Chapter 13
Radiation Therapy for Orbital and Adnexal Tumors

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Abstract Radiation therapy is used in the multimodality treatment of many orbital and adnexal tumors to enhance local control and possibly, in some patients, overall survival. In this chapter we will review the indications, modern techniques, potential toxic effects, and expectations of tumor control for a variety of orbital and adnexal tumors. Typically, treatments are delivered in fractions of 1.8–2.0 Gy per day, with the total number of fractions depending on the inherent radiosensitivity of the lesion. Radiotherapy technique and field design depends on the required dose, the tumor type, and the surrounding normal structures such as the lens, which is at risk of a cataract after a dose as low as 2 Gy. Excellent functional outcomes are evident for patients with optic nerve meningiomas with 5-year local control rates greater than 90% after local radiation therapy alone. In patients with orbital rhabdomyosarcoma, chemotherapy with radiation therapy results in excellent 5-year survival rates. Recently, we have been evaluating the role of oculoplastic procedures followed by adjuvant radiation therapy in lieu of orbital exenteration for patients with locally advanced ocular adnexal cancers.

13.1 Indications

Radiation therapy is used in the multimodality treatment of many orbital and adnexal tumors. Benign orbital and adnexal tumors and conditions that are successfully treated with radiation therapy alone include hemangioma, meningioma, orbital pseudotumor, and Graves ophthalmopathy. Malignant orbital and adnexal tumors that may require the use of radiation therapy include lymphoma, sarcoma, carcinoma, and metastatic disease. Radiation therapy may be used as the sole treatment modality or in combination with surgery and/or chemotherapy. For all of the

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B. Esmaeli (ed.), *Ophthalmic Oncology*, M.D. Anderson Solid Tumor Oncology Series 6, DOI 10.1007/978-1-4419-0374-7_13,

indications described above, the role of radiation therapy is to enhance local control and possibly, in some patients, overall survival.

13.2 Radiation Therapy Terminology

Radiation therapy is prescribed in the unit of Gray (Gy), which measures the energy absorbed in a material (J/kg). Typically, orbital and adnexal radiation treatments are delivered in fractions of 1.8–2.0 Gy per day. The total number of fractions varies according to the inherent radiosensitivity of the lesion; for example, Graves disease may be treated in 10 fractions with a total dose of 20 Gy, whereas a sarcoma may require up to 30 fractions with a total dose of 60 Gy. Another factor that determines final treatment dose is the normal tissue in the irradiated volume and the associated morbidity risk (see Section 13.7).

Three-dimensional (3D) radiation therapy planning allows careful optimization of a plan to improve the tumor control probability while minimizing the normal tissue complication rate. The tumor volumes and normal tissue are identified on a planning computed tomography scan that is usually obtained in the radiation therapy department. These images can be fused with other diagnostic scans, including magnetic resonance imaging scans, positron emission tomography scans, or angiograms, to better visualize the regions of interest. Once all of the areas of concern and the tumor are delineated, a plan is generated on one of many available treatment planning systems. The treatment plan is then assessed through evaluation of the isodose curves and dose–volume histograms. These histograms are graphical representations of the volume of each region of interest receiving a particular dose. This analysis provides the radiation oncologist an objective method of appraising a heterogeneous dose distribution. Typically, normal tissue receives a nonuniform dose; however, an effort is made to maintain a uniform dose distribution within the tumor volumes.

13.3 Radiation Therapy Techniques

A variety of different radiation therapy techniques and modalities are available for treatment of the orbit and adnexal areas. All of the current treatment techniques use 3D algorithms that calculate dose in all planes and display dose in the axial, coronal, and sagittal views.

The basic form of radiation therapy based on 3D planning is called 3D conformal radiation therapy (3DCRT). With 3DCRT, conformal fields from different angles are optimized to meet the individual patient's needs. Any radiation therapy modality—i.e., photons, electrons, or protons—can be used for 3DCRT.

Stereotactic radiosurgery and fractionated stereotactic radiation therapy are techniques that use stereotactic positioning accomplished with an external fiducial system to immobilize and position patients, allowing submillimeter precision for

radiation therapy treatments. With stereotactic radiosurgery, a large single fraction of radiation is given; with fractionated stereotactic radiation therapy, multiple fractions of radiation are given, and the patient is positioned before delivery of each fraction by using a noninvasive stereotactic frame.

Intensity-modulated radiation therapy (IMRT) is typically delivered with photon beams; a few centers now deliver it with proton beams ("intensity-modulated proton therapy"). Intensity modulation can also be implemented with the stereotactic approach, which may allow an increase in precision of delivery and conformality. IMRT plans use multiple beams optimized for the tumor location and patient. For each beam, the multileaf collimation varies during the dose delivery to modulate the dose from that beam to "paint" the dose and allow improved conformality and reduction in normal tissue doses.

Electron and proton radiation therapy differ from photon radiation therapy (X-ray or Cobalt) in that they lack an exit dose. Electron radiation therapy is an excellent modality for treating shallow, superficial tumors while sparing the underlying tissues. A lead eye shield is necessary when ocular adnexal lesions are treated with KV photons, and a tungsten eye shield is necessary when adnexal lesions are treated with electrons because of the risk of acute and late side effects from definitive or adjuvant radiation therapy.

Proton radiation therapy is becoming more available worldwide and allows treatment of larger, deeper tumors without an exit dose, thereby reducing the volume of normal tissue receiving low to moderate doses and potentially reducing acute and late toxic effects [1]. Proton radiation therapy may be a useful technology for young patients with curable tumors.

Radiation therapy implants (brachytherapy) are not typically used for orbital or adnexal tumors; the experience with brachytherapy for orbital tumors is limited to a few case reports of brachytherapy for lacrimal gland tumors and recurrent conjunctival tumors. We currently do not use brachytherapy at our center for lesions involving the orbit or ocular adnexal structures.

13.4 Radiation Therapy for Squamous Cell Carcinoma of the Eyelid

For patients presenting with squamous cell carcinoma of the eyelid, radiation therapy can be used in both the definitive and adjuvant settings. Recently, we have reviewed our institutional experience from 1950 to 2005 with 42 tumors in 39 patients [2]. Thirty-two of the tumors were treated with primary radiation therapy to a dose of 66–70 Gy, and 10 tumors were treated with adjuvant radiation therapy to 60 Gy. With a median follow-up of 76 months, the local disease-free, regional disease-free, and overall disease-free survival rates at 5 years in the entire group were 88, 95, and 90%, respectively. There was no significant difference between the patients treated with radiotherapy alone versus those treated after surgery. While

there were no grade 3 or 4 complications, patients did experience grade 1 and 2 complications, including epiphora, symptomatic cataract, neovascular glaucoma, dry eye syndrome, and keratitis.

We recommend primary radiation therapy for patients refusing surgery and patients who are poor surgical candidates because of medical comorbidities or large lesions, removal of which would result for poor function and cosmesis. Adjuvant radiation therapy is recommended for patients with residual disease, positive or close margins, perineural invasion, lymph node-positive disease, lymphovascular invasion, or deep muscle invasion. Our institutional experience has revealed no difference in 5-year regional lymph node control in those patients who received radiation therapy to the regional nodes in comparison to those who did not—100 versus 93%, respectively. Prophylactic nodal irradiation is, therefore, not recommended.

13.5 Adjuvant Radiation Therapy for Ocular Adnexal Tumors

Recently, we have begun to investigate the role of adjuvant radiation therapy following oculoplastic procedures in lieu of orbital exenteration for some patients with locally advanced or aggressive ocular adnexal tumors. A review of our orbit-sparing approach from 2000 to 2006 with 20 consecutive patients presenting with primary eyelid or conjunctival tumors was recently published [3]. Pathologic subtype varied within this cohort of patients and included melanoma (three patients), Merkel cell carcinoma (three patients), squamous cell carcinoma (three patients), sebaceous gland carcinoma (three patients), basal cell carcinoma (one patient), mucinous eccrine adenocarcinoma (one patient), adenoid cystic carcinoma (one patient), and myxoid sarcoma (one patient). Most patients in this study (12 patients) presented with lower eyelid lesions; nine patients had tumors involving more than one site. In the majority of cases, oculoplastic surgery consisted of placement of local flaps or direct closure of the eyelid; also used were tarsoconjunctival flaps and grafts, full-thickness skin grafts, amniotic membrane grafts, and lacrimal stenting. The indications for adjuvant radiation therapy were high-grade disease, recurrent tumor, positive or close margins, perineural invasion, and advanced-stage disease. Radiation therapy for melanoma was 30 Gy delivered in 6-Gy fractions over 2.5 weeks. Radiation therapy for other tumors was 60 Gy delivered in 2-Gy fractions over 6 weeks.

With a median follow-up of 21 months, there were no local or regional relapses, and no salvage surgery was required. Fifteen patients had 20/40 vision or better, and the majority maintained their visual acuity after radiation therapy. Complications following surgery and adjuvant radiation therapy were dry eye syndrome (13 patients), keratinization of the conjunctivae (3 patients), blepharitis (1 patient), trichiasis (1 patient), optic neuropathy (1 patient), and exposure keratopathy (1 patient). We have observed that in patients with ocular adnexal cancers, local control rates after oculoplastic procedures and external-beam radiation therapy are acceptable; however, for an orbit-sparing approach to be considered, meticulous

radiation techniques are a prerequisite, and realistic expectations regarding risk of ocular toxicity need to be discussed with the patient.

13.6 Radiation Therapy for Optic Nerve Meningiomas and Orbital Rhabdomyosarcomas

Optic nerve meningiomas are typically diagnosed on the basis of their characteristic radiographic appearance. A pathologic diagnosis is not mandatory if an orbital biopsy would entail risk to visual function. With definitive radiation therapy with doses ranging from 50.4 to 54 Gy in 28–30 fractions, the 5-year overall control rate is 90% [4, 5]. Potential morbidities include retinal injury, cataract, further visual compromise, and neuroendocrine compromise. Vision may improve or stabilize after radiation therapy. Typically, 3DCRT, fractionated stereotactic radiation therapy, or IMRT is used. Proton radiation therapy may be used if late toxic effects are of concern. Stereotactic radiosurgery is usually not recommended because of the unacceptable risk to vision.

The treatment strategy for orbital rhabdomyosarcoma usually involves a biopsy and surgical debulking of tumor followed by chemotherapy with radiation therapy. The recommended dose is 45 Gy given in 25 fractions. Particular concerns in individuals with this tumor, who tend to be young, are potential adverse effects of radiation on orbital bone growth and vision and the risk of secondary malignancies. These morbidities may be reduced with the use of highly conformal techniques such as IMRT or proton radiation therapy [6, 7]. The 5-year overall survival rate is excellent, and efforts to minimize late toxic effects are paramount. For further discussion of orbital rhabdomyosarcoma, please see Chapter 4.

13.7 Toxic Effects of Radiation Therapy

Toxic effects of radiation therapy are divided into two categories: acute toxic effects, which occur during or shortly after treatment, and late toxic effects, which can occur months or years after treatment. The probability and nature of toxic effects depends on the area of treatment, the volume of the organ being treated, and dose that it receives. For the orbit and the ocular adnexal structures, the anatomic structures at risk are the eyelid, lacrimal gland, nasolacrimal duct, intraocular structures, optic nerve(s), optic chiasm, bone (in young patients), brain, and neuroendocrine structures.

Acute toxic effects that are not unusual are eyelid erythema and swelling, eyebrow and eyelash alopecia, and conjunctival irritation with mild dry eye. The lacrimal gland secretes the aqueous layer of tear film; keratoconjunctivitis sicca (also known as dry eye syndrome) occurs when the gland receives doses in excess of 30 Gy [8]. The eyelashes protect the eye; a dose of 20 Gy will lead to eyelid alopecia, which in turn causes irritation of the conjunctivae and cornea. Subsequent regrowth may be associated with trichiasis and eyelid entropion. Additionally,

meibomian gland dysfunction as a result of irradiation results in dry eye symptoms [9, 10].

Late toxic effects of radiation therapy are important because they can permanently affect visual function or cosmetic outcome. The cornea serves as the "clear window" for the eye and refracts light. Doses up to 30 Gy are well tolerated by the cornea; however, doses exceeding 50 Gy can result in keratitis, stromal edema, ulceration, and resultant vision loss [11]. The lens transmits and refracts light and is considered the most radiosensitive organ in the body. Doses exceeding 2 Gy in a single fraction can result in cataract formation; the time of onset and severity of the cataract can vary with lens exposure [11]. The retina contains the neuroreceptors for the eye and produces the image-forming signals. Doses greater than 45 Gy can result in retinopathy, including retinal hemorrhages, microaneurysms, hard exudates, cotton-wool spots, telangiectases, and retinal neovascularization [12]. The optic nerve transmits signals from the retina to the brain; optic neuropathy can occur if greater than 1 cm of the nerve receives 60 Gy or greater [11, 13]. The optic nerves cross at the optic chiasm, where doses exceeding 54 Gy in 2-Gy fractions can result in bilateral blindness [11]. The sclera maintains the globe shape and is, fortunately, extremely radioresistant, tolerating doses up to 200 Gy. The tolerance of the sclera has allowed orbit-sparing approaches and improved outcomes for patients presenting with intraocular melanoma. Doses to the sclera exceeding 200 Gy result in atrophy of the globe [13].

The nasolacrimal duct allows tears to drain into the nasal cavity. When the duct receives a dose of 60 Gy or more, stenosis of the duct can occur, leading to epiphora, which may necessitate silicone intubation or dacryocystorhinostomy with Pyrex glass tube placement to relieve epiphora [14].

In the pediatric population, orbital bone hypoplasia and facial asymmetry are of concern in areas receiving more than 20 Gy. Secondary malignancies are of particular concern in younger patients who are expected to have an extended survival. Proton radiation therapy may reduce the risk of secondary malignancies because of the low dose of radiation that is "sprayed" out with the photon techniques because of the exit dose [15].

13.8 Summary

In summary, radiation therapy is an integral component in the management of orbital and adnexal tumors. Various technologies are used in this treatment, and the optimal treatment technique should be chosen for each patient's needs.

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