium of indications for radiotherapy in ophthalmology continues to grow and now includes many conditions such as the treatment of lid and adnexal disease, ocular surface disorders and both benign and malignant disease of the posterior segment and optic pathways. The radiotherapeutic modalities employed to manage these conditions are numerous and include both radioactive plaques (brachytherapy) and external beam radiation techniques. New techniques such as stereotactic radiosurgery are delivering benefits in the management of conditions such as optic nerve sheath meningioma, where the treatment of this blinding and occasionally life-threatening intracranial neoplasm now results in fewer adverse effects. The purpose of this review is to give a brief overview of the indications and treatment modalities, and a more in-depth discussion of the potential side-effects when radiotherapy is used for ocular and periorbital disease.

**Key words:** complications – indications – ocular – orbital – radiotherapy – treatment modalities

Acta Ophthalmol. Scand. 2007; 85: 240–250

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doi: 10.1111/j.1600-0420.2006.00822.x

## Introduction

### Radiobiology

The biological effects of radiation, particularly at the molecular level, are becoming increasingly well understood. Both photons (X-rays and gamma-rays) and particles (e.g. protons) interact with matter and may

lead to either direct damage to DNA or indirect injury through interactions with nearby molecules (such as water) and subsequent free radical formation (Hall 2000; McMillan 2003). Radiation can also cause cell death through the induction of apoptosis (programmed cell death) (Peltenburg 2000).

The efficacy of radiotherapy is determined by aspects of radiation delivery and the biological consequences to the tumour and normal tissues. By giving radiation doses over a number of fractions, damage to normal tissues can be reduced due to the repair of sublethal damage between fractions and repopulation of cells during the course of treatment. Although the radiosensitivity of different tumours varies considerably (Steel 1997), in general tumour cells are more susceptible to radiation than normal tissues as they are less able to reduce the amount of DNA damage inflicted by radiation and have less fidelity of DNA repair.

Just as tumour cells differ in their vulnerability to ionizing radiation, so too do normal tissues. The tolerance dose (TD) 5/5 (probability of a 5% complication rate at 5 years) and the TD 50/5 (probability of a 50% complication rate at 5 years) are terms used to express this variability in tissue sensitivity. In 1991, Emami et al. (1991) reviewed the literature to determine TD 5/5 and TD 50/5 using conventional fractions of 1.8–2.0 Gy for various structures including the lens, retina and optic nerve. Subsequently, others have published varying tolerance doses, some of which conflict with the results published by Emami et al. (1991) (Parsons et al. 1983, 1994a, 1994b, 1996; Jiang et al. 1994).

**Table 1.** Tolerance doses of the optic nerve, retina, ocular surface and lens.

Ophthalmic structure	Manifestation of toxicity	TD 5/5 (Gy)	TD 50/5 (Gy)
Optic nerve	Optic neuropathy	> 55	> 65
Retina	Retinopathy	45–50	55
Ocular surface	Severe dry eye	35	50
Lens	Cataract	10	18

TD = tolerance dose.

Table 1 represents a synthesis of these data.

**Radiotherapy types**

The major modalities employed in ocular radiotherapy are external beam radiotherapy and brachytherapy (application of plaques). The location and type of pathology inform the choice of technique (Table 2).

*External beam radiotherapy*

External beam radiotherapy (EBRT) utilizes radiation types such as pho-

tons, electrons and protons. Photons of lower energies (kilovoltage, kV) are produced by superficial and orthovoltage X-ray machines. Higher energy photons (megavoltage, MV) are produced by linear accelerators (Linacs). High-energy MV photons penetrate deeply through tissue and exhibit a ‘skin-sparing’ property (the surface dose is less than the dose delivered to the underlying tissue) (Khan 2003), which allows for the delivery of adequate doses to deep-seated tumours without the limitations imposed by a

**Table 2.** Ophthalmic indications for radiotherapy and their respective treatment options.

Ophthalmic indications for radiotherapy	Type(s) of radiotherapy used
Malignant tumours	
Primary intraocular tumours	
Choroidal melanoma	Primary treatment: EBRT (protons), brachytherapy <sup>125</sup> I, <sup>198</sup> Au, <sup>103</sup> Pd, <sup>106</sup> Ru Post-enucleation: EBRT (MV photons), brachytherapy
Retinoblastoma	Primary treatment: EBRT (MV photons), brachytherapy ( <sup>106</sup> Ru)
Adenocarcinoma of the RPE	Brachytherapy
Primary orbital and periocular tumours	
Tumours of the adnexa (e.g. lymphoma, rhabdomyosarcoma)	EBRT (MV photons) or brachytherapy (electrons)
Lacrimal gland carcinoma	EBRT (MV photons) or brachytherapy
Optic nerve tumours (e.g. meningioma)	EBRT (MV photons) or stereotactic radiosurgery
Chiasmal tumours	MV photons (EBRT) or stereotactic radiosurgery
Pituitary lesions	EBRT (MV photons) or stereotactic radiosurgery
Periocular BCC, SCC	EBRT (kV photons, MV)
Periocular and conjunctival Kaposi’s sarcoma	EBRT (kV photons) or brachytherapy ( <sup>90</sup> Sr)
Secondary intraocular, orbital or periocular tumours	
Choroidal deposits	EBRT (MV photons) or brachytherapy (electrons)
Orbital/periorbital metastases	
Benign conditions	
Thyroid ophthalmopathy	EBRT (MV photons)
Pterygium	Brachytherapy ( <sup>90</sup> Sr)
Exudative inflammatory processes of the posterior segment	EBRT (MV photons)
Age-related macular degeneration	EBRT (MV photons)
Choroidal haemangioma	EBRT (MV photons) or brachytherapy
Non-specific orbital inflammatory syndrome	EBRT (MV photons)

RPE = retinal pigment epithelium; EBRT = external beam radiotherapy; MV = megavoltage; kV = kilovoltage; BCC = basal cell carcinoma; SCC = squamous cell carcinoma.

prohibitively large skin dose (Fig. 1). Lower energy kV photons give their maximum dose at or very near the skin surface and penetrate less deeply into tissue (Fig. 2). Hence, they are clinically more useful for superficial tumours such as periocular squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).

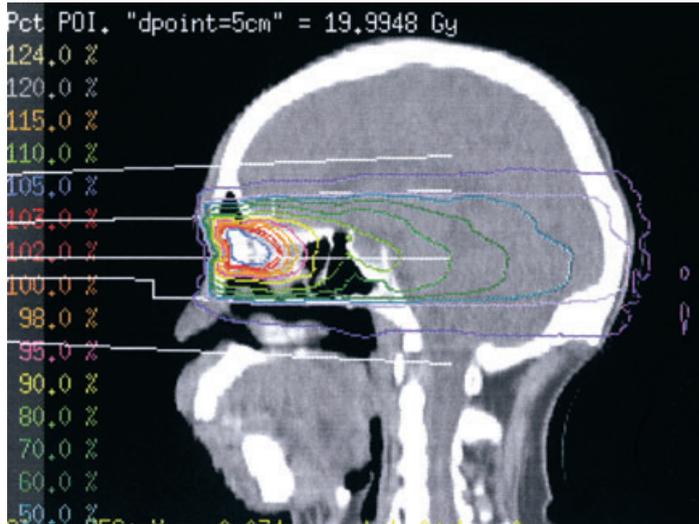
Stereotactic radiosurgery (as a large single fraction or multiple fractions) involves the use of multiple, small MV photon fields (typically < 3–4 cm diameter). These are delivered through several arcs or fixed fields of radiation centred on the same point to treat well defined intracranial lesions. The treatment concentrates the dose in the target tissue and spares the normal brain as much as possible. Stereotactic fractionated radiotherapy is being used increasingly in the management of meningiomas in close proximity to the visual pathway, such as those of the optic nerve sheath or parasellar region (Behbehani et al. 2005). Stereotactic radiosurgery (gamma-knife) has also been used experimentally for uveal melanoma (Mueller et al. 2000) and for choroidal metastases (Bellmann et al. 2000) as an alternative to enucleation. It has also been employed in the treatment of choroidal haemangioma (Shields et al. 2004).

Electron beams are used for treating superficial tumours with a characteristic sharp drop-off in dose beyond the tumour. This makes electrons another useful modality for the treatment of periocular SCC and BCC (Anscher & Montana 1993; Dutton 1993; Leshin & Yeatts 1993).

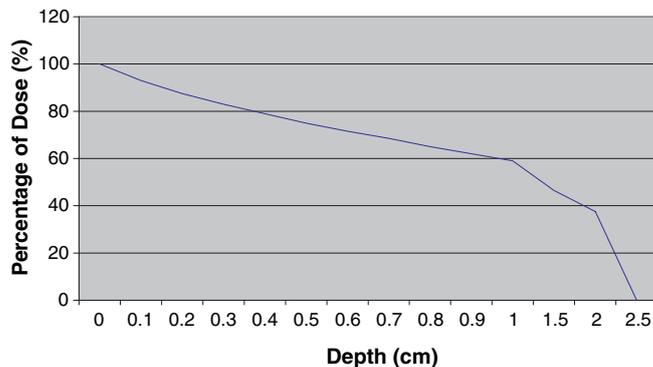
Protons deposit their dose very slowly with depth and then very sharply near the end of the range (the characteristic ‘Bragg peak’), before dropping off to an almost zero value beyond (Khan 2003). By confining the high-dose region to the tumour volume, the dose to surrounding normal tissue can be minimized. Some researchers consider protons to be the treatment of choice for choroidal melanoma (Hall 2000).

*Brachytherapy*

Plaque brachytherapy involves the use of radioactive sources such as strontium-90, ruthenium-106, iodine-125 and palladium-103. These take the form of ophthalmic applicators, which are placed on or sutured to the sclera.



**Fig. 1.** Isodose curves for an Aboriginal patient who underwent external beam radiotherapy following exenteration for a choroidal melanoma. Note the relative skin-sparing effect, with the majority of the dose concentrated on the area of the lesion. It should also be noted that some radiation reached the occipital lobe.



**Fig. 2.** Depth-dose curve for external beam radiotherapy (kV photons) on a superficial tumour. The majority of the dose is delivered to the skin, whereas at a depth of 2.5 cm there is negligible residual radiation.

These sources emit beta-particles (electrons) with short ranges (millimetres), making them clinically useful for the treatment of lesions such as uveal melanoma and retinoblastoma (Fig. 3). Whereas the beta-particles emitted from these applicators are potentially damaging to important structures, older applicators (e.g. cobalt-60) used sources that emit more penetrating gamma-rays (photons). The deeper penetration of these rays had greater potential to give damaging doses to vital structures such as the macula and optic nerve (Bomford 2003).

**Indications for radiotherapy**

Radiotherapy has many ophthalmic applications (Table 2). These range from malignant to benign conditions and vary with the location of the pathology from periocular and orbital

disease, to disease of the retina, choroid and optic nerve pathways. However, these indications are not the only scenarios where radiotherapy can lead to ocular and adnexal complications. Radiotherapy used for treatment of nasal, paranasal sinus and intracranial disease also has the potential to cause adverse ophthalmic effects if the periorbital area is included within the treatment field.

**Complications of ocular and periocular radiotherapy**

**Periocular skin**

The periocular skin undergoes acute and late phase reactions following radiotherapy. Radiation dermatitis

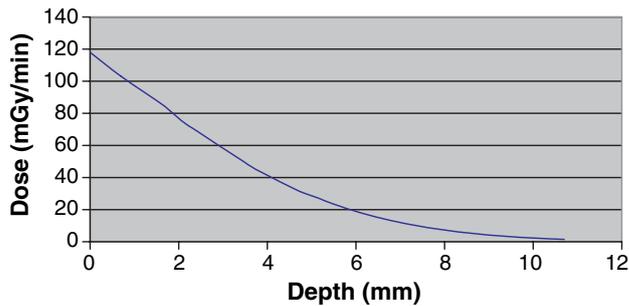
(Fig. 4) and madarosis are classed as acute effects, whereas telangiectasia, skin atrophy and depigmentation present as late effects (Fig. 5A, B).

The initial reaction is seen within 2 weeks of fractionated EBRT. This delay correlates with the time required for cell migration from the basal to the keratinized layer of skin (Mettler & Upton 1995). Initially, erythema is observed, and this is soon followed by dry desquamation. The skin at this time can be erythematous, warm, and sometimes oedematous. Microscopically, the upper dermal vessels are dilated and inflammatory infiltration with granulocytes, macrophages, eosinophils, plasma cells and lymphocytes is seen. Hamilton et al. (1996) demonstrated that factors such as male gender, age and prior sun exposure increase the occurrence of skin erythema independent of the dose of radiotherapy. The same study found that even with doses of < 1.5 Gy per fraction, the occurrence of acute radiation erythematous reaction was almost ubiquitous.

The severity of the reaction depends on skin dose per fraction and the total dose delivered. The most severe reactions often occur where the beam strikes the skin tangentially, inducing moist desquamation. This is a more severe reaction, marked by disruption of the epidermal layer. Treatment may need to be interrupted to allow the cells of the less affected basal layer to re-epithelialize.

In the longer term, periocular skin, like skin elsewhere, undergoes a fibrosing reaction after exposure to ionizing radiation. These changes are thought to be mediated via connective tissue changes such as stiffening of elastic fibres and cytokine activation. Activation of angiogenic factors may be responsible for telangiectasia (Riekkki et al. 2001). These late changes can lead to difficulties in diagnosing the recurrence of the primary pathology, especially in the case of skin malignancy. In addition, the reduced vascularity of the irradiated tissues may make further surgery more problematic, particularly if techniques such as skin grafting are used.

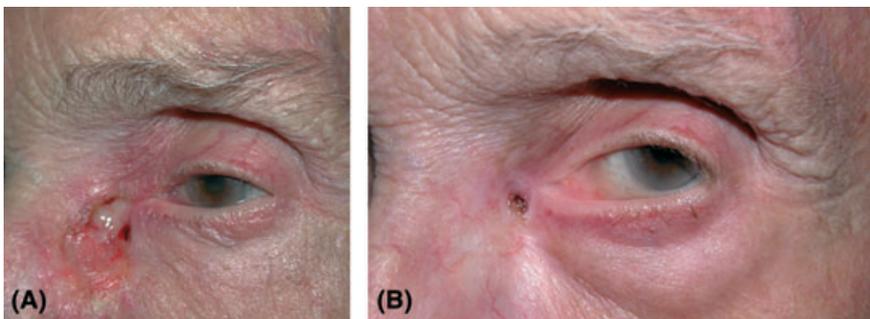
There is also evidence to suggest significant DNA damage to the skin cells as a result of radiotherapy. This may be made manifest by the



**Fig. 3.** Depth-dose curve for brachytherapy where a 15.5-mm ruthenium-106 plaque has been measured. The majority of the dose (118 mGy/min) is delivered at a depth of 0.0 mm and only 1.46 mGy/min is left at a depth of 10.7 mm. This demonstrates that in episcleral brachytherapy for choroidal tumours, the sclera receives the highest dose.



**Fig. 4.** Erythema in radiation dermatitis 2 weeks after radiotherapy. In this case radiotherapy was used as an adjuvant therapy following exenteration for lacrimal gland adenocarcinoma.



**Fig. 5.** (A) Squamous cell carcinoma at the left medial canthus prior to radiotherapy. (B) The same patient 9 months after radiotherapy, with telangiectasia, atrophy and depigmentation of the skin, as well as madarosis involving the medial upper and lower eyelids.

induction of various neoplasms (see section on secondary neoplasia).

The management of complications affecting the skin has not been extensively studied. One double-blind, randomized study found a significant reduction in acute radiation dermatitis with the use of potent corticosteroid cream (Bostrom et al. 2001). Another recent randomized, controlled trial found no additional benefit in applying prophylactic creams (such as aqueous cream or sucralfate) to the skin over washing with mild soap and

water. This led the authors to advise that patients be informed that the use of aqueous cream is not associated with harm or benefit and that they should therefore make an individual decision as to whether to apply it to inflamed skin (Wells et al. 2004).

#### Ocular surface, conjunctiva and lacrimal gland

Xerophthalmia occurs as a result of damage to glands within the eyelid, decreased conjunctival mucous

production and reduced lacrimal gland secretion. Early effects are conjunctival inflammation, chemosis and tear film instability with a resultant dry eye sensation. These generally subside but may, on occasion, be persistent.

Dry eye syndrome occurs with increasing frequency as the total dose of radiotherapy increases (Parsons et al. 1994c, 1996; Brady 1996). This phenomenon is related to the toxic effects on cells with high turnover, as well as specific alterations in cell type and function. For example, it is known that increased conjunctival epithelial stratification and reduction in goblet cell numbers contributes to a dry eye following radiotherapy (Heimann et al. 2001). Similarly, loss of serous acinar cells from the lacrimal gland is contributory (Stephens et al. 1991).

These effects are dose-dependent (Parsons et al. 1994c; Kennerdell et al. 1999; Stafford et al. 2001) and the incidence of dry eye increases steeply at doses > 40 Gy (Parsons et al. 1996). Parsons et al. (1994c) suggested that EBRT at doses > 57 Gy to the lacrimal gland resulted in a 100% (17/17) incidence of severe dry eye (defined as dry eye resulting in corneal opacification, ulceration or vascularization and secondary visual loss). At doses of 30–45 Gy and < 30 Gy severe dry eye occurred with an incidence of 30% and 0%, respectively.

Bessell et al. (1987) found similar results to Parsons et al. (1994c), but a further study involving radiotherapy for orbital lymphoma suggested that doses  $\geq 35$  Gy result in a significant incidence of late complications to the ocular surface (Stafford et al. 2001). In another series on radiotherapy for orbital lymphoma, Kennerdell et al. (1999) used doses of 24 Gy or 25.5 Gy. They described no treatment-limiting complications, but did note that 50% (27/54) of patients experienced early side-effects of mild xerophthalmia and chemosis, and the only chronic side-effect was mild xerophthalmia in 33% (18/54) of patients. Roth et al. (1976) also noted changes at doses < 30 Gy, describing tear-oil deficiency and corneal drying as a result of meibomian gland obliteration at doses of 8–30 Gy.

A synthesis of these results suggests that doses > 57 Gy are predictive of certain xerophthalmia and those < 30 Gy are less likely to have a

lasting effect on the ocular surface. In lower dose radiotherapy (30–45 Gy) the time from treatment to the appearance of these complications is reported to be 4–11 years, whereas with high doses (> 57 Gy) corneal vascularization and opacification are usually apparent within 9–10 months. There is some evidence to suggest that using a lacrimal shield in situations where this would not compromise tumour control may reduce these adverse effects. Similarly, proton beams and intensity modulated radiotherapy (IMRT) may minimize these effects. Treatment modalities for radiation-induced xerophthalmia include topical lubricants, punctal occlusion and, rarely, salivary gland transplantation.

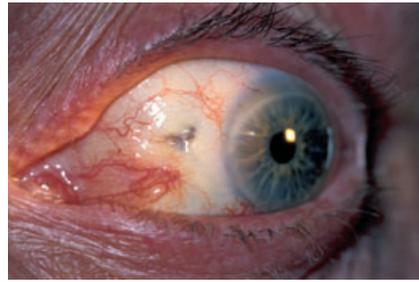
**Cornea**

The effects of tear film dysfunction may contribute to the temporary keratopathy seen after radiotherapy. This is most often manifest as punctate epithelial erosions or, in the case of severe dry eye, corneal scarring. The former normally occurs at doses of 30–50 Gy in 4–5 weeks and settles within a few weeks or months of irradiation. Topical steroids and antibiotics may alleviate discomfort (Bomford 2003).

The cornea itself is also directly vulnerable to ionizing radiation that may result in delayed corneal dystrophy and eventually necrosis. This radiation-induced corneal decompensation is more likely associated with the loss of stem cells than direct corneal ‘melting’. This effect of radiotherapy upon the cornea has been described as an early result of high-dose radiotherapy, but it is very rare and is more likely to become apparent months after treatment (Blodi 1958; Bedford 1966; Linnell & Wolter 1967). A marker of this late complication is decreased corneal sensation to the point of complete anaesthesia, which may then progress to occult corneal ulceration. The ulceration is typically insidious, involving the majority of the corneal thickness, and can be located centrally or marginally. Where ulceration involves the corneal margin it can be either localized or circumferential. Few recent papers have described this complication.

**Sclera**

The sclera is predominantly avascular and is therefore more radioresistant



**Fig. 6.** Scleral atrophy in a patient more than 10 years after plaque radiotherapy. The brachytherapy was used as an adjuvant following surgical excision of the pterygium.

than other ocular tissues. However, scleral atrophy and necrosis (Fig. 6) have been reported to occur in eyes receiving radiotherapy (Tarr & Constable 1980; Petrovich et al. 1994; Shields et al. 2001, 2003) for various indications, including uveal melanoma, retinoblastoma and in the adjuvant treatment of pterygium (Hirst 2003). The wide variation in its prevalence appears to be unrelated to radiation dose, degree of fractionation or patient age, but the majority of papers that describe scleral atrophy following radiotherapy do so in the setting of brachytherapy. Scleral atrophy and necrosis are serious dose-limiting factors in episcleral brachytherapy. One study reported the incidence of histological scleral atrophy in 38 enucleated eyes that had undergone EBRT, brachytherapy or enucleation alone for uveal melanoma. Scleral atrophy was present in 33% of eyes treated with brachytherapy and in none treated with EBRT or enucleation alone (Petrovich et al. 1994).

The occurrence of scleral atrophy has particular relevance in the setting of postoperative brachytherapy following pterygium excision. Tarr & Constable (1980) reported a prevalence of scleral atrophy of 80% among 63 eyes treated with an average dose of 35 Gy. Follow-up ranged from 3 to 20 years, with a mean of 144 months. More recent studies have reported the prevalence of scleral atrophy following brachytherapy as 13% (99 cases of 747 treatments, 95% of which received 22 Gy and 5% 18 Gy in single fractions) with follow-up over 10 years (MacKenzie et al. 1991), 5% (five eyes of 100 treated with total doses of 20, 30 and 60 Gy) with a median follow-up of 49 months (Monteiro-Grillo et al. 2000) and 0.5%

(two cases of 393, with doses of either 30 or 35 Gy in three fractions) with a median follow-up of 17 months (Fukushima et al. 1999). None of these series reported statistically significant correlates, such as total dosage or fractionation, to predict the occurrence of this complication. However, it was postulated by Tarr & Constable (1980) that factors such as surgical damage, degree of scleral exposure, damaged conjunctiva and dry eye may facilitate the development of this late complication.

Diagnosis may be difficult as the condition may masquerade as posterior scleritis, serous retinal detachment or pseudotumour, and it has a prolonged latency ( $\geq 20$  years). In addition, scleral atrophy is not necessarily a sterile event as it can be complicated by corneoscleritis and endophthalmitis with bacterial or fungal organisms (Moriarty et al. 1993).

**Iris and anterior chamber**

Complications affecting the anterior chamber are becoming less common with reducing doses of radiotherapy. Several side-effects can occur, including iridocyclitis (Tyradellis 1979; Brovkina et al. 1991), iris atrophy (Tarr & Constable 1980) and neovascular glaucoma (NVG). The latter and most worrying complication arises in one of two settings: firstly after radiotherapy (by EBRT or brachytherapy) for iris or ciliary body malignant melanoma, and secondly, as a result of radiation retinopathy.

Ischaemia of the retina in radiation-induced retinopathy may act to drive the proliferation of new iris vessels. Similarly direct damage to iris vessels and the resultant ischaemia may drive the formation of iris atrophy and the local proliferation of iris vessels. It is also hypothesized that the release of humoural factors from irradiated tumour tissue may stimulate neovascularization in the iris (Foss et al. 1997). These mechanisms may then lead to rubeotic glaucoma.

Neovascular glaucoma is a complication that arises in up to 35% of eyes treated with radiotherapy (Shields et al. 1989, 2001, 2003; Bacin et al. 1998) and may lead to enucleation following radiotherapy. The reasons for the variable prevalence of NVG have been documented in a number of

papers. Daftari et al. (1997) reported on the prevalence of NVG among 347 patients who underwent helium ion EBRT for uveal melanoma. They determined that the development of NVG was correlated with the amount of lens exposed, amount of anterior chamber in the treatment field, tumour volume, proximity to the fovea, history of diabetes and the development of vitreous haemorrhage. Zehetmayer et al. (1998) confirmed that complications in the anterior segment were mainly related to tumour volume, as did Foss et al. (1997), who also added that the presence of retinal detachment was a significant independent predictor of NVG. Shields et al. (1989) discussed the reasons for enucleating 59 of 1019 (6%) eyes following plaque radiotherapy for posterior uveal melanoma. Of these 59 eyes, 31% were enucleated for NVG. This uncontrollable NVG occurred an average of 38 months after plaque radiotherapy and, most commonly, after cobalt-60 plaques, which are now less frequently used (see Introduction).

#### Lens

Exposure to several forms of electromagnetic radiation can lead to cataract formation. The best studied are those caused by ionizing radiation (Cogan et al. 1952). In animal studies, X- or gamma-irradiation causes characteristic changes in the cells of the lens, leading to posterior subcapsular and cortical cataracts. The initial insult in the cataractogenic process is damage to the proliferating cells in the germinative zone of the lens epithelium, which leads to extensive cell death (Worgul & Rothstein 1975, 1977; Worgul et al. 1976; Palva & Palkama 1978). This is followed by a wave of compensatory mitosis. When the epithelial cells resulting from this increased proliferation begin to differentiate, the usually precise organization of the fibre cells is disrupted (Worgul & Rothstein 1977). Eventually these abnormal fibres form 'balloon cells' or 'Wedl cells' at the posterior pole, resulting in the formation of a cataract.

Exposure to ionizing radiation has led to several types of cataract. Early papers described doughnut-shaped cataract, posterior subcapsular cata-

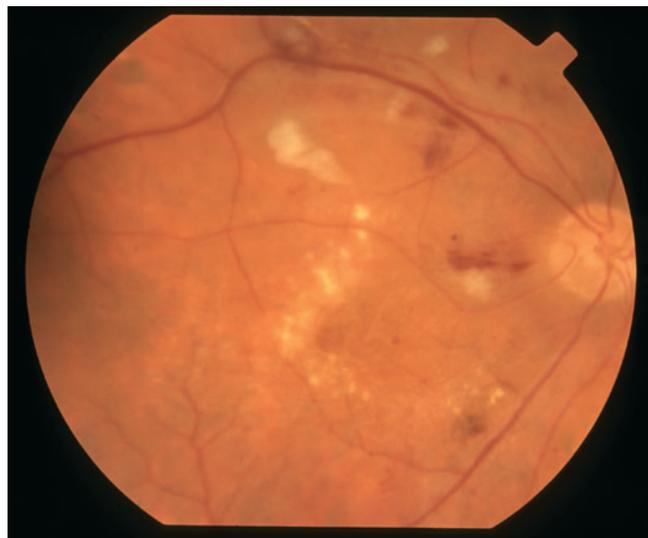
ract, sectoral posterior-subcapsular cataract, cortical cataract and complete opacification of the lens (Alter & Leinfelder 1953; Macfaul & Bedford 1970). The degree to which these occur is correlated with the total radiation dosage, the way in which it is delivered and the rate at which it is given. For example, a prevalence of 0% was obtained when EBRT and lens-sparing techniques were employed to treat intraocular metastases. The mean dose of radiation received was 46 Gy, with average follow-up of 12 months (Bajcsay et al. 2003). A much higher incidence (70%) was noted where plaque radiotherapy delivered an average of 80 Gy across the cornea to treat non-resectable iris melanoma (Shields et al. 2003).

Radiation-induced cataract generally occurs at doses > 8–10 Gy (although there are reports of it occurring with doses as low as 2 Gy) (Schipper et al. 1985; Hall 2000). There is also evidence to suggest that this adverse effect is dependent on fraction size (Merriam & Focht 1957, 1962; Deeg et al. 1984). In addition, the use of more highly penetrating electrons and brachytherapy appears to increase the rate of cataract (Stallard 1933; Takeda et al. 1999). Radiation-induced cataracts typically occur 2–3 years after radiotherapy, with a range of 6–64 months (Anteby et al. 1998). They are often not regarded as a 'severe' complication due to the availability of treatment by phacoemulsification.

#### Retina

Radiation retinopathy was first described by Stallard (1933). It has a delayed presentation as a progressive pattern of degenerative and proliferative vascular changes. These changes have been reported to occur with either EBRT or brachytherapy (Chee 1968; Brown et al. 1982; Archer & Gardiner 1994; Parsons et al. 1994a, 1994b; Anteby et al. 1998; Gunduz et al. 1999; Suarez Baraza et al. 2003; Subramanian et al. 2004; Monroe et al. 2005). The signs include capillary occlusion, dilatation, microaneurysm formation, telangiectasia, intraretinal microvascular abnormalities, neovascularization and retinal pigment epithelial changes (Fig. 7). Interruption to choroidal circulation has also been described; (Archer & Gardiner 1994; Midena et al. 1996). Histologically, there is occlusion of vessels within the choroidocapillaris, pigment dispersion with reduced numbers of melanocytes and corresponding areas devoid of photoreceptor cells. Attenuation of photoreceptors and the nerve fibre layer, invasion of retinal tissue with macrophages, and subretinal fibrosis have also been reported (Gragoudas et al. 1979; Krebs et al. 1992).

The pathogenesis of radiation-induced retinopathy is dependent on total dose, fraction size, number of fractions and coexisting morbidity. The condition does not usually occur at total doses < 45 Gy unless an additional risk factor such as diabetes is



**Fig. 7.** Radiation retinopathy in a patient with type 2 diabetes. There was no retinopathy prior to radiotherapy; these changes developed within 12 months of external beam radiotherapy for thyroid ophthalmopathy.

present (Parsons et al. 1994b, 1996). In a study where 68 eyes received EBRT for the treatment of primary extracranial head and neck tumours, the incidence of retinopathy steadily rose in the dose range of 45–55 Gy where fractions > 1.9 Gy were used (Parsons et al. 1994b). It was also noted by Parsons et al. (1996) that the incidence of retinopathy increased steeply after doses of 50 Gy. A recent retrospective review suggests that this incidence can be significantly reduced by hyperfractionated (twice daily doses of 1.1–1.2 Gy) EBRT, especially when the retina receives more than 50 Gy (Monroe et al. 2005). The effect of radiation is, however, augmented by comorbidities such as diabetic retinopathy, hypertension, simultaneous chemotherapy and by pregnancy (Brown et al. 1982; Viebahn et al. 1991; Kumar & Palimar 2000).

The latency between radiotherapy and onset of clinically significant retinopathy can range from 1 month to 15 years, but most commonly occurs between 6 months and 3 years. The onset is more rapid where treatment regimens have involved high-dose, single-fraction radiotherapy.

Radiation-induced retinal ischaemia has sequelae such as preretinal, papillary and iris neovascularization that can lead to preretinal fibrosis, vitreous haemorrhage, retinal detachment and neovascular glaucoma. The literature suggests that radiation maculopathy and proliferative retinopathy respond to laser photocoagulation (Kinyoun et al. 1988; Amoaku & Archer 1990). Similarly, vitreous haemorrhage and retinal detachment following radiation-induced retinal damage can be managed by vitrectomy and retinal detachment surgery (Buzney et al. 1984).

#### **Optic nerve**

First described by Forest et al. (1956), optic neuropathy is a rare but important complication of radiotherapy with a potentially devastating impact upon vision. It is commonly reported to follow irradiation of primary extracranial head and neck tumours (including the nasal and paranasal sinuses) (Wijers et al. 1999; Zhou et al. 2003), but has also been described after radiotherapy for age-related macular degeneration (Mauget-Faysse et al. 1999), intraocular tumours (Meyer et al. 2000; Finger

et al. 2002; Emara et al. 2004; Puusari et al. 2004) and tumours of the optic nerve sheath, parasellar region, skull base and nasopharynx (Serova et al. 2001; Bowyer et al. 2003; Zhou et al. 2003; Shrieve et al. 2004; Weber et al. 2004).

The effect of radiation upon the optic nerve appears to be both vascular and neuropathic in nature. Microscopically, there are reduced perineural vascular endothelial cells, perivascular inflammation, hyalinization, fibrosis of vessel walls, infarction and reactive gliosis (Kline et al. 1985; Levin et al. 2000). There is also evidence of an effect on replicating glial cells. The induction of genetic mutations in these cells by ionizing radiation is thought to lead to demyelination and neuronal degeneration (Fike & Gobbell 1991). As noted by Miller (2004), this model is consistent with the long latency expected with the slow cellular turnover of both glial and endothelial cells and with the observation that neuronal demyelination and degeneration occur prior to the development of any vascular changes (Zeman & Samorajski 1971).

The presentation of radiation-induced optic neuropathy is variable but most patients develop an irreversible, progressive visual loss 3 months to 8 years following treatment, with a peak onset at 18 months (Roden et al. 1990; McClellan et al. 1995). This may be preceded by transient visual loss and is usually the result of a non-arteritic posterior ischaemic optic neuropathy. There are, however, reports of an acute onset non-arteritic anterior ischaemic optic neuropathy, manifest as disc swelling with surrounding exudate, haemorrhages and subretinal fluid (Brown et al. 1982).

The incidence of optic neuropathy can be as high as 37% depending on the volume of tissue irradiated, the total dose given, the fraction size and premorbid conditions. Jiang et al. (1994) reported on the results of 219 patients who had undergone radiotherapy for cancers of the nasal cavity and paranasal sinuses. They found that no optic neuropathy occurred at total doses < 50 Gy. Between 1964 and 1989 Parsons et al. (1994a) collected similar results following fractionated EBRT upon 215 optic nerves in 131 patients who were being treated

for extracranial head and neck tumours. They found no injury to nerves that had received total doses of < 59 Gy and reported that in patients who received ≥ 60 Gy, the dose per fraction was more important than total dose in producing optic neuropathy. The 15-year actuarial risk of optic neuropathy after doses ≥ 60 Gy was 11% when treatment was given in fraction sizes of < 1.9 Gy, compared with 47% in treatment given in fraction sizes of ≥ 1.9 Gy. In another review, Parsons et al. (1996) found that after treatment at approximately 1.8–2.0 Gy per fraction, the incidence of optic neuropathy steeply increases after doses of 60 Gy. A more recent review of radiotherapy for pituitary adenoma causing acromegaly identified case reports of optic neuropathy following doses in the 40–45 Gy range with fraction sizes of < 2 Gy (Van den Bergh et al. 2003). These authors and others noted that factors such as diabetes mellitus, hypertension, older age, prior chemotherapy and possibly acromegaly itself increase tissue sensitivity to radiation.

The optimal management of radiation optic neuropathy remains elusive. A recent editorial by Miller (2004) outlined a lack of benefit from either systemic corticosteroids or warfarin. The same article alluded to a limited role for hyperbaric oxygen, but the timing of an appropriate regimen and its efficacy are yet to be defined.

#### **Lacrimal drainage apparatus**

The punctae, canaliculi and nasolacrimal ducts can also be affected by radiotherapy. Early series on the complications of radiotherapy (Macfaul & Bedford 1970) and also those reported more recently (Buatois et al. 1996) note stenoses of the lacrimal drainage system. This most commonly occurs within the lateral one-third of the system, manifesting as either punctal or canalicular stenosis. The presumed pathogenesis is a radiation-induced canaliculitis that eventually leads to fibrosis and obstruction. It is not clear whether prophylactic intubation of the lacrimal drainage system prior to radiotherapy decreases the risk of stenosis.

Symptomatic canalicular stenosis often requires insertion of a Jones

tube; in a series of 13 patients with radiation-induced canaliculus stenosis, 12 were relieved of their symptoms after conjunctivodacryocystorhinostomy (Call & Welham 1981). Nasolacrimal duct and canaliculus obstruction may also occur in patients treated with intravenous radioactive iodine (I131), perhaps as a result of the passive passage of tears containing radioactive iodine or active uptake into the tissues of the drainage system (Burns et al. 2004). In addition, it should be noted that concurrent chemotherapy with agents such as 5-fluorouracil or docetaxel may also be responsible for punctal-canalicular stenosis (Eiseman et al. 2003; Esmaeli et al. 2003).

### Orbital bone

Radiotherapy to the ossification centres of bone in children can lead to severe hypotelorism and orbital deformation. This can also result from radiation bone atrophy and necrosis of cartilaginous structures (Macfaul & Bedford 1970; Raney et al. 1999; Nahum et al. 2001). The doses at which these effects occur are not well defined in the literature. It is known, however, that the use of a single fraction of 35 Gy by EBRT to infant rabbits results in reduction of orbital-zygomatic complex linear bone growth, bone volume and bone density (Forrest et al. 2002). Similarly, whereas osteoradionecrosis may rarely involve orbital bone, it is not extensively documented. It is a complication more commonly mentioned as an indication for orbital reconstructive surgery (Mu et al. 1999).

### Secondary neoplasia

Second malignancy is also concerning and has been the subject of many reports (Forrest 1961; Soloway 1966; Smith et al. 1993; Kroll et al. 1994; Scaradavou et al. 1995; Rich et al. 1997; Raney et al. 1999; Matsumoto et al. 2002). A Japanese survey found that of 2000 patients who had received radiotherapy for various indications (not only ocular or periorbital disease), 54 developed second malignancies. The most common was squamous cell carcinoma (44%), followed by sarcoma (29.6%), glioma (9.25%), adenocarcinoma (5.5%), leukaemia (5.5%), and others (5.5%) (Matsumoto et al. 2002). This effect has a latency

of a few years to several decades and bears a complex (non-linear) relationship to dosage. Complicating its occurrence is the use of chemotherapy and the individual patient's genetic predisposition to malignant neoplasia.

The risk of second malignancy following radiotherapy for retinoblastoma has been widely reported. It most commonly occurs where the patient initially has bilateral retinoblastoma or harbours the Rb mutation, and increases in frequency with time (Anteby et al. 1998; Abramson et al. 2004). Abramson et al. (2004) suggest that at 1 year after diagnosis and treatment of retinoblastoma with EBRT, the probability of a second malignancy is 2.3% and at 5 years it is 11.2%. The same authors suggest that 29.7% of patients develop a secondary cancer within 10 years of initial treatment of retinoblastoma, and that there is a cumulative risk of 29.7% at 10 years (Abramson et al. 2004). Second tumours included orbital bone osteosarcoma, pineoblastoma, fibrous histiocytoma, hidradenoma, facial leiomyosarcoma or lip angiosarcoma, and squamous cell carcinoma. It is known from this and other studies that radiotherapy contributes to this risk, especially with the induction of sarcoma (Fig. 8) where a dose-response curve is known to exist (Abramson et al. 1982; Eng et al. 1993).

Concerns regarding tumour induction are even more pertinent to the treatment of benign conditions such as thyroid ophthalmopathy. A number of authors (Snijders-Keilholz et al. 1996; Broerse et al. 1999) have published theoretical data suggesting that the risk of any malignancy following



**Fig. 8.** This patient was treated with external beam radiotherapy for retinoblastoma at the age of 2 years. His eye was later enucleated after the tumour recurred. At the age of 18 years he presented unable to fit his prosthesis. Histology proved the mass to be osteosarcoma.

EBRT for thyroid ophthalmopathy ranges from 0.3% to 1.4%. The theoretical risk of developing a fatal malignancy following this form of therapy has been estimated as ranging from 0.3% to 0.7% (Akmansu et al. 2003). However, series with longterm follow-up suggest that these figures may be overestimated (Schaefer et al. 2002). They must also be seen in the context of the lifetime cancer probability of 25–33%, but may indicate a need to consider the use of radiotherapy in younger patients more carefully.

Radiotherapy also induces DNA damage to the skin. This is manifest by increases in proteins such as p53 and p21, which are involved in the surveillance and correction of genetic errors (Ponten et al. 2001). The potential for radiotherapy to induce the growth of a variety of cutaneous neoplasms is well documented. These include benign lymphangiomatous papules (Diaz-Cascajo et al. 1999), well differentiated angiosarcoma (Cancellieri et al. 1991), SCC, BCC and malignant melanoma (Di Pietro et al. 1979; Swerdlow et al. 1997; Chuang & Brashear 1999). Squamous cell carcinoma in the setting of previous radiotherapy has a much higher risk of metastasis than does cutaneous SCC in general (Weedon 1997). These neoplasms may occur 15 years or more after radiation therapy and a dose of > 20 Gy is generally required to induce malignant change (Weedon 1997).

## Conclusions

Radiotherapy has been used for ocular and periocular indications since the beginning of the 20th century. Both external beam and radioactive plaque techniques have been employed for malignant and benign disease, with varying degrees of efficacy. Cataract, dry eye and retinopathy were once common sequelae to the use of radiation. However, with a better understanding of the tolerance doses of these structures, fractionated therapy, targeted stereotactic beams and utilization of the variable penetrance of various energy forms, radiotherapy has become invaluable in the management of many ophthalmic and periorbital pathologies. Complications involving ocular and adnexal

structures do, however, occur; knowledge of these will help in their identification and ongoing management.

## Acknowledgements

We would like to thank Drs John L. Crompton and Garry J. Davis, Department of Ophthalmology and Visual Sciences and the staff of the Departments of Medical Physics and Radiation Oncology, Royal Adelaide Hospital. Their input into the collation of this review and the collection of images was invaluable.

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Received on February 5th, 2006.  
Accepted on September 5th, 2006.

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