Eye and Orbit

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Contents

Abstract

- *Introduction*: Radiation-induced eye damage occurs from direct ocular irradiation, or when the eye is in the treatment field of another malignancy.
- *Eyelids*: Madarosis is common at low radiation doses, while a number of lid deformities may result from higher doses of radiation in the range of 60–75 Gy, such as ectropion (out-turning of lid margin) or ectropion (in-turning of lid margin). Aberrations in eyelid structure may result in ocular surface compromise.
- *Conjunctiva*: Severe complications include symblepharon formation (adhesions between the bulbar and palpebral conjunctiva following denuded epithelium) and subsequent forniceal shortening, trichiasis (inward turning of the lashes on the ocular surface) and other eyelid malpositions.
- *Sclera*: Fractionated doses of 20–30 Gy can cause thinning, melting or atrophy of the sclera, while its perforation is a rare complication (Brady et al. 1989).
- *Cornea*: The frequency of radiation-induced corneal damage is dose-dependent and most likely at doses greater than 40 Gy (Parsons et al. 1994, 1996). Effects include keratoconjunctivitis sicca (dry eyes) and, less frequently, the end result of ocular surface dysfunction such as corneal ulceration.

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- *Lens*: Cataracts are the most common effect to the lens induced by radiation and are dependent upon dose, dose rate, energy of the source, age of the patient and fractionation.
- *Uvea*: Iris neovascularization, or rubeosis iridis, may occur several months to years following radiation and could result in neovascular glaucoma, permanent nerve damage and visual loss.
- *Optic Nerve*: Optic nerve is deemed to have a radiation threshold of approximately 50–60 Gy, at which point optic neuropathy may develop.
- *Retina*: The threshold for radiation retinopathy is approximately 40 Gy and typically develops at 6 months to 3 years post-radiation. It can be influenced by concomitant vasculopathies such as diabetes and previous chemotherapy.
- *Orbital Bone*: Radiotherapy to ossification centers of children can result in boney deformities from bone growth arrest.
- *Chemotherapy and biologicals*: Chemotherapeutic agents and biologicals can cause a number of ocular side-effects at various levels of the eye.
- *Special Topic- Corticosteroids*: Corticosteroids have a wide range of side effects on the different ocular tissues comprising the eye.
- *Special Topic-Bone Marrow Transplant*: Ocular complications have been reported in 22–82 % of patients with GvHD affecting all layers of the eye (Kerty et al. 1999; Livesey et al. 1989; Franklin et al. 1983).
- *Special Topic- Secondary Cancers*: Retinoblastoma (Rb) patients are at risk for secondary cancers particularly if they harbor the germline Rb mutation.

Abbreviations

BMT	Bone marrow transplant
CSCR	Central serous chorioretinopathy
COMS	Collaborative Ocular Melanoma Study
CTCAE v3.0	Common terminology criteria of adverse events version 3
EGFR	Epidermal growth factor receptor
GvHD	Graft versus host disease
KCS	Keratoconjunctivitis sicca
LENT	Late effects of normal tissues
SOMA	Subjective, objective, management, and analytic descriptors
Rb	Retinoblastoma
SCC	Squamous cell carcinoma
VEGF	Vascular endothelial growth factor

1 Introduction

The eye is a palindrome reflecting both its three part architectural anatomy, and its embryonic origin. The tissues of the eye and orbit "derived from" the trigerminal elements neuroectoderm, surface ectoderm, and mesoderm. Its histogenesis determines its unique construct designed for perception of light, color, and distinguishing different forms and their motion. Different neoplasms arise in each component and vary as a function of age. Both radiation therapy and chemotherapy are often utilized for eye preservation. However, all treatment modalities as well as various cancers arising in and around the eye and orbit can result in loss of vision (Fig. 1).

The embryogenesis determines its histogenesis:

- Neuroectodermal outpouching of the optic cup forms the *retina* and *optic nerve*.
- Surface ectoderm forms the *eyelid epidermis* and its epithelial extensions which become the *conjunctival* cover inside the eyelid and cover the eye globe. As in skin epithelial cells give and cover the eye globe.
- Mesoderm forms the connective tissue and mesenchyme of eye and includes the *sclera* of the eye, the *vasculature in retina and choroid*, its arterial and venous drainage, as well as the *extraocular muscles* and orbital soft tissues, and boney orbit.

Many tissues compose the eye, and each varies greatly in its sensitivity to cytotoxic cancer therapy. Radiation-induced eye damage can occur following direct ocular irradiation for a malignancy of the eye, or incidentally when the eye is in the treatment field of another malignancy, such as paranasal sinus or central nervous system. Chemotherapy, biologics, and bone marrow transplantation cause ocular side effects via systemic exposures and consequential tissue effects. The chapter section begins with relevant anatomical and physiological descriptions of the ocular or adnexal structure—thereby providing a basis for the discussion on the late effects of cancer treatment on the various eye structures. The effects of radiation, chemotherapy, and biologicals are discussed along with a description of the late effects of steroids, bone marrow transplantation, and the concept of secondary cancers. Finally, the later part of the chapter describes therapeutic management and preventative measures.

A toxicity scoring system for the eye was created by the EORTC/RTOG (Rubin et al. 1995) in 1995 as a component of the combined late effects of normal tissues (LENT)/subjective, objective, management, and analytic descriptors (SOMA) grading system for radiation-induced late effects of normal tissue. As part of that effort, Gordon et al.

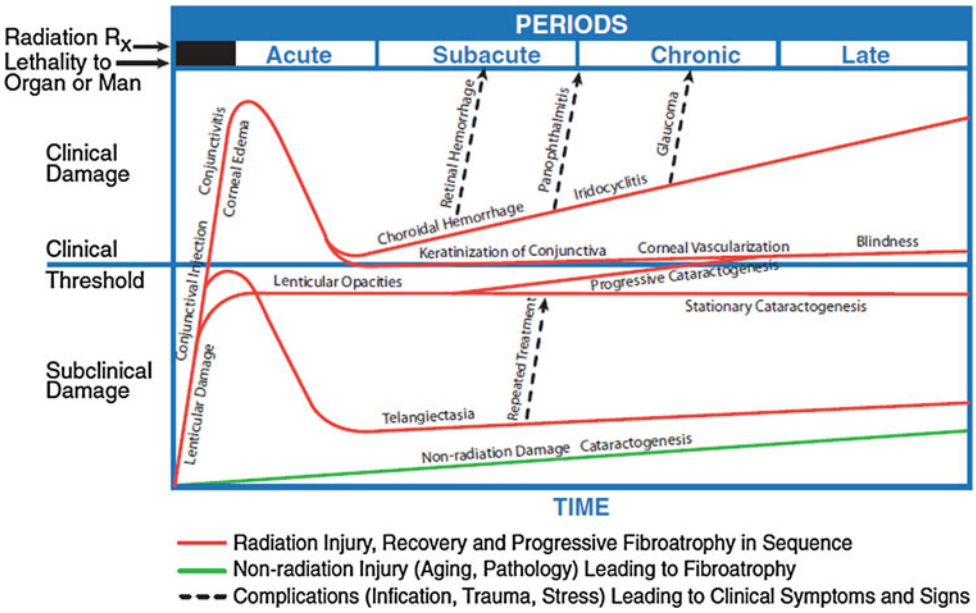


Fig. 1 Biocontinuum of adverse early and late effects of the eye and orbit (with permissions from Rubin and Casarett 1968)

proposed a clinically useful classification system to be used in prospective trials to evaluate the effects of radiation on the visual system (Gordon et al. 1995). Like the LENT/SOMA of other tissues, the purpose of this ocular focused grading system was to standardize and improve data recording on the radiation effects of the eye and ocular adnexa. The National Cancer Institute also created a series of grading systems that best describe chemotherapeutic effects, of which the Common Terminology Criteria of Adverse Events version 3 (CTCAE v3.0) is most recent. Ocular and adnexa tissue is one of the 35 anatomic sites and includes 21 eye-specific adverse event criteria for grading. By providing a system for standardized data, both the LENT/SOMA and CTCAE v3.0 offer a format through which to develop and compare the toxicity profiles of different cancer regimens, and to enhance future treatments (CTE 2006). Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The eye globe is the anatomic isocenter with the anterior component containing the eyelid, the lacrimal gland, and the posterior component containing the orbital content of muscles and nerves (Fig. 2).

The orbital contents consist of the globe, adipose tissue, extraocular muscles (medial, lateral, superior, inferior recti and the superior and inferior obliques). These muscles are innervated by cranial nerves III, IV and VI.

2.2 Histology

The histology of the eye can be described as follows (Fig. 3a, b, c):

- The eyelid can be partitioned into the anterior and posterior lamella.The anterior lamella consists of the skin and orbicularis muscle while the posterior lamella is made up of the eyelid retractors, tarsus and conjunctiva.
- The tear film is made up of three layers: mucous, aqueous and lipid layers. The inner mucous layer is produced by the goblet cells of the conjunctiva and helps tears adhere to the eye. The middle aqueous layer is predominantly produced by the accessory lacrimal glands, while the outer lipid layer is produced by meibomian glands and prevents evaporation.
- The nasolacrimal system is composed of upper and lower puncta in the medial eyelids which collect tears, descend into the canaliculi, then into the lacrimal sac and the nasolacrimal duct which opens below the inferior turbinate of the nares.
- The outer portion of the globe is composed of the sclera and cornea, while the posterior segment is lined with retina and retinal pigment epithelium (RPE). The choroid is a vascular bed that lies between the RPE and sclera.
- Chambers of the eye consist of (i) the anterior chamber, between the cornea and iris, (ii) the posterior chamber is between the posterior surface of the iris and anterior surface and equator of the lens, and (iii) the vitreous chamber, the space between the lens and retina. The vitreous is a gelatinous substance (Fig. 3b, c).
- Uvea contains the iris, ciliary body, and choroid with special emphasis on the canal of Schlemm which drains

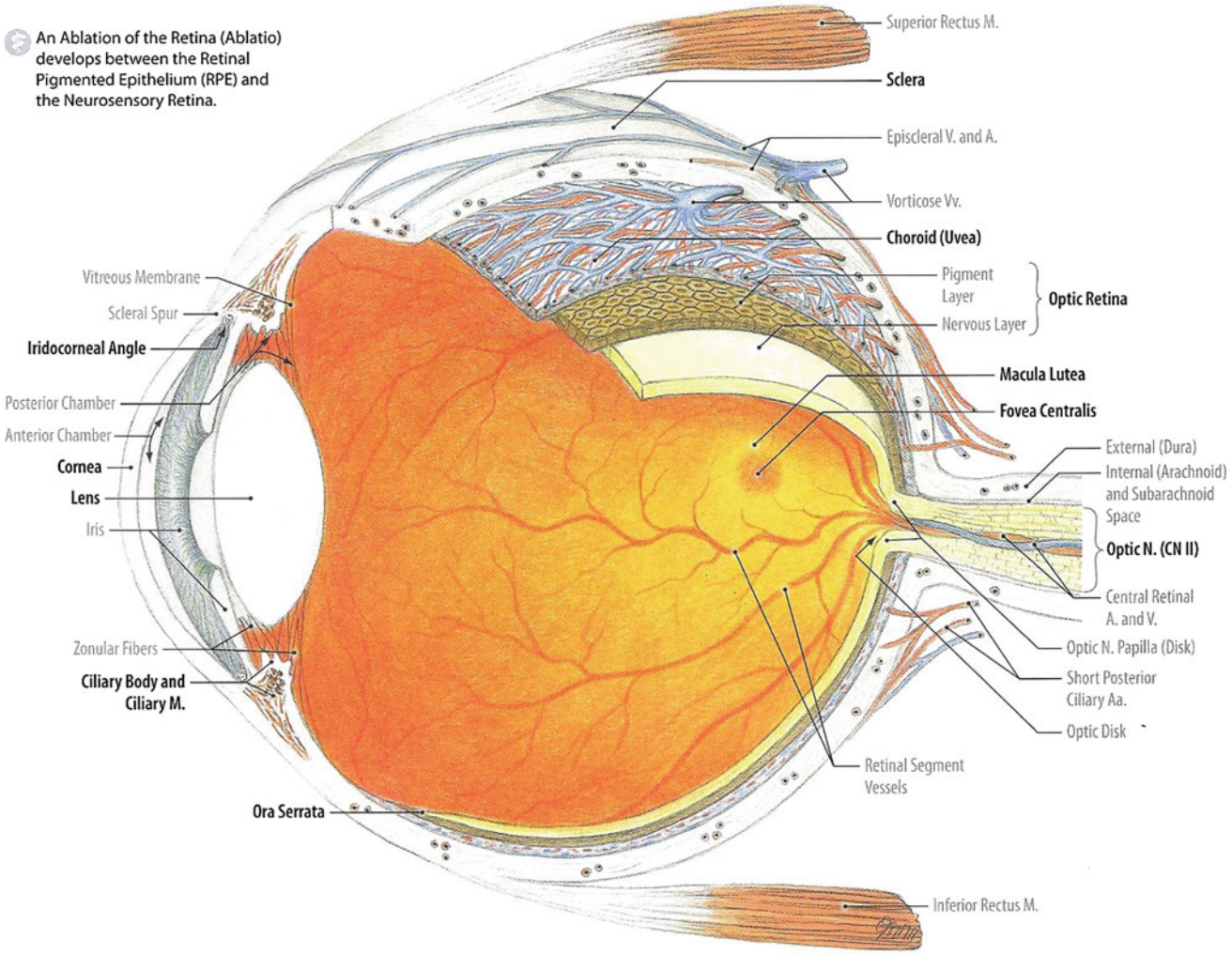


Fig. 2 Illustation (in layers) of the Retina, Choroid, and Sclera in the Outer Area: Median Sagittal Section through the Anterior Eye (with permissions from Tillman 2007)

into episcleral venous system via minute channels through sclera. Obstruction to drainage of aqueous humor through the trabecular meshwork results in increased intraocular pressure, which may lead to optic nerve damage and glaucoma.

- Pupil of the eye consists of 3 sets of circular muscles: outer ciliary muscle, mid-dilator pupillae, and inner sphincter pupillae innervated by 3 different nerves: parasympathetic (outer), sympathetic (mid), and V1 (inner).

3 Physiology and Pathophysiology

3.1 Physiology

The physiology of each component of the eye will be correlated with its anatomy and histology (Fig. 4a, b).

3.1.1 Eyelids, Periorbital Skin, Lacrimal Apparatus

The thinnest skin in the body is located on the outer surface of the eyelids. It is devoid of subcutaneous fat allowing for the accumulation of fluid to manifest rapidly as swelling. The upper and lower eyelids contain fibrous connective tissue, known as the tarsal plates, which function as structural support. The eyelashes are located on the anterior portion of the eyelids and aid in protection of the eye.

The tears drain from the ocular surface via two puncta located on the medial aspect of the upper and lower lid margin. The puncta lead to the canaliculi that empty into the lacrimal sac and, in turn, into the nose via the nasolacrimal duct.

3.1.2 Conjunctiva and Sclera

The conjunctiva is a thin, transparent mucous membrane that lines both the posterior aspect of the eyelids (palpebral

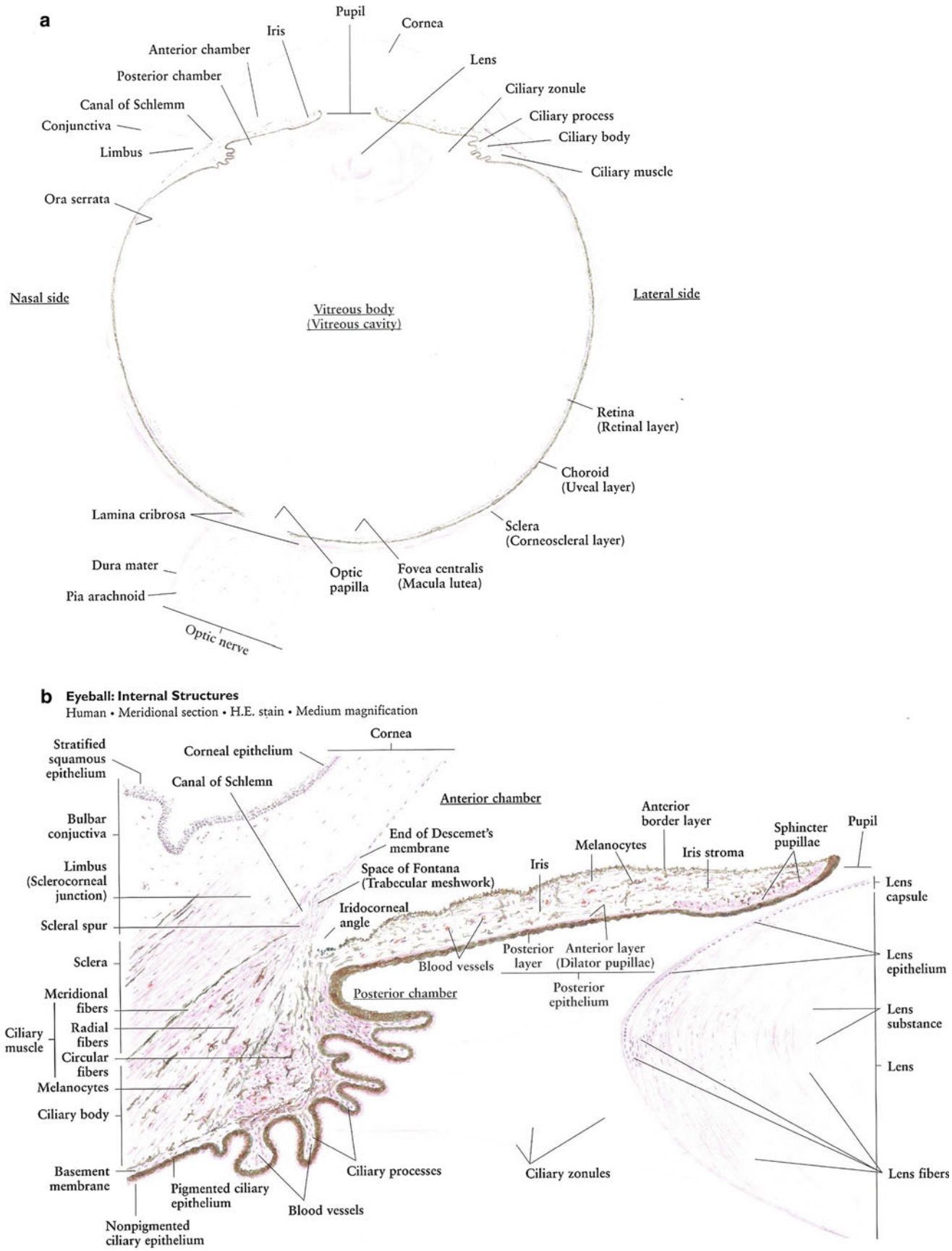
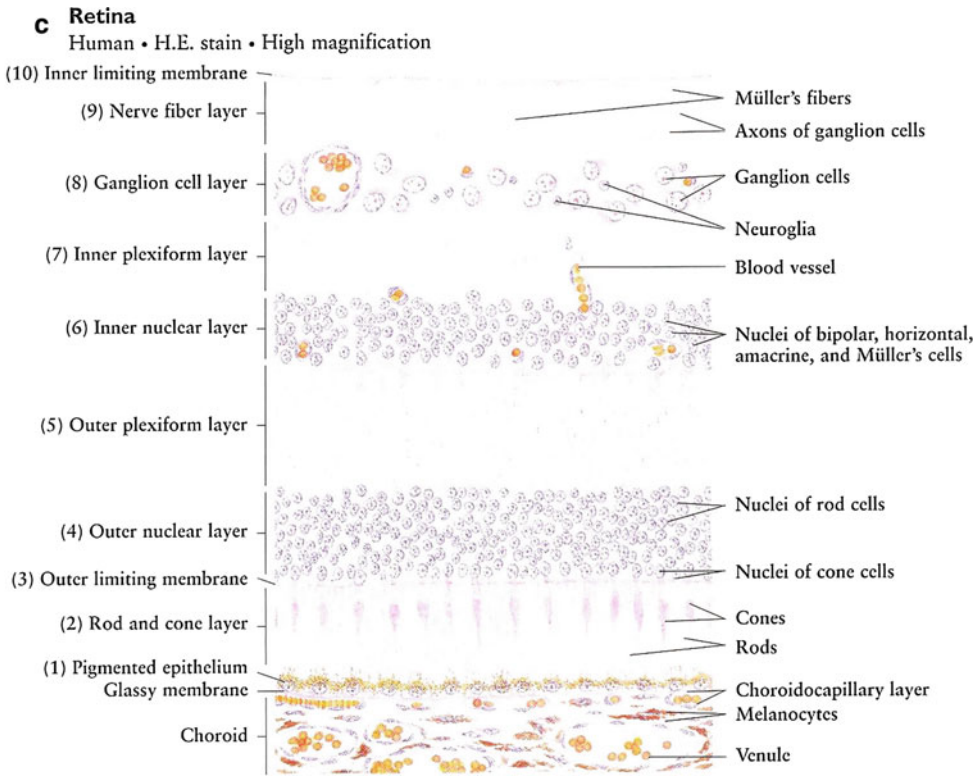


Fig. 3 **a** Eye globe: low magnification. **b** Iris and ciliary body. **c** Retina (with permissions from Zhang 1999)

Fig. 3 (continued)



conjunctiva) and the anterior surface of the eye (bulbar conjunctiva). The folds between the palpebral and bulbar conjunctiva are known as the superior and inferior fornices, respectively. Tissue is redundant in the fornices to allow for adequate movement of the globe. The main lacrimal gland, which functions during reflex tearing, empties into the superior fornix, while the accessory lacrimal glands, supplying basal tear secretion, are found throughout the conjunctiva, concentrating in the fornices.

The conjunctiva contains a stratified non-keratinized epithelium overlying a stroma, known as the substantia propria. Goblet cells supplying the mucin layer of the tear film are found intermixed with the epithelial cells. The mucin produced by goblet cells contains a mucopolysaccharide which is crucial in allowing for adherence of tears to the corneal epithelium. With goblet cell damage and a lack of this mucin substance, the tears lose their adhering qualities, become unstable and contribute to surface desiccation even in the presence of adequate aqueous production. Besides acting as a physical barrier, the conjunctiva aids in host defenses by hosting immune cells as well as colonizing bacteria.

The sclera is an acellular, avascular, collagenous protective layer of the eye. It is continuous with the cornea at the limbus and covered anteriorly by the conjunctiva. The superficial coating of the sclera, known as the episclera, consists of a loose, transparent, vascular coating.

3.1.3 Lacrimal Gland, Conjunctiva, Cornea

The tear film covers the anterior surface of the conjunctiva and cornea. It serves the vital role of supplying the cornea with moisture and nutrients in the form of mucins, enzymes, immunoglobulins antimicrobial proteins, and growth factors. It also allows for the maintenance of a clear, non-keratinized epithelium in the visual axis. Furthermore, the tear film comprises the smooth outer refractive coating essential to vision by filling in corneal irregularities. The tear film consists of three layers. The aqueous layer is produced by the lacrimal gland and accessory lacrimal glands found in the conjunctiva. Meibomian glands located within the tarsal plates produce an oily layer that sits on top of and acts to stabilize the aqueous layer. The goblet cells of the conjunctiva produce the third, or mucous, layer. The overall function of the tear film is vitally dependent on each of these individual layers, and a deficiency in any layer will adversely affect the entire ocular surface.

The cornea is the transparent, avascular anterior portion of the eye that refracts and transmits light to the inner structures of the eye, while also absorbing some of the harmful UV radiation. Along with the overlying tear film, it provides approximately two-thirds of the refracting power of the eye. The conjunctiva borders the cornea in an area known as the limbus. This region contains corneal stem cells; therefore, compromising this zone leads to the loss of corneal transparency and often its integrity. The cornea is an avascular

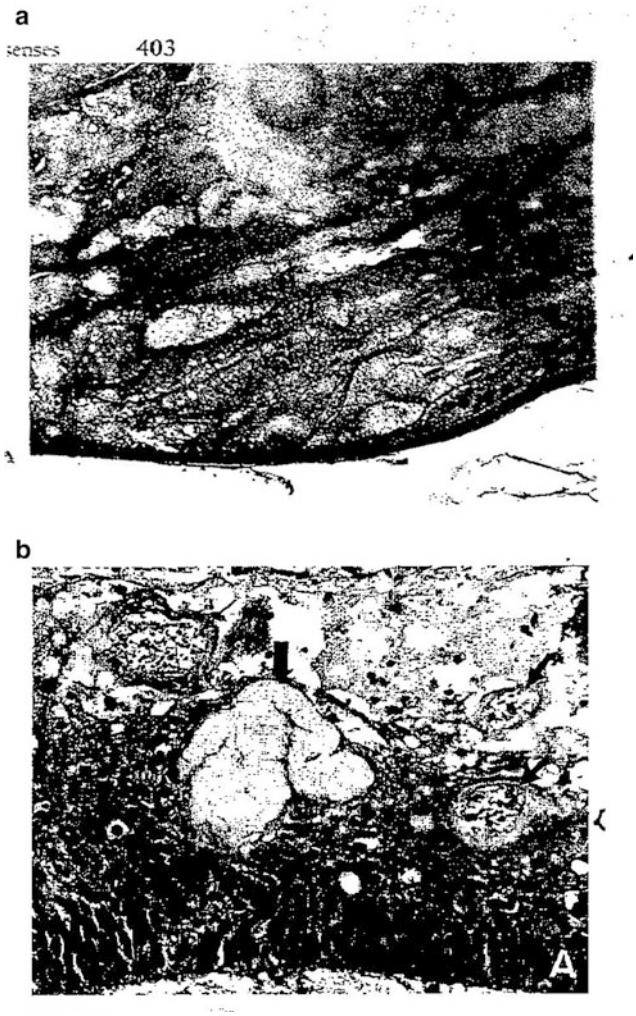


Fig. 4 **a** Lens-cataract: posterior subcapsular cataract in an irradiated lens. Notice the epithelial cells (*lower right*) that have migrated to the posterior pole. Prominent "Morgagnian globules" derived from preexisting fibers appear in the lower center as sharply demarcated polygonal spaces of variable gray density. **b** Retina-atrophy: eye resected 6 months after irradiation with 60 Gy in 25 fractions over 44 days. There is marked atrophy in the innermost layers, with irregular thickening and dilation of capillaries (*small arrows*). An arteriole in the center (*large arrow*) is totally replaced by convoluted fibrillary material (mostly collagen) (with permissions from Fajardo et al. 2001)

tissue and thus depends on the limbal vessels along with the tear film and aqueous fluid from the anterior chamber for nutrients and waste removal. The direct derivation of oxygen from air gives the cornea a unique characteristic compared to other body tissues. The cornea consists of five specialized layers, including, from anterior to posterior: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The epithelium is stratified, non-keratinized and replaces itself every 5–7 days. The stroma contains approximately 90 % of the overall corneal thickness, including a specialized superficial region known as Bowman's membrane. Descemet's membrane is a tough, thickened basement membrane secreted by the endothelium. The endothelial cells form a monolayer, which controls corneal hydration via ionic pumps. Small changes in corneal hydration (thickness) drastically change the optical properties of the cornea; therefore, the endothelial pumps are essential to maintain clear vision. Endothelial cells can migrate to fill a damaged area, but they do not regenerate; therefore, all loss of endothelial cells is permanent. Inflammation of the cornea, known as keratitis, may cause edema, increased corneal thickness and blurred vision.

3.1.4 Lens

The crystalline lens is a biconvex refractive structure that provides the second major refractive surface of the eye after the cornea. It is located behind the iris and pupil and is suspended circumferentially by ligaments known as zonule fibers. Anteriorly it is immersed in aqueous humor and posteriorly in vitreous humor. The encapsulated structure is devoid of blood vessels and nerves and depends on nutrients from the aqueous and vitreous humor. The lens is composed of densely packed fibers that arise from lens epithelial cells. These cells, located within the anterior periphery of the lens, undergo mitotic division at the germinative zone (the most mitotically active zone), elongate, lose their nuclei, and extend anteriorly and posteriorly to meet at the "Y" shaped suture lines in the center of the lens. The fiber cells contain specific proteins called crystallins that keep the lens transparent by inhibiting aggregation of proteins (Yanoff et al. 2004). The avascular nature of the lens prevents dispersing heat efficiently and the arrangement of the lens does not allow for removal of cells. Thus, any injured cells leave a permanent, visible defect; and like the rings of a tree, the timing of the insult is evident and irreparable.

3.1.5 Uvea: Iris, Ciliary Body, and Choroids

The uvea consists of three structures with a common embryologic origin: the iris, ciliary body, and choroid. The iris acts as the light aperture of the eye. It is a muscular membrane with a central circular opening (the pupil). Despite the wide variation in iris color on the anterior surface, the posterior surface of the normal iris characteristically contains a thick layer of heavily pigmented cells that act to absorb and thus limit the influx of light. The size of the pupil is controlled by the autonomic nervous system with input from both sympathetic and parasympathetic systems.

The ciliary body is a muscular structure located posterior to the iris and peripheral to the lens. The ciliary body produces the aqueous humor, the fluid that fills the anterior segment of the eye. This fluid drains through a structure known as the trabecular meshwork located anterior to the iris. As a result, the fluid must travel through the pupil in order to exit the eye. Any disruption to this flow will result in a backup of fluid and increased pressure within the eye,

known as glaucoma. The ciliary body is also responsible for adjusting the tension on the zonule that allows for lens accommodation. The choroid, located between the retina and sclera, is the posterior segment of the uveal tract. It is a highly vascular structure that supplies the outer retina with oxygen and acts as a heat sink to the highly active photoreceptors; thereby preventing them from getting overheated when converting light energy to electrical stimuli.

3.1.6 Optic Nerve and Retina

The retina is a thin, transparent structure that functions to convert light energy into electrical stimuli for the brain to interpret. The macula, located temporal to the optic disc, is responsible for central vision and contains the highest concentration of photoreceptors. It is thought the retinal vasculature contributes roughly 5 % of the oxygen used by the retina, while the choroid provides the rest. The retinal vessels are sensitive to changes in vascular permeability which may lead to swelling of the retinal layers (i.e., macular edema). The nine layers spanning from the inner to outer aspect of the retina are histologically distinguishable, and may distort retinal pathologies in characteristic ways depending on their location.

The optic nerve contains 1,100,000 axons from the superficial layer of the retina. These axons leave the eye through an area known as the optic disc and comprise the pathway through which visual stimuli reach the brain.

3.1.7 Orbital Bones and Tissue

The orbital cavity is composed of seven bones: the maxilla, palatine, frontal, sphenoid, zygomatic, ethmoid, and lacrimal bones. They form the shape of a quadrilateral pyramid with the apex forming posteriorly and the medial walls parallel. The soft tissues of the orbit consist of the extraocular muscles, orbital fat, fascia, and vascular structures. The function of the orbital bones is to protect the eye, while the soft tissues act to cushion the eye and optic nerve during movement.

3.2 Pathophysiology

Each structure of the eye, because of its complex structure will be described separately:

3.2.1 Eyelids, Lacrimal Gland

Eyelid reaction to irradiation is similar to skin and its appendages, depending on dose/time factors. It may result in acute erythema to desquamation, loss of eyelashes, inward turning of re-grown lashes and meibomian gland disturbance. Late effects include keratoconjunctivitis sicca and squamous metaplasia of the conjunctiva.

3.2.2 Lens

The formation of cataracts is most often cited as an adverse event due to radiation. The lens is an ectodermal structure, as is the skin. The germinal epidermal cell (stratum granular) is located at the equator of the lens, migrates posteriorly, and loses its nucleus to form clear epithelial layers (stratum clear) to the lens. Radiation has been primarily associated with posterior sub-capsular cataracts owing to abnormal epithelial cells migrating posteriorly and centrally. The exact mechanism of damage remains unclear, but proposals have included free radical formation or thermal effects of radiation.

3.2.3 Uvea

Inflammation can result in synechiae or scarred attachments between the iris and anterior lens capsule. Scarring of these structures can lead to narrow angles, obstruction of trabecular meshwork outflow, elevated intraocular pressure and possibly glaucoma.

3.2.4 Retina

The mechanism of radiation retinopathy is still debated. One proposal suggests the primary site of damage is the vasculature. Endothelial cell damage with secondary loss of pericytes leads to leaky vasculature and retinal edema, while microaneurysm formation can cause intraretinal hemorrhage. Capillary loss leads to ischemia, instigating release of vasoproliferative factors and eventual neovascularization of the retina and optic disc. In very advanced cases, proliferative retinopathy can result in a tractional retinal detachment.

3.2.5 Optic Nerve

Radiation to the optic nerve may result in free-radical mediated damage to the glial cells and vascular endothelium of the white matter. With time this may result in a pale optic disc from degenerated nerve fibers.

4 Clinical Syndromes: Radiation-Induced

4.1 Eyelids, Periorbital Skin, Lacrimal Glands

Radiation can cause a number of insults to the eyelids including pigment changes, telangiectasia, madarosis (or eyelash loss), lymphedema, and architectural alterations to the eyelids and nasolacrimal system. Hyperpigmentation may follow the acute stages of erythema within a year of treatment. It is speculated that activation of angiogenic factors may contribute to telangiectasia formation (Riekki et al. 2001), which occurs at doses greater than 55 Gy, and typically at 1–5 years post treatment. In one study, lid

Table 1 Clinical syndromes (LENT SOMA) of the Eye-orbit

Eye				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Vision	Indistinct color vision	Blurred vision, loss of color vision	Severe loss of vision, symptomatic visual field defect with decrease in central vision, some ability to perform daily living activities	Blind, inability to perform daily living activities
Light sensitivity	Photophobia, no change in vision	Increased photophobia, decreased vision	Photophobia, major loss of vision	
Pain/ Dryness	Occasional & minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Tearing	Occasional	Intermittent	Persistent	
Objective				
Best corrected vision	>20/40	20/50–20/200	<20/200 count fingers at 1 meter	Cannot count fingers at 1 m
Cornea	Increased tearing on exam	Non-infectious keratitis	Infectious keratitis, corneal ulcer	Panophthalmitis, corneal scar, ulceration leading to perforation/loss of globe
Iris	Rubeosis only	Rubeosis, increased intraocular pressure	Neovascular glaucoma with ability to count fingers at 1 m	Neovascular glaucoma without ability to count fingers at 1 m, complete blindness
Sclera	Loss of episcleral vessels	≤50 % scleral thinning	>50 % scleral thinning	Scleral or periosteal graft required due to perforation
Optic nerve	Afferent pupillary defect with normal appearing nerve	≤1/4 pallor with asymptomatic visual field defect	>1/4 pallor or central scotoma	Profound optic atrophy, complete blindness
Lens	Asymmetric lenticular opacities, no visual loss	Moderate lenticular changes with mild-moderate visual loss	Moderate lenticular changes with severe visual loss	Severe lenticular changes
Retina	Microaneurysms, nonfoveal exudates, minor vessel attenuation, extrafoveal pigment changes	Cotton wool spots	Massive macular exudation, focal retinal detachment	Opaque vitreous hemorrhage, complete retinal detachment, blindness
Facial bones	Cosmetically undetectable facial asymmetry	Minimal cosmetic asymmetry	Moderate orbital contracture	Severe hypoplasia of orbital bones

margin epilation occurred in 20 % of patients receiving external beam radiation at doses of 60 Gy, followed by regrowth of sparse and differently pigmented cilia (Nakissa et al. 1983). In the Collaborative Ocular Melanoma Study (COMS), madarosis was the only complication that was significantly greater in those patients whom had received pre-enucleation external beam radiation therapy compared to those whom received enucleation only (COMS 1998) (Tables 1, 2, 3).

A number of lid deformities may result from higher doses of radiation in the range of 60–75 Gy, such as ectropion (out-turning of lid margin) or entropion (in-turning of lid margin) (Nakissa et al. 1983). However, these complications are rare and seldom seen today. Radiation to the tarsus may result in its atrophy or contracture. Lid necrosis may develop months to years after treatment and is exacerbated by excess sun to previously irradiated tissue (Brady et al. 1989; Ober et al. 2012). Aberrations such as these can impair the eyelids' ability to adequately cover and maintain the integrity of the ocular surface, leading to its possible compromise (see next section on ocular surface).

Destruction or occlusion of the puncta may occur when the medial portions of the eyelid are irradiated. Radiation induced canaliculitis leads to fibrosis and obstruction,

Table 2 Detection: analytic (LENT SOMA eye-orbit)

Management				
Tearing, Cornea, Lacrimation	Lubrication as needed	Lubrication with or without pressure patch, antibiotics	Topical antibiotics with or without cycloplegia	Corneal graft, Enucleation
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Parenteral narcotics
Neovascularization	Pan-retinal photocoagulation for neovascular changes	Medical management of glaucoma, pan-retinal photocoagulation	Surgical management of glaucoma, Cytodestructive procedure	Enucleation
Lens			Cataract extraction depending on visual potential	
Retina		Medical management of glaucoma, focal photocoagulation	Surgical management of glaucoma, with or without pan-retinal photocoagulation	Cytodestructive procedure, repair of retinal detachment
Facial bones			Cosmetic repair ± orbital augmentation for anophthalmic socket	Enucleation, orbital augmentation for anophthalmic socket
Analytic				
Slit lamp exam	Assessment of intraocular pressure, pupils, ocular motility, dilated fundoscopic exam, and gonioscopy			
Cultures and stains	Assessment of corneal infiltrates			
Ultrasound	Examination of posterior pole if opaque media, i.e., cornea, lens, vitreous			
Fluorescein angiogram	Evaluation of retinal neovascularization, macular edema/exudates			
Color vision	Assessment if afferent pupillary defect, or optic nerve asymmetry			
Automated visual field	Bilateral-assessment of optic nerve, pupillary or color vision abnormality			
MRI	Assessment of sudden visual loss and abnormal optic disc or normal appearing optic disc and no other visible reason for visual loss			

Table 3 Examples of clinical and subclinical endpoints of radiation induced eye toxicity

	Focal	Diffuse
Subclinical	Telangiectasia	
	Pigment deposition	–
	Neovascularization	
	Asymptomatic keratopathy	
	Asymptomatic cataract	
	Asymptomatic glaucoma	
	Iris atrophy	
	Asymptomatic retinopathy	
	Asymptomatic optic neuropathy	
Clinical	Eyelid deformities	Vision loss
	Symptomatic keratopathy	Diplopia
	Symptomatic cataract	Sympathetic ophthalmia
	Uveitis	Endophthalmitis
	Symptomatic glaucoma	
	Visual field defect	
	Symptomatic retinopathy	
	Symptomatic optic neuropathy	
	Boney deformities	

typically to the lateral one-third of the nasolacrimal system (Buatois et al. 1996). Stenosis or obstruction along any part of the nasolacrimal ductal system can cause impaired tear drainage and symptoms of epiphora.

Lacrimal gland dysfunction can lead to a dry eye and associated chronic symptoms such as pain, and may result in corneal ulceration and visual loss. A series of analyses from the University of Florida and elsewhere relate the incidence of dry eye to the dose of radiation delivered to the lacrimal gland. Dry eye is unusual at doses <30 Gy, is occasionally seen at slightly higher doses, is very common following doses >40–45 Gy, and can be severe at doses >57 Gy (doses usually delivered at 1.8–2.0 Gy per fraction). The interval between RT and the onset of dry eye can be years following modest doses (e.g., >4 years after 30–40 Gy), but are often shorter at higher dose levels (e.g. 9–10 months after >57 Gy) (Parsons et al. 1994, 1996; Jeganathan et al. 2011).

4.2 Conjunctiva and Sclera

Radiation effects to the conjunctiva may occur via direct damage or through secondary effects on the ocular surface. At 1–2 years post-treatment, prolonged conjunctival injection may develop, particularly at exposures of 30–50 Gy. Also at doses of 30 Gy, telangiectatic vessels may follow at 3–6 years. With minor trauma or valsalva efforts, the fragility of these vessels may result in their rupture and accumulation of subconjunctival hemorrhage (Fig. 5).

At radiation doses over 50 Gy, keratinization of the epithelium has been observed (Gordon et al. 1995). These eyes should be evaluated for cornea irritation from adjacent keratin plaques. In severe cases and exposures of 60 Gy, chronic conjunctival ulceration may develop. Feared complications include symblepharon formation (adhesions between the bulbar and palpebral conjunctiva following denuded epithelium) and subsequent forniceal shortening, trichiasis (inward turning of the lashes on the ocular surface) and other eyelid malpositions. Conjunctival necrosis has also been observed in retinoblastoma patients when radioactive plaque therapy provided conjunctiva doses of 90–300 Gy (Haik et al. 1983; Brady et al. 1989; Ober et al. 2012; Donnenfeld et al. 1993). Loss of goblet cells may occur and exacerbate dry eye symptoms through the subsequent dearth of mucin.

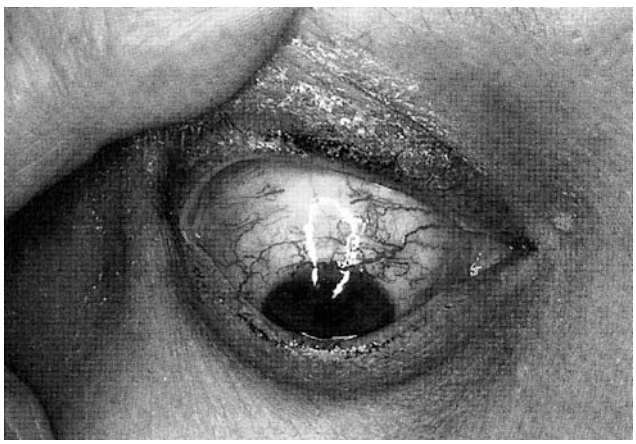


Fig. 5 Clinical syndromes: telangiectasia of conjunctival blood vessels

The avascular property of sclera renders it relatively radioresistant. For example, the sclera is able to tolerate doses of radiation up to 900 Gy from an iodine or cobalt plaque when administered over 4–7 days. However, scleral atrophy and necrosis has been documented in irradiated eyes, and is most common following the use of brachytherapy. In fact, scleral atrophy is a dose-limiting factor in ocular plaque dosing. Fractionated doses of 20–30 Gy can cause thinning, melting or atrophy of the sclera, while its perforation is a rare complication (Brady et al. 1989). Sclera atrophy should be monitored for infection, corneoscleritis (concomitant inflammation of the sclera and cornea) and perforation.

Pigmented deposits on the episclera have been reported following brachytherapy for uveal melanoma. They developed within 6 months of treatment, occurred in 85 % of patients at 1 year and their quantity was associated with proximity to the tumor or irradiated area (Toivonen and Kivelä 2006).

4.3 Lacrimal Gland, Conjunctiva, Cornea

The health of the ocular surface relies greatly upon the tear film, which is generated by a careful balancing of three components: the aqueous, mucin, and lipid layers. Deficiencies in any one of these may result in a compromised tear film and risk the maintenance of the ocular surface. Radiation can disrupt many of the key structures that produce these tear film elements, and place the eye at risk for ocular surface damage (or dry eyes) via a number of mechanisms. For example, radiation induced atrophy of the lacrimal gland, which occurs at 50–60 Gy, causes a decrease in aqueous tear substance. Furthermore, atrophy of meibomian glands at doses less than 30 Gy (Roth et al. 1976) and damage to conjunctival goblet cells (which also have low radiation tolerance) cause reductions in the lipid and mucin constituent of tears, respectively. The subsequent instability of the tear film and its surface tension results in an evaporative dry state. When all of the three tear film constituents are compromised by radiation, it is inevitable that a dry eye state will follow. The frequency of radiation-induced dry eye is dose-dependent and most likely at doses

greater than 40 Gy (Parsons et al. 1994, 1996). However, while changes are evident within 9–10 months at higher doses (>57 Gy), it is suggested that low doses (30–45 Gy) cause later-onset ocular surface disease at an estimated 4–11 years post-treatment (Durkin et al. 2007). Symptoms of keratoconjunctivitis sicca (KCS), or dry eyes, include foreign body sensation, burning, photophobia and blurry vision. High dose radioiodine used in the treatment of thyroid carcinomas results in reduction of lacrimal gland tears; however, the subsequent association to dry eye symptoms is unclear (Fard-Esfahani et al. 2007).

The anterior surface of the cornea can likewise be affected by a number of radiation-induced pathologies. The tear film baths the cornea but when altered by radiation, can lead to an epitheliopathy. Radiation-induced impairment of the fifth cranial nerve causes decreased corneal sensation and neurotrophic harm, while decreased blink mechanism and exacerbation of surface changes can result from aberrations of the seventh cranial nerve. Furthermore, radiation can damage the corneal stem cells located at the limbus (the transition between cornea and conjunctiva along the peripheral edge of the cornea), thereby injuring the cornea's source of epithelial turnover (Dua et al. 2003). This may cause chronic epithelial defects or filamentary keratitis, which share the symptoms of irritation, photophobia, pain, and epiphora. Without an intact epithelium, the underlying stroma is at risk for damage. In fact, either epithelial or endothelial dysfunction can cause stromal edema. In addition, stromal ulceration results from direct radiation damage to the stromal keratocytes at doses of greater than 60 Gy (Nakissa et al. 1983). Both epithelial and stromal defects can elicit vision-limiting neovascularization and opacification. Years after treatment, keratinization and even lipid deposition in the stroma can occur, both of which further compromise vision. A nonhealing ulcer can be a treatment dilemma and requires close observation for panophthalmitis and perforation.

Without an adequate tear film, the ocular surface has limited contact to the accompanying nourishment, lubrication, immunoglobulins, and enzymes. This may increase the cornea's susceptibility to colonization or microbial invasion and thereby accelerate ulceration and perforation (Haik et al. 1983; Brady et al. 1989; Donnenfeld et al. 1993; Barabino et al. 2005; Blondi 1958).

4.4 Lens

Cataract is a well known complication following radiation to the eye. A cataract is a loss of optical clarity within the lens. It is usually attributed to a disruption of the regular structure of the lens fibers. Radiation has been primarily associated with posterior subcapsular cataracts secondary to the abnormal epithelial cells migrating posteriorly and centrally. Damage to the radiosensitive germinative epithelium is likely responsible for most post radiation cataracts. The exact mechanism of damage remains unclear. However, evidence exists for free radical formation causing DNA and cell membrane damage and mitotic arrest. Thermal effects of radiation are also likely to contribute to injury of lens fiber cells secondary to the heat being inefficiently dissipated (Fig. 6).

An association between cataract formation and exposure to ionizing radiation was first recognized in 1897. In humans an increased incidence of cataracts was noted in nuclear plant workers, survivors of atomic bombs, and later in patients treated with local radiation for head and neck cancers (Abelson and Kruger 1949; Cogan et al. 1949; Merriam and Focht 1957). Cataract formation ranges from a latency period of 6 months to over 30 years with an approximate average of 2–3 years. The development of lens opacity is heavily influenced by patient age, the method of delivery, size and location of the tumor, and total dose, fractionation, energy of the source, and dose rate of radiation.

In patients with choroidal melanoma, tumor size is a risk factor for the development of cataracts with either brachytherapy or external beam radiation. Tumor basal diameter greater than 10–15 mm (Summanen et al. 1996), and height greater than 4–6 mm (Summanen et al. 1996; Beitler et al. 1990; Gunduz et al. 1999a, b, c; Gragoudas et al. 1995), are strong predictors of developing radiation cataracts. Tumor height, which is believed to be a good approximation of tumor volume, has been found to be an independent risk factor and associated with time to cataract formation (Summanen et al. 1996; Kleineidam et al. 1993; Puusaari et al. 2004a). This could be partially secondary to elevated tumors undergoing more necrosis contributing to increased intraocular inflammation, which is known to cause cataracts.

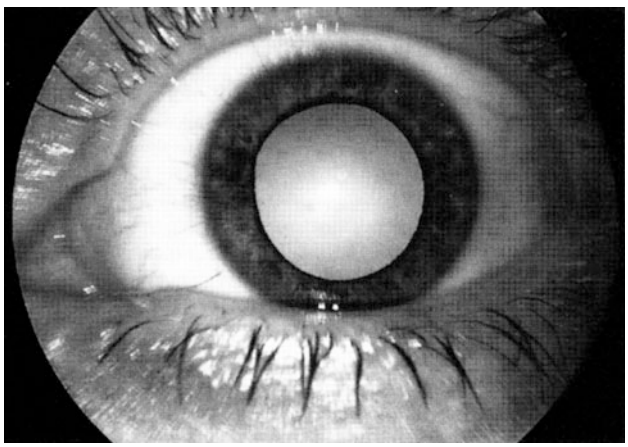


Fig. 6 Clinical syndromes: cataract

Tumor location also influences cataract formation. It is well accepted that anterior tumors are more likely to develop cataracts after brachytherapy than posterior tumors, secondary to the difference in radiation dose to the lens. For example, one study found cataract rates to be as high as 85 % in anterior tumors treated with Pd^{103} brachytherapy compared to 17 % for posterior tumors (Finger 1997). Additionally, there is a lower rate and longer time to onset of cataract formation for tumors located posterior to the equator (Fontanesi et al. 1993; Summanen et al. 1996). Cataracts have been noted after an average of 11 months in patients with anterior, iris, or ciliary body lesions compared to 26 months in patients with posterior based lesions (Summanen et al. 1996).

Several studies have investigated the minimal amount of radiation that would induce cataract development. Merriam and Foch, the first to describe the relationship between radiation dose and cataract formation, suggested that the amount of radiation delivered at a single period may be as important as the total dose (Merriam and Focht 1957). A single dose of 2 Gy or a cumulative dose of 5.5 Gy given over longer than 3 months was enough to induce cataract formation. Subsequent studies have reported a slightly higher threshold of single dose of 5 Gy or lower (Henk et al. 1993). In brachytherapy, eyes treated with doses less than 12 Gy of iodine 125 have a significantly lower rate of cataract and cataract surgery compared with doses greater than 24 Gy (COMS 2007). Additionally, for each 10 Gy increase of iodine 125 to the center and posterior pole of the lens, the rate of cataract formation has been reported to increase around 15 % (Puusaari et al. 2004b).

The effect of fractionation can influence cataract incidence. For example, Benyunes et al. reported 85 % of their patients developing cataracts when exposed to a single dose of 10 Gy versus 34–50 % when given fractionated doses of 2 Gy even to a higher total dose of 12 Gy or greater (Benyunes et al. 1995). Fractionation is also associated with delaying the development of cataracts, the severity of lens opacification, and the need for cataract surgery (Tichelli et al. 1993; Aristei et al. 2002; Benyunes et al. 1995). In addition, hyperfractionation with greater than 6 fractions can decrease the incidence of cataracts (Belkacemi et al. 1998).

Dose rate is another known risk factor that affects cataract formation. Low exposure rates, ranging from less than 0.035–0.06 Gy/min, may have significant sparing effect in the form of lower incidence of cataracts and cataract surgery (Belkacemi et al. 1998; Ozsahin et al. 1994; Fife et al. 1994).

4.5 Uvea: Iris, Ciliary body and Choroid

Iris neovascularization, or rubeosis iridis, occurs several months to years following RT, particularly with fractionated doses of 70–80 Gy over 6–8 weeks. Ocular ischemia instigates new, abnormal vessel formation through the release of vascular growth factors from ischemic retina, irradiated tumor tissue or direct damage to iris vessels. Without abatement, it is feared these vessels will grow into the anterior-chamber angle accompanied by myofibroblasts. The latter contract, form fibrous adhesions within the angle, and thereby obstruct aqueous outflow and increase pressure in the eye. High intraocular pressure may cause damage to the optic nerve, resulting in neovascular glaucoma, which is thought to occur in 35 % patients treated with brachytherapy (Shields et al. 2003). In plaque brachytherapy treatment, both iris neovascularization and glaucoma may be influenced by involvement of the anterior tumor with the iris, and with high intraocular pressures at diagnosis (Gunduz et al. 1999a, b, c; Puusaari et al. 2004a, b). With helium-ion irradiation in uveal melanoma patients, Daftari et al. found development of neovascular glaucoma correlated with amount of lens and anterior chamber exposed, tumor volume, proximity to the fovea, history of diabetes, and development of vitreous hemorrhage (Daftari et al. 1997).

Another mechanism for radiation-induced glaucoma involves the formation of posterior synechiae, which are iris adhesions to the lens caused by inflammation. They prevent fluid from moving behind the iris to the more anteriorly placed trabecular meshwork; thus placing the eye at risk for glaucoma due to high intraocular pressures. Although of little clinical consequence, iris atrophy has been reported 3 years after high doses of beta-irradiation with 170–250 Gy (Brady et al. 1989; Ober et al. 2012).

While anterior uveitis may be an acute complication following radiation, sympathetic ophthalmia is an autoimmune hypersensitivity phenomenon, which can occur between 10 days to 50 years after injury. It involves antibodies that are produced to exposed uvea of an injured (exciting) eye, which are then directed against the fellow (sympathizing) eye. This response has been reported in eyes treated with both irradiation and plaque brachytherapy for ocular melanoma (Ahmad et al. 2007; Fries et al. 1987). While a rare phenomenon, a suspicion of sympathetic ophthalmia warrants prompt management of the exciting (responsible) eye, since its enucleation within 2 weeks is most influential in preserving the health of the sympathizing eye.

4.6 Retina and Optic Nerve

In 1933, Stallard was the first to describe radiation retinopathy, and it has since been extensively described following external bean radiation, proton beam radiation and brachytherapy (Stallard 1933). The macula is the most visually ominous location for radiation pathology, and results from damage to the vessels that course around the

macula and feed the foveal area (which is essential for central vision). The risk for retinopathy is reported at exposures as little as 15 Gy, although the threshold is regarded at 40–50 Gy and others have suggested the threshold is higher. Monroe et al. propose that the incidence can be significantly reduced by hyperfractionated external beam radiation, with twice daily doses of 1.1–1.2 Gy; with this protective effect being most profound when the retina receives more than 50 Gy (Monroe et al. 2005) (Fig. 7).

On histology, there is pigment epithelial cell reduction and corresponding areas of photoreceptor atrophy. The choriocapillaris vessels are occluded, the retinal vessels are ensheathed in collagen fibrils, the retinal tissue is invaded with macrophages, and the nerve fiber layer is attenuated (Krebs et al. 1992). The ocular features of radiation retinopathy mimic other hypoxic etiologies of retinal damage with findings such as: microaneuryms, angiographic leakage, capillary nonperfusion, hard exudates, telangiectasia, retinal pigment epithelial changes, macular edema, hemorrhages, and neovascularization. These pathologies accumulate over time, while foveal retinal detachments and cotton wool spots (a marker for ganglion cell destruction and retrograde axonplasmic flow) predominate at 2 yrs post-treatment (Boldt et al. 2009). Retinopathy may develop as early as 3 weeks and as late as 15 years post-treatment, although it typically develops between 6 months and 3 years. The prevalence of radiation retinopathy at 5 years following plaque brachytherapy is close to 50 % (Gunduz et al. 1999a, b, c; Puusaari et al. 2004a) and is associated with tumor height and tumor distance to the macula; both possible indicators for radiation dose.

COMS found that radiation retinopathy is worse in those patients with underlying vascular disorders such as diabetes, which is not surprising given the risk of microvascular changes and retinopathy in uncontrolled diabetes. Researchers have also found that chemotherapy may exacerbate radiation retinopathy (Boldt et al. 2009). Poor prognostic factors for radiation retinopathy include papillopathy and proliferative retinopathy. The latter which causes the visually impairing complications of vitreous hemorrhage and tractional retinal detachment.

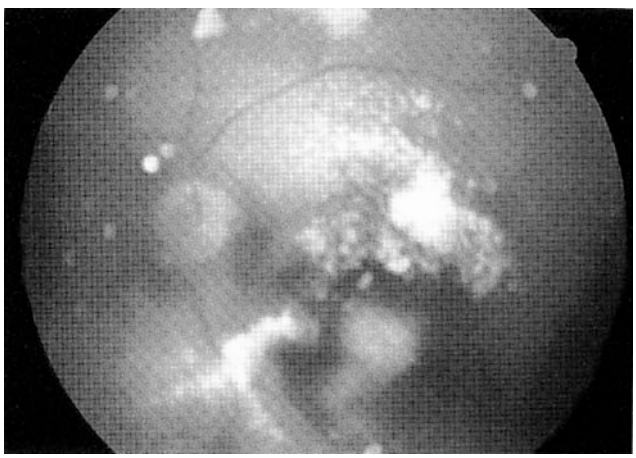


Fig. 7 Radiation retinopathy

Irradiation to tumors in proximity to the optic nerve, chiasm, and retrogeniculate visual pathways can cause optic neuropathy and vision loss. DNA exposure to radiation is thought to generate free radicals, which induce vascular endothelial damage and result in white matter injury (Lessell 2004). In fact, optic nerve pathology reveals narrowed, occluded blood vessels with decreased endothelial cells, and fibrin exudates (Levin et al. 2000). Demyelination and neuronal degeneration may result from the ionizing effects on replicating glial cells (Fike and Gobbell 1991).

The range of the reported prevalence of optic neuropathy is broad at 11–57 % (Boldt et al. 2009) due to the use of different endpoints and co-medical morbidities in treated patients. While the optic nerve is deemed to have a threshold of approximately 50 Gy, this threshold is lower in patients with coexistent diabetes, Cushing syndrome or previous chemotherapy (Lessell 2004). Typically, the radiation-induced neurological damage will result in presentation of vision loss on an average of 18 months after treatment, although the latency is shorter with higher radiation dosage (Lessell 2004). At exposures greater than 60 Gy, the fractioned dose becomes influential in optic nerve injury, with more risk for injury with larger daily fraction size (Durkin et al. 2007).

Other neurophthalmological complications of radiation exist. Four children who received periocular carboplatin injections for intraocular retinoblastoma developed ischemic optic neuropathy. One of these children received prior radiation, which may have been a contributing factor (Schmack et al. 2006). Ocular neuromyotonia is a rare syndrome and is characterized by episodic involuntary discharge of cranial nerves 3, 4, and 6 which control extraocular movements. It occurs months to years post-radiation and causes recurrent short-lived episodes of diplopia (Shults et al. 1991).

4.7 Orbital Bones and Tissue

Radiotherapy to ossification centers of children can result in boney deformities from bone growth arrest, necrosis of cartilaginous structure, and lead to hypotelorism (abnormally close eyes) and other orbital deformations (Raney et al. 1999). Anophthalmic socket syndrome, or soft tissue atrophy, and contracture of the socket following removal of the eye, has been documented after radiotherapy in patients treated for retinoblastoma (Abramson 1988). Osteonecrosis is rare and only results after very high doses of radiotherapy, but may be associated with concurrent orbital infections.

Table 4 Radiation effects on the eye and orbital tissues (LENT SOMA, Int. J. Radiation Oncology, Biology, Physics Volume 31, Number 5, 1995)

Tissue	Effect	Dose (Gy)	References
Conjunctiva	Conjunctivitis	5500–7500	Buatois et al. (1996)
	Telangiectasis	3000	Buatois et al. (1996), Parsons et al. (1994)
Cornea	Keratitis, edema, mild ulcer	3000–5000	Parsons et al. (1994)
	Ulcer, scarring, perforation	>6000	Buatois et al. (1996), Parsons et al. (1994)
Lens	Cataract	200 (threshold)	Ozsahin et al. (1994)
		1600	Buatois et al. (1996)
Retina	Retinopathy	>4650	Fife et al. (1994)
Optic nerve	Optic neuropathy	>5500	Buatois et al. (1996), Bajcsay et al. (2003)
Lacrimal system	Atrophy	5000–6000	Buatois et al. (1996)
	Stenosis	6500–7500	Buatois et al. (1996), Parsons et al. (1994)
Eyelid	Lash loss	4000–6000	Buatois et al. (1996), Parsons et al. (1994)
	Erythema	3000–4000	Buatois et al. (1996), Parsons et al. (1994)
	Telangiectasis	>5000	Buatois et al. (1996)
Orbit	Implant extrusion	Not specified	Bajcsay et al. (2003)

Note these are effects seen with conventionally fractionated (<250 Gy/day) megavoltage photon therapy. Adapted from Bardenstein and Char, with permission

5 Radiation Tolerance

The tolerance doses have been discussed in the clinical syndromes section and are summarized noting important studies (Table 4).

5.1 Dose Time Fractionation

The Tolerance Doses utilized 250 Gy fractions are summarized in Table 4. Important contributions to understanding the radiation time dose factors for cataract formation is due to the meticulous studies of Merriam and Focht, the extremely low level of radiation dose TD_5:200 Gy and $TD_{50} \geq 1000$ cGy, establishing the lens of the eye as one of the most radiosensitive tissues (Fig. 8).

6 Chemotherapy Tolerance

Chemotherapeutic agents and biologics can cause a number of ocular side-effects at various levels of the eye (Table 5). These complications are illustrated in Fig. 9.

Beginning with the anterior aspect of the orbit and eye, chemotherapeutic agents have been associated with stenosis of the punctum and tear (canalicular) drainage system, while other agents can rarely cause excessive lacrimation, cicatricial eyelid malpositioning or pallor of the periorbital skin. Conjunctivitis is a commonly reported symptom with chemotherapy use, while scleral complications from systemic chemotherapy applications are mild and uncommon. However, scleral ulcerations, scleritis and scleral calcifications are a known side effect of topical mitomycin C, which is used as an adjunct treatment for ocular surface tumors (Al-Tweigeri et al. 1996).

Many chemotherapeutic agents alter the normal tear film physiology either by causing inflammation of the lacrimal glands or by being excreted directly into tears, which leads to dry eye symptoms and inflammation around the eyelids and anterior segment of the eye (Al-Tweigeri et al. 1996). Following the use of chemotherapy, patients may develop keratitis, punctate corneal opacities, corneal hypoesthesia, other surface keratopathies, and whirl-like corneal inclusions known as verticillata (Albert et al. 1967; Al-Tweigeri et al. 1996; Kaiser-Kupfer and Lippman 1978). Severe uveal reactions have been described following intracarotid treatment with chemotherapeutic agents, including one reported patient treated with intracarotid cisplatin infusion who developed serous retinal detachment (Anderson and Anderson 1960; Margo and Murtagh 1993) likely from choroidal disturbance. Moving to the posterior segment, chemotherapeutic insult to the retina can result in retinal hemorrhages, cotton wool spots, optic disc edema, exudative retinal detachment, retinopathy (including pigmentary and crystalline), retinal edema and ischemia (Ashford et al. 1988; Margo and Murtagh 1993; Millay et al. 1986; Miller and Pecxon 1965; Miller et al. 1985; Ostrow et al. 1978; Rankin and Pitts 1993). Optic nerve damage includes optic neuritis, papilledema, optic nerve ischemia, optic neuropathy, color blindness and optic nerve atrophy (Albert et al. 1967; Al-Tweigeri et al. 1996; Ashford et al. 1988; Capri et al. 1994; Chun et al. 1986; Margileth et al. 1977; Margo

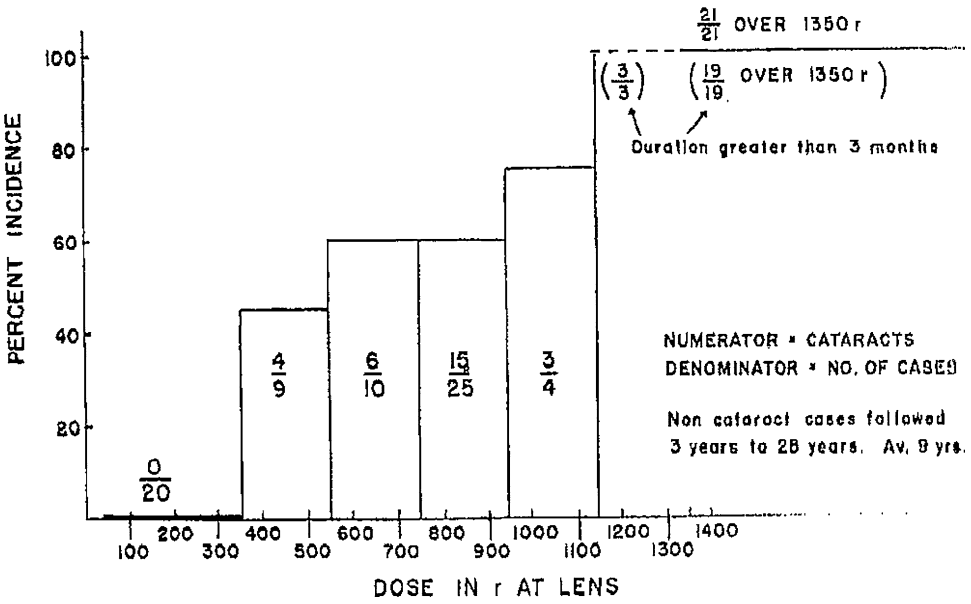


Fig. 8 Dose time: incidence of cataracts. The eye, variable factors; time-dose, incidence of cataraclx x- and gamma irradiation. **a** doses of x-gamma radiation of lous in 07 errors of radiation comfort and 70 errors without lens opacities. **b** Incidence of entararts. The treatment period was three weeks to three months (with permissions from Rubin and Casarett 1968)

and Murtagh 1993; Millay et al. 1986; Miller and Pecxon 1965; Miller et al. 1985; Ostrow et al. 1978; Porges et al. 1998; Rankin and Pitts 1993; Shurin et al. 1982). Paralysis of the eye muscles (ophthalmoplegia) has been reported with some agents due to cranial nerve palsy (Albert et al. 1967; Bixenman et al. 1968).

6.1 Biologicals

Biologicals comprise a relatively emerging field of medicine and a number of ocular complications have been associated with these agents. For example, the epidermal growth factor receptor (EGFR) inhibitors produce complications in cell types specific for EGFR including the periorbital skin, cilia, conjunctiva and cornea. Paradoxically, some agents concomitantly demonstrate both adverse and favorable effects on the eye, leading to their use for the treatment of ocular pathology in certain situations. As their use widens and new therapies are added to the compendium, more complications are likely to be documented and our understanding of their affects on the eye, both good and bad, will continue grow.

7 Special Topics

7.1 Effects of Corticosteroids

Corticosteroids inhibit the release of arachidonic acid, thereby exerting an anti- inflammatory and immunosuppressive effect. It is well documented that corticosteroids cause a host of ocular complications whether administered systemically (orally or intravenously) or locally via topical, intranasal, inhaled, or injected applications. These side effects target the eye at various tissue, anatomical and functional levels.

Corticosteroids are known to cause complications of the adnexa and anterior segment. Long-term corticosteroid use can cause ptosis, or a drooping of the upper eyelid, as a result of levator muscle myopathy (Carnahan and Goldstein 2000; Miller and Pecxon 1965; Miller et al. 1985). Exophthalmos, or protrusion of the globe is a known cause of endogenous steroids in Cushing's disease, but also rarely arises from long-term systemic exogenous use (Van Dalen and Sherman 1989). Slight mydriasis of the eye receiving topical steroids has been observed, and a few instances of myopia during systemic corticosteroids have been documented (Grant 1974). Corticosteroids may cause retardation of corneal healing and delay in generation of tensile strength, but these impairments are temporary (Grant 1974). Phosphate preparations of topical steroids show development of corneal stromal opacification likely via calcium phosphate precipitation (Schlotzer-Schrehardt et al. 1999); but this can be avoided with non-phosphate formulas. In addition, systemic administration of corticosteroids has been associated with scleral thinning and discoloration.

In 1960, Black et al. were the first to suggest that systemic steroids could lead to posterior subcapsular cataract formation (Black et al. 1960). Now, it is perhaps, the most frequently reported side-effect. While steroid-induced cataracts are highly variable and dependent on dose and duration, the incidence ranges from 15 to 52 % of patients and the threshold for formation is approximated at 10 mg oral prednisone daily for 1 year (Braver et al. 1967; Loredo et al. 1972). However, steroid-induced cataracts have been

Table 5 Chemotherapy agents and associated toxicities (with permission from Abramson 2008)

reported to develop after as little as 5 mg of daily oral prednisone for 2 months duration (Black et al. 1960; Urban and Cotlier 1986). For example, 30–40 % of patients with rheumatoid arthritis treated for 2 years with 10 mg prednisone develop cataracts, while this incidence approaches 80–100 % at an increased dose of 15 mg prednisone over 4 years (Becker 1964). The mechanism for steroid-induced cataract formation is still under investigation, but proposals include: glucocorticoid receptor-mediated mechanisms present on the lens, disruptions in lens structure by steroid binding of lens proteins, altered growth factor effects on epithelial cell differentiation, and increased susceptibility to oxidative stress (Bucala et al. 1985; James et al. 2003;

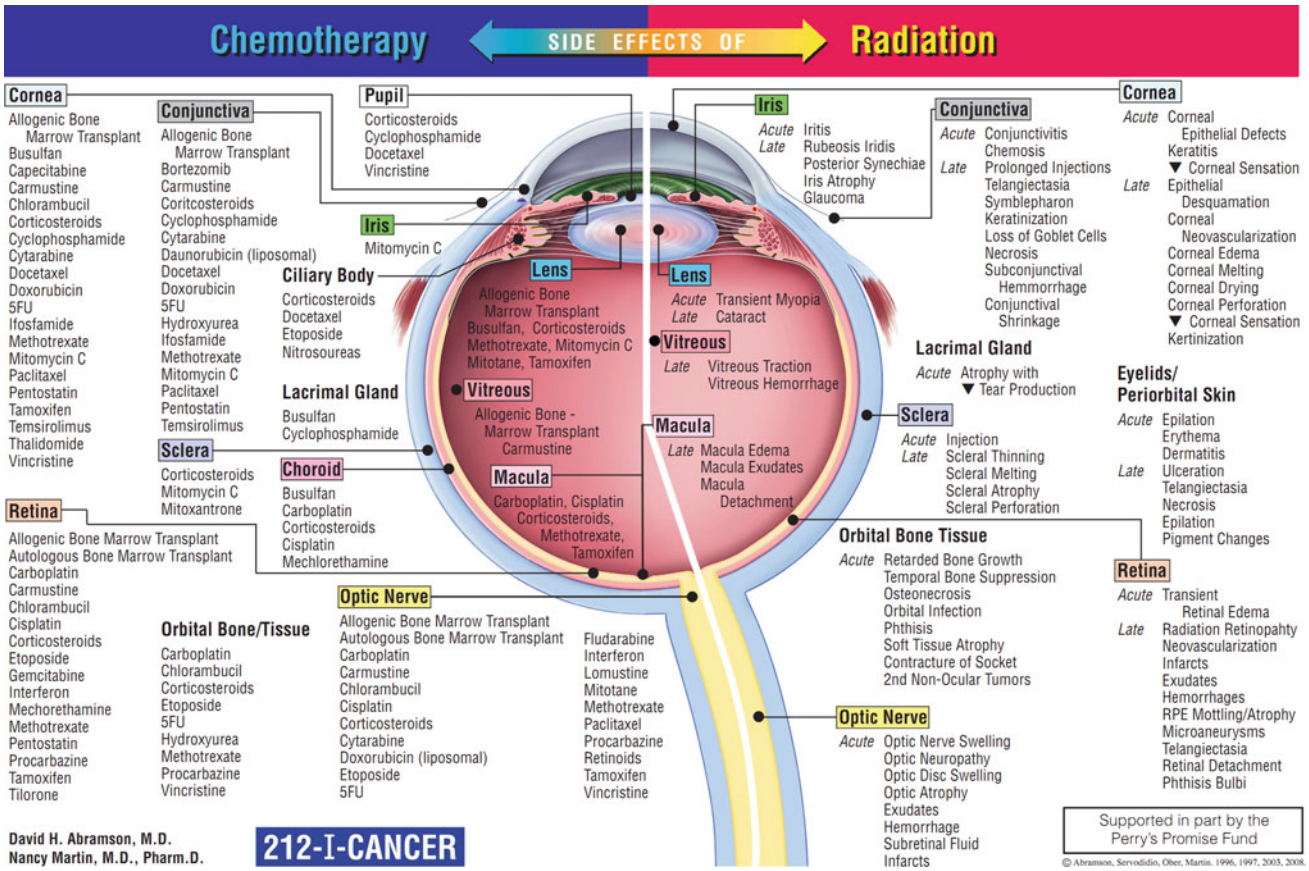


Fig. 9 Side effects of chemotherapy and radiation (with permission from Abramson 2008)

Jobling and Augusteyn 2002). Cataracts can be removed and vision typically improved with surgical extraction.

Some patients have corticosteroid-associated increased intraocular pressures, which may predispose them to glaucoma. For instance, about one-third of patients have been shown to generate elevated intraocular pressures with steroid eyedrops (Becker 1964). Systemic use can have a similar effect and has been estimated to cause elevated pressures at a little over 50 % of topical treatments (Carnahan and Goldstein 2000). Elevated intraocular pressures may be influenced by existing glaucoma, hypertension, high myopia, diabetes mellitus, family history, ethnicity, and rheumatoid arthritis (Carnahan and Goldstein 2000). Patients who are "steroid-responders" are more vulnerable to glaucoma progression when combined with other factors such as older age, ocular architecture, genetic predisposition, and length and increased dose of treatment (Armaly 1963a, b, 1966). Increased intraocular pressure is typically reversible within 2–4 weeks of steroid cessation (Tripathi et al. 1999). The mechanism for steroid-induced glaucoma is under debate but theories include receptor-mediated mechanisms via steroid-specific receptors in the trabecular meshwork, altered genes, or stabilization of lysosomal membranes leading to an accumulation of materials in the trabecular meshwork that increase resistance to flow (Carnahan and Goldstein 2000).

Steroids have been implicated in posterior segment pathologies. For instance, they have been associated with pseudotumor cerebri and accompanying papilledema, particularly during steroid withdrawal or tapering of dose (Newton and Cooper 1994; Liu et al. 1994; Ray et al. 2008). They are believed to be a possible contributing factor in central serous chorioretinopathy (Koyama et al. 2004) and have been reported to cause multiple retinal hemorrhages and transient vision loss of lumbar epidural injection (Young 2002). In addition, the immunosuppressive effects of corticosteroids can have an impact at multiple levels of the eye by facilitating opportunistic infections; this includes bacterial, viral and fungal derivatives of conjunctivitis, keratitis, corneal ulcers, uveitis, and retinitis (Palmer and Hyndiuk 2000).

7.2 Effects of Bone Marrow Transplant

Long-term ocular complications following bone marrow transplant (BMT) are well described. Aside from the complications that arise from exposure to high dose

chemotherapy and/or radiation, ocular changes associated with graft versus host disease are unique and are not uncommon among patients who undergo BMT. Graft versus host disease (GvHD) is a cell-mediated immune reaction in which the donor T cells mount an attack against the recipient tissue. The acute form of GvHD occurs within 3 months after transplantation and generally carries a better prognosis than the chronic form that is ongoing from 3 months after transplantation.

Ocular complications have been reported in 22–82 % of patients with GvHD affecting all layers of the eye (Kerty et al. 1999; Livesey et al. 1989; Franklin et al. 1983). Keratoconjunctivitis sicca (KCS) is the most frequent manifestation of ocular GVHD. The primary etiology of dry eyes in GVHD is thought to be secondary to lacrimal gland dysfunction. Histopathologic evaluation by Jabs et al. revealed PAS-positive material deposited within the lumina of acini and ductules of lacrimal glands in GvHD patients causing luminal obliteration and ductal dilatation (Jabs 1989). The typical time from transplantation to diagnosis of dry eye can range from around 100 to 200 days (Ogawa et al. 1999). KCS may cause corneal breakdown which leads to epithelial defects, peripheral neovascularization, keratinization, punctuate keratitis with sterile or infectious ulcerations, and perforation. Additionally, cutaneous manifestations of GvHD such as cicatricial lagophthalmos, ectropion, and eyelid stiffening may contribute to or exacerbate these corneal changes.

Pseudomembranous conjunctivitis is a cardinal ocular complication in GvHD, occurring in 12–17 % of patients with acute GvHD (Bray et al. 1991; Jabs et al. 1989) and 11 % in chronic GvHD (Jabs et al. 1989). Four stages of conjunctivitis have been described by Jabs et al. (1989). Stage 1 presents as conjunctival hyperemia. Stage 2 includes hyperemia with chemosis or serosanguinous exudates. Stage 3 manifests as conjunctival pseudomembrane which can lead to cicatricial fibrotic scarring of the tarsus. Stage 4 involves corneal epithelial sloughing in the setting of pseudomembrane conjunctivitis and usually occurs in the acute or hyperacute post transplant setting (Kim 2006). A study from John's Hopkins suggests that conjunctival involvement is a marker of severe acute GvHD and patients with lower stages of conjunctivitis without pseudomembranes have a better prognosis (Jabs et al. 1989).

Cataracts are a common ocular complication of BMT. Cataract genesis in patients with post-transplantation GvHD is caused by a combination of factors, including radiation, corticosteroids, and in some reports GvHD itself (Bray et al. 1991; Dunn et al. 1993).

Uveitis in the form of iridocyclitis and or choroiditis has been demonstrated in patients with GvHD. Hettinga et al. reported three patients who developed anterior uveitis in the setting of chronic GvHD without any other identifiable causes (Hettinga et al. 2007). Increased levels of inflammatory cytokines were found in the ocular fluid of these patients making GvHD a likely cause of the uveitis.

Posterior segment complications may also occur in patients post BMT with or without GvHD. Retinal findings, such as microvascular retinopathy, cotton-wool spots, and intraretinal and vitreous hemorrhage, have been reported in 12.8 % of patients post BMT. Most retinal and vitreous hemorrhages occur in the setting of pancytopenia and generally resolve without long-term sequelae (Coskuncan et al. 1994). Chronic GVHD has been reported to be the only significant risk factor associated with microvascular retinopathy (Coskuncan et al. 1994). Other posterior segment findings seen in the setting of GvHD include posterior scleritis, and central serous chorioretinopathy (CSCR). Posterior scleritis can be the initial manifestation of acute GvHD following BMT (Kim et al. 2002). CSCR is generally seen 50–120 days post BMT (Cheng et al. 2002; Karashima et al. 2002). CSCR development is thought to be secondary to choroidal infiltration in GvHD leading to choroidal hyperpermeability.

Drugs associated with the treatment of GVHD have characteristic ocular complications. Cyclosporine, an immunosuppressant agent used to prevent GvHD, has been linked to optic disc edema, optic neuropathy, and ischemic retinal lesions (Avery et al. 1991; Walter et al. 2000). In the setting of GvHD, BMT recipients are also highly susceptible to ocular infections secondary to persistent abnormalities of the immune system which is further inhibited by the treatment of GvHD with immunosuppressants. Pseudomonal corneal ulcers, herpes simplex keratitis, herpes zoster retinitis, toxoplasma gondii retinitis, cytomegalovirus chorioretinitis, and fungal endophthalmitis may cause permanent visual deficits following BMT (Chung et al. 2008; Coskuncan et al. 1994; Crippa et al. 2001; Robinson et al. 2004; Uchino et al. 2006).

A variety of treatments for ocular complications secondary to GvHD have been reported in the literature. The mainstay treatment is aimed toward treating the underlying GvHD while balancing the degree of immunosuppression. Systemic treatment for chronic GVHD includes corticosteroids and T-cell modulators (Cutler and Antin 2006). Recent reports have found targeting B-cells with Rituximab and photopheresis to be successful in the setting of steroid refractory GvHD (Couriel et al. 2006; Cutler et al. 2006).

7.3 Secondary Neoplasms

In some cases, the treatment modality for one malignancy increases risk for a secondary cancer. For instance, retinoblastoma patients are at risk for a secondary cancer particularly if they harbor the germline Rb mutation. It is believed

the radiation-induced chromosome instability, confers the second hit in the two-hit model of retinoblastoma. Importantly, this risk increases in irradiated patients treated before 12 months of age (Abramson and Frank 1998). For example, 50 years after radiotherapy for hereditary retinoblastoma, patients have an 8.9 % cumulative risk of developing a soft tissue sarcoma in the radiation field (Kleinerman et al. 2005, 2007). Soft tissue and osteosarcomas have significantly higher rates in the field of radiation. Therefore, periocular tumors such as these are possible in previously treated retinoblastoma patients.

Radiation can also induce DNA damage in the skin and result in a number of periocular skin neoplasms, including basal cell carcinoma, squamous cell carcinoma (SCC) and sebaceous cell carcinoma. Radiation doses greater than 20 Gy produce the malignant change necessary for SCC, which may occur 15 years or more after radiation therapy and has a higher risk of metastases in the setting of previous radiotherapy (Weedon 1997). One patient developed sebaceous cell carcinoma on all four of his eyelids following facial radiation (Rumelt et al. 1998).

8 Prevention and Management

8.1 Eyelids, Periorbital Skin, Lacrimal Drainage

During cancer treatment, skin can be cared for with the use of mild soaps and skin lubricants for hygiene and moisture. Ultraviolet protection should be established through a variety of means and skin-sensitizing drugs such as tetracyclines should be avoided. Antibiotic creams can be used to prevent superinfections while topical corticosteroid preparations may be useful in tempering skin inflammation.

Ptosis or other eyelid malpositions may require surgical manipulation and should be referred to an ophthalmologist in clinically significant cases (Seiff et al. 1985). Punctal stenosis may be relieved by punctoplasty, while nasolacrimal duct obstruction may necessitate silicone intubation or dacryocystorhinostomy (Barabino et al. 2005). Others have suggested the use of a stent before and after irradiation to prevent nasolacrimal duct obstruction (Gordon et al. 1995). Dry eye can be treated symptomatically with topical agents such as moisturizing eye drops.

8.2 Conjunctiva and Sclera

Artificial teardrops replace lost tear volume, dilute toxic chemotherapeutic metabolites, provide lubrication and thereby aid in relieving conjunctival irritation (see Sect. 4.3 for more on ocular surface management). In cases of conjunctival ulceration or even prolonged conjunctivitis, antibiotic eye drops, sometimes in combination with corticosteroids can be used. In advanced cases of inflammation, squamous metaplasia and loss of vascularization from scar formation may be reversed with vitamin A ophthalmic ointment (tretinoin 0.01 or 0.1 %) (Tseng 1986). Endstage, severe conjunctival reactions such as symblepharon and forniceal shortening should be referred for immediate ophthalmic interventions such as symblepharon lysis, mucous membrane grafting with forniceal reconstruction. Infectious conjunctivitis is highly contagious and patients should be counseled on contact precautions.

Subconjunctival hemorrhage typically reabsorbs without intervention; although patients should be warned and reassured of possible expansion, and advised to use artificial tears for alleviation of foreign body sensation.

Scleritis is treated with a number of oral anti-inflammatory agents including corticosteroids, NSAIDS and other immunomodulatory agents. Infections can be mitigated or treated with topical and systemic antimicrobials: fluoroquinolones are a common choice for their good tissue penetration. When there is significant risk for perforation, such as with scleral melting and profound thinning, scleral patch grafting can be employed. These patients should be warned about avoiding eye trauma and wearing eye protection at all times.

8.3 Tear Film, Ocular Surface, Cornea

One method in the treatment of dry eyes involves increasing the volume of tears. This can be achieved in two ways: either by reducing tear drainage or by supplementing the tear film with topical tear substitutes. The tenet of dry eye therapy is artificial tears, which contain a number of demulcents, which are polymers added to improve lubricant properties. Preservative-free formulas are preferred, given the toxic effect of preservatives on increasing corneal desquamation. These lubricants come in a variety of viscosities, with the most viscous being reserved for overnight use given its tendency to blur vision. Additives to increase viscosity include methylcellulose and hyaluronic acid; the latter promotes epithelial cell proliferation and has a longer ocular surface time to help stabilize the tear film (Troiano and Monaco 2008). Artificial tears require intermittent but persistent application, which can be tiresome for some patients. More convenient methods have been developed such as the lacrisert®, an ophthalmic insert which is placed into the inferior fornix and remains in place throughout the day to provide lubrication as it dissolves.

A number of anti-inflammatory agents are being employed to treat the inflammatory component of dry eyes. For instance, cyclosporine A is an immunomodulatory agent

that inhibits T cell activation and downregulates inflammatory cytokines. Likewise, steroid drops are used for a similar anti-inflammatory effect. Other agents under clinic trial are focused on stimulating tear components, such as the P2Y2 purinergic receptor agonist, which increases chloride, fluid and mucin secretion by the conjunctiva (Jumblatt and Jumblatt 1998). Vitamin A regulates proliferation and differentiation of corneal epithelial cells and aids in goblet cell preservation (Kobayashi et al. 1997). In one study, both cyclosporine A and vitamin A were both found to improve dry eye symptoms, but at least one month of their use is advised to obtain an adequate effect (Kim et al. 2009).

Autologous serum drops have beneficial effects on dry eyes by containing the growth factors normally present in tear fluid, which stimulates conjunctival mucous production. Environmental alterations such as humidifiers and moisture shield glasses can alleviate dry eye symptoms, as well as avoiding eye irritants such as rubbing, wind, smoke, and fans. Surgical interventions include reversible punctal occlusion with collagen or silicone punctual plus, and irreversible occlusion with cautery, hyfrecator or radiofrequency probe. Tarsorrhaphy can decrease the palpebral aperture and reduce exposure of the ocular surface, aiding dry eyes but also allowing for corneal wound healing. Finally, treatment of confounding eye diseases is imperative: for example, hot compresses and eyelid massage use in blepharitis may improve meibomian gland function and help generate a more stable lipid component to the tear film.

Epithelial defects, corneal infections, and ulcerations are treated with broad-spectrum antibiotic drops (typically a 4th generation fluoroquinolone) as frequently as every 15 min, based on severity. Non-healing epithelial defects can be treated with a bandage contact lens or tarsorrhaphy along with antibiotic drops. Corticosteroid drops (dexamethasone) are given as prophylactic treatment for corneal and conjunctival irritation in patients receiving antimetabolite treatment, especially cytosine arabinoside. Some types of sterile keratitis can also be alleviated with steroid drops. With impending or apparent corneal perforation, emergency surgical intervention is necessary.

Precaution measures during the time of radiation can help to reduce the radiation effect on key ocular structures. Selective blocking, angulations of the radiation fields and enhanced dose homogeneity with beam attenuators are examples of methods to achieve this. For instance, the accessory lacrimal glands concentrated in the upper lid can be displaced from the treatment field with a lid retractor. There is a misconception that the relatively radiosensitive lacrimal gland must be protected from the radiation field to maintain the aqueous component of the tear film. However, interestingly its removal fails to result in dry eyes, suggesting its protection is not necessary and may also be shielding micro foci of malignant cells.

8.4 Lens

Prevention of cataract formation may be accomplished by lens-sparing radiation techniques such as angle modification of external beam radiation or lens shielding. The Schipper's lens sparing retinoblastoma treatment method, which involves positioning the radiation beam to pass lateral to the orbits and beneath the lens posterior pole, has been shown to prevent radiation cataracts in patients with uveal metastases treated with external beam radiation (Bajcsay et al. 2003). Lens shielding is another effective method and has been described to decrease the total dose of radiation to the lens by as much as 50 % (Esik et al. 1996; Henk et al. 1993).

Cataract extraction is the only potential curative treatment for clinically significant radiation induced cataracts. During the early postoperative period several studies have shown an improvement in visual acuity of 2–5 lines compared with preoperative measurements (Fish 1991; Collaborative Ocular Melanoma Study 2007). However, vision-limiting complications usually lead to patients returning to either their preoperative visual acuity or worse within a few years after the surgery. The decrease in visual acuity is typically attributed to the effects of radiation rather than cataract surgery itself. In the COMS the most commonly reported complication was presumed radiation retinopathy (Collaborative Ocular Melanoma Study 2007). Complications that may be related to cataract surgery include cystoid macular edema, retinal detachment, and worsening of diabetic retinopathy.

Since free radical formation is postulated to be involved in the development of cataracts, antioxidant supplements, such as vitamin E and glutathione isopropyl ester, may help prevent or slow down the process. In animal models antioxidants have been shown to decrease oxidative stress and the risk of cataract formation (Karslioglu et al. 2004). However, to date, no compound has been identified to be effective in humans to prevent radiation related cataracts.

8.5 Uvea: Iris, Ciliary body, and Choroids

The mainstay treatment of noninfectious uveitis includes steroids. Typically, frequent dosing of topical steroid drops are used, although oral steroids maybe added in refractory cases. A number of other steroid-sparing immunomodulatory agents can be employed; although given their toxicity profile, use in conjunction with medical surveillance is advised. Cycloplegic drops are also recommended in the context of uveal inflammation: the paralysis of the ciliary body may relieve the associated pain, while also pulling the iris away from the lens and preventing posterior synechiae formation and its complications.

A number of intraocular pressure lowering agents are available, each with their unique side effects and thus patient indication. Beta-blockers, alpha-agonists, carbonic anhydrase inhibitors decrease aqueous production. Conversely, cholinergics increase trabecular outflow, while prostaglandin analogues increase uveoscleral outflow.

When medical management of intraocular pressures is inadequate, a number of surgical techniques are available. Commonly, a laser is used to create an opening in the iris (peripheral iridotomy) and thus provide an outlet for aqueous flow from the ciliary body to the trabecular meshwork. Laser is also used in trabeculoplasty to open the drainage angle and in cyclophotocoagulation to destruct the ciliary epithelium and decrease aqueous production. Other filtering procedures include goniotomy and trabeculotomy in which tissue incisions are created to provide an alternate means of outflow for aqueous drainage. In progressive cases, aqueous shunt devices can be placed to facilitate aqueous flow through a tube implanted in the anterior chamber to the subconjunctival space. Panretinal photocoagulation of the retina is used in neovascular glaucoma since it can help dissipate the ischemic retina as the inciting cause of angiogenic factors. Recently, vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) has been used as a treatment for neovascular glaucoma (Kahook et al. 2006), and these agents have since supplanted all other treatments for neovascular glaucoma and rubeosis iridis.

8.6 Optic Nerve and Retina

The management of radiation retinopathy is similar to that for diabetic retinopathy. Retinal hemorrhages and cotton wool spots are a clear indication of retinal damage, and while they typically resolve without treatment, an ophthalmologic referral for their evaluation and associated pathology is appropriate. Of note, macular edema is typically diagnosed by abnormal fluorescein angiogram or optical coherence tomography, which provides a high-resolution cross-sectional image of the retina. Panretinal photocoagulation can be applied to peripheral zones of ischemia and neovascularization. The goal of photocoagulation is to ablate ischemic tissue and thus remove the instigating factor for angiogenic growth factors. The rationale of focal laser photocoagulation to macular edema is to reduce vascular leakage via a series of laser burns at leaking microaneuryms. Intravitreal triamcinolone acetonide has also been used for macular edema; however, while the visual acuity may stabilize or improve, the effects are short-lasting (Shields et al. 2005). A number of cases have reported on the beneficial effects of intravitreal placement of a VEGF inhibitor (bevacizumab) on radiation retinopathy, citing decreased vascular leakage, improved vision, and resolving recent onset macular edema (Finger 2008; Gupta and Muecke 2008). However, despite temporary improvements with these treatments, no therapy has been proven to alter the course of the disease and most centers do not treat radiation retinopathy.

The treatment for optic neuropathy is controversial and outcomes are disappointing. Heparin and warfarin have been used in an effort to promote blood flow to irradiated tissue. Hyperbaric oxygen is thought to stimulate oxygen revascularization via alterations in oxygen gradation, but has proven useful only if employed within 72 h of visual symptoms (Lessell 2004). Some believe prompt diagnosis of optic neuropathy is crucial and early detection has been suggested through the use of magnetic resonance imaging or electrophysiological testing which may demonstrate findings that predate symptoms (Lessell 2004). While the use of systemic corticosteroids and pressure-lowering medications may be effective in optic disc edema, observation is also a viable option. Ocular neuromyotonia responds to the membrane-stabilizing medication, carbamazepine.

8.7 Orbital Bones and Tissue

Unfortunately, there is no medical treatment to reverse the bone growth retardation caused by radiation. The anophthalmic socket may be improved with orbital volume augmentation with self-inflating expanders or custom-made conformers, and with orbital reconstructive surgery in advanced cases. Anophthalmic sockets and their ocular prosthesis require frequent cleaning with mild soaps, and regular examinations for abnormal tissue or other lesions. Osteonecrosis requires aggressive antibiotic therapy and surgical debridement on occasion.

The radiation effects on bone retardation can be disfiguring and devastating for some patients, and access to counseling should be available.

9 Future Research

Ocular toxicity of cancer treatment by radiation, chemotherapy, bone marrow transplant, or biologicals is a growing field. As new therapies are being introduced and as patients are offered longer survivals times with more promising treatments, the ocular insults become increasingly important. Our collaborative efforts in understanding these toxicities, at the chemical, physiological, and clinical level will help establish safer protocols and adequate management to guide our patients through these complications.

The most promising new studies have been the use of molecular agents as, avastin, to mitigate retinal vascular alternations; the introduction of retinal stem cells are becoming available to restore radiation damaged retina.

10 Review of Literature and Landmarks

1897 Chalupecky: Noted that roentgen rays cause severe destructive changes, especially in the structures of the anterior segment of the eye.

1908 Birch-Hirschfield: Concluded that blood vessel changes due to irradiation may play some part in later phases but that corneal changes are direct effects.

1931 Desjardins: Offered a complete and exhaustive review of the experimental and clinical literature up to 1931, establishing the order of radiosensitivity of the various structures of the eye.

1933 Foster-Moore: Treatment of retinoblastoma with interstitial insertion of radiation. Moore RF: Proc Soc Med; 26:1036.

1936 Leinfelder and Kerr: Published one of the earlier reports correlating clinical and microscopic studies of non-progressive cataract, and found this opacity to be the usual result of irradiation of the rabbit lens with ordinary therapeutic doses of X-rays.

1952 Cogan, Donaldson and Reese: Published an excellent article correlating the clinical appearance of radiation cataract with histopathologic changes in humans, and evolved a thesis for their occurrence.

1955 Merriam: In an excellent article, defined the late effects of beta radiation on the eye and their relationship to the dose administrated.

1957 Merriam and Focht: Presented a classic paper on a clinical study of radiation cataracts and the relationship to dose-time factors.

1965 Perrers-Taylor, Brinkley and Reynolds: Described choroidoretinal damage of varying types as a complication of radiotherapy.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

1995 Rubin: Presented the LENT-SOMA toxicity scales for radiation effects to evaluate the grade of severity.

2003 Trotti and Rubin: Modified and developed the Common Toxicity Criteria CTCAE V3.0 which applied similar scales to grade adverse effects of all major modalities-surgery and chemotherapy in addition to irradiation.

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