Evolution of Care of Orbital Tumors with Radiation Therapy

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Abstract

Orbital tumors are rare lesions comprising 0.1% of all tumors and less than 20% of all ocular diseases. These lesions in children and adults differ significantly in their incidence, tumor type, and treatment management. Although surgery and systemic therapies are commonly used in the management of these diseases, radiation therapy has become a widely used treatment for both benign and malignant tumors of the orbit. Radiotherapy is used as a definitive treatment to provide local control while avoiding morbidity associated with surgery for some tumors while it is used as an adjuvant treatment following surgical resection for others. For many tumors, radiation provides excellent tumor control with preservation of visual function. This article is dedicated for presenting the most common applications of orbital radiotherapy. A brief overview of the commonly available radiation therapy modalities is given. Dose constraint goals are reviewed and acute and long-term side effects are discussed. Orbital tumors covered in this article include optic glioma, ocular melanoma, retinoblastoma, orbital rhabdomyosarcoma, orbital lymphoma, and lacrimal gland tumors. Background information, indications for radiotherapy, and goals of treatment for each case example are described.

Keywords
- radiation
- proton therapy
- IMRT
- carbon-ion
- melanoma
- retinoblastoma
- sarcoma
- glioma
- lymphoma
- carcinoma

Introduction

Radiation therapy plays an essential role in the cure of many orbital tumors. Care must be taken, however, to minimize radiation to structures of the eye and surrounding soft tissues and bone to minimize morbidity that ranges from visual loss to decreased growth of bone and soft tissues of the orbit. With the early application of radiation therapy, late morbidity was substantial. For this reason, attempts have been made to avoid radiation for some patients, especially young children, but this sometimes results in a loss of function due to tumor progression. Major technical advances in both diagnostic and therapeutic radiology along with increased knowledge regarding the doses that critical structures of the eye can tolerate have allowed for great changes in the way we deliver radiation. Targets are now well defined, smaller, and allow for a great deal of sparing of the normal healthy ocular tissues. Radiation should be considered as an option for local control with the expectation of visual preservation for most patients and minimization of other side effects for most ocular tumors for which other vision and eye-preserving therapies are not available.

Treatment Planning

Modern planning utilizes computed tomography (CT) scans and magnetic resonance imaging (MRI) and occasionally positron emission tomography (PET)/CT. The majority of radiation centers have CT simulation and obtain a CT scan in the radiation oncology department in the treatment position. MRI and PET/CT treatment planning is available at some centers but typically MRI and PET/CT are obtained in a radiology department and fused to CT treatment planning scans. For orbital tumors, MRI is most often the imaging modality that best defines the orbital tumor and the surrounding tissues. The most useful MRI sequences for an individual

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Pearls and Tips

- Radiation therapy remains a mainstay in the multidisciplinary treatment management of benign and malignant orbital tumors.
- There is an increasing interest in the use of particle radiotherapy in the management of ocular malignancies by delivering a high dose to the target volume while sparing the surrounding critical normal structures.
- Proper contouring and accurate delineation of organs at risk is a crucial step in radiation treatment planning.
- Despite the high cure rates, radiotherapy is usually reserved for optic pathway gliomas that relapse following systemic therapy regimens or due to threatened vision.
- Uveal melanoma is the most common primary intraocular malignancy in adults. Overall survival rates are comparable between surgery and radiation modalities. Local control rates are higher for protons vs episcleral plaques. Tumor recurrence or complications are treated with orbital exenteration.
- Lymphoma is the most common primary orbital malignancy in adults. Excellent local control rates are seen with radiation alone for low-grade or CRT for intermediate/high grade tumors.
- Retinoblastoma is the most common primary intraocular malignancy in children. Radiation (proton RT or plaques) is used for disease resistant to alternative therapies (cryotherapy, laser, chemotherapy) or for metastatic disease.
- Rhabdomyosarcoma is the most common primary orbital malignancy in children. IRS studies guide treatment management. Radiation is generally given to Groups II and III following cytotoxic chemotherapy regimens.
- Adenoid cystic carcinoma of the lacrimal gland can be safely treated with globe-preserving surgery followed by high-dose proton RT.

patient's orbital tumor are tumor type and patient dependent and best determined after careful review with a neuroradiologist, but orbital MRI with thin slice pre- and postcontrast as well as fast imaging employing steady-state acquisition (FIESTA) sequences is often helpful for delineating tumors and small structures of the orbit. For CT planning, a slice thickness no greater than 1.25 mm is recommended. PET/CT is used less often but may be helpful for ocular lymphoma or sarcomas. For tumors such as retinoblastoma and ocular melanoma, retinal photos and ultrasound may be incorporated into treatment planning systems. Because tumor extent is better visualized and anatomical barriers of the orbit may prevent tumor extension, margins for error around this volume can be made much smaller. Care should be taken to be inclusive of areas at risk of spread for specific malignancies. For example, nerves must be tracked for tumors with perineural spread such as lacrimal gland adenoid cystic cancer. Daily treatment verification has also evolved over time with most institutions now utilizing cone beam CT to verify daily alignment and reducing setup error necessitating only a very small margin for the uncertainty of daily setup.

Photon Therapy

Photon therapy is delivered by a machine referred to as a linear accelerator (LINAC) and is the most widely available form of external beam radiation. Simple photon plans that use a single or multiple beam angles are referred to as three-dimensional conformal radiation therapy (3DCRT). This treatment is used for some orbital tumors and has the benefits of a short delivery time and it is less costly compared with other more complex forms of photon therapy or particle therapy. Electron therapy can also be produced by a LINAC. Electrons are light charged particles that are useful for very superficial tumors and may be used for orbital lymphomas, tumors of the lid, or other superficial tumors of the orbit.

Intensity-Modulated Radiation Therapy/Volumetric Modulated Arc Therapy

With the development of very sophisticated radiation treatment planning software, we have the ability to simulate multiple complex photon beam arrangements far more efficiently than a human could possibly perform. Intensity-modulated radiation therapy (IMRT) refers to highly complex photon radiation planning that delivers small beamlets of photon radiation of various intensity from multiple angles to best shape high dose to the target volume while avoiding high- and moderate-dose radiation to normal healthy structures. For IMRT planning, the physician defines all structures and inputs the desired target dose and volume limitations for normal structures and prioritizes these goals. The software program then runs numerous iterations of the treatment plan until it finds the best possible plan for the given constraints. While IMRT plans decrease high and moderate dose to nearby structures, these plans typically result in the delivery of low-dose radiation to a larger volume of tissue outside of the target. Volumetric modulated arc therapy is an even more innovative form of photon delivery similar to IMRT but delivering radiation continuously as the machine rotates. These more conformal and precise forms of radiation therapy give less room for error compared with 3DCRT and daily setup imaging is recommended.

Proton Radiation

Proton radiation therapy (PRT) has become a more widely used radiation modality for orbital malignancies over the last decade.[1] PRT is a form of particle radiation that allows for complete sparing of tissue beyond the target volume for a given beam as well as often less dose proximal to the target compared with photon radiation. PRT can be delivered using three-dimensional conformal proton radiation therapy (3DCPRT), also referred to as double-scattered proton

technique. For this treatment, individual proton beams of the required energies are stacked to create a modulated beam or spread out Bragg peak. This beam is passed through a brass aperture to shape the beam to the outline of the tumor and a Lucite compensator to allow the beam to conform to the distal edge of the tumor. Protons can also be delivered using a scanning technique.[2] For this treatment, individual proton beams are scanned across the tumor in the required location and depth. Scanning can improve conformity and this treatment creates minimal scatter radiation and requires less hardware. While most proton centers built before 2010 were built for the delivery of 3DCPRT with capability to convert to pencil beam scanning (PBS), most modern centers are built for only PBS delivery. ►**Fig. 1** demonstrates PRT delivery for a patient with left orbital tumor. Up until 2006, only three proton centers existed in the United States. Currently, 31 centers exist, and many others are in either construction or planning phase despite the high capital costs involved with building a center and the higher operational costs.[3] The physical properties of protons result in superior sparing of tissues compared with photons and for a given dose in gray relative biological effectiveness (Gy (RBE)), it is considered to be biologically equivalent to photons. While clinical experience is still limited, many publications have supported disease outcomes that are comparable to photons and early indications that morbidity may be less.[4–6] It is important to continue to collect data to confirm both efficacy and toxicity to justify increased costs.

Carbon Ion Radiotherapy

Similar to PRT, carbon-ion radiotherapy (CIRT) presents a new promising treatment option for tumors, which are resistant against conventional radiotherapy. Radiobiologically, carbon-ion beams result in two to three times the RBE (the ratio of the doses required by two radiations to cause the same level of effect) of proton and photon radiation, while they exhibit a larger energy loss. In contrast to conventional radiotherapy, CIRT does not show an oxygen effect, does not show repair of potentially lethal damage, and has less radiosensitivity throughout the cell cycle.[7]

Although CIRT is not available in the United States, 11 cancer therapy centers worldwide offer CIRT, with the majority of these being located in Asia and a few in Europe. Until 2016, approximately 21,580 patients were recorded to have been treated with CIRT internationally.[8] For ocular tumors, CIRT has been delivered to choroidal melanoma and lacrimal gland tumors with an acceptable morbidity and sufficient local control, but experience is very limited.[9–11]

Key Structures, Dose Tolerance, and Toxicity

The orbit is an anatomic structure which describes the bony cavity containing the globe, the optic nerve, the extraocular muscles, and other orbital soft tissue. Both ocular and orbital structures are at risk when delivering radiation for ocular malignancies. Due to a wide range of dose-dependent sensitivities to radiation, there is a risk for functional, cosmetic, visual, and, for some tumors, neuroendocrine or vascular consequences. These side effects depend on the total dose and the dose per fraction. In general, standard fractionated radiation with daily doses between 1.8 and 2 Gy has to be distinguished from hypofractionated radiotherapy, which gives a larger dose per treatment. When thinking about visual toxicity, it is important to consider the actual impact on vision, the patient's vision status at the time of treatment, and competing risks of tumor progression in addition to dose constraints of these structures. For instance, RT-induced injury to optic nerve or retina will cause unilateral vision loss, while injury to the chiasm could result in total blindness. Damage to the lacrimal gland may be treated with punctal plugs or cauterization and lubricating eye drops and

Fig. 1 Proton radiotherapy plan in a 33-year-old male with left orbital tumor, treated with double-scattering proton beam to a total dose of 54.0 Gy (RBE)/30 fractions.

cataracts may be surgically treated. The area of the retina receiving radiation is also important as the fovea would result in central visual loss, whereas retinal damage in the superior retina would result in lower visual field loss and perhaps difficulty going down stairs.

Lens

The lens (►**Fig. 2**) is very sensitive to the formation of cataract. Cataracts that develop after RT can be distinguished from those that form as a result of aging as they start with subcapsular opacifications as opposed to anterior opacifications.[12] It may take years for cataracts to develop following radiation therapy and usually many years to impact vision to the extent that surgical intervention is indicated. With 6 Gy, one-third of patients develop a cataract within 8 years. Though cataract surgery is considered common and a relatively low-risk procedure, it may be more complex in patients who have had additional ocular problems or treatments, for example, patients who have undergone treatment for retinoblastoma as a child.

Retina

The retina (►**Figs. 2** and **3**) is somewhat sensitive to radiation and some orbital tumors do require doses above retinal tolerance. Retinopathy is thought to occur at doses of 45 Gy and higher and is due to damage to or reorganizing of small vessels supplying the retina.[12] If a portion of the retina is damaged, the field of vision affected corresponds to the area of the retina damaged. Retinopathy of the macula or fovea will lead to central visual loss, which would have a greater effect on overall visual function and should be spared if possible.

Conjunctiva and Cornea

Acute conjunctivitis may develop with a radiation dose of >30 Gy. Conjunctival telangiectasia, conjunctival squamous cell metaplasia, and conjunctival keratinization are late effects seen at higher radiation doses (>50 Gy).[12,13]

High radiation doses can also injure the corneal surface epithelium due to loss of the tear film. Epithelial erosions develop after 30 to 50 Gy, corneal edema after 40 to 50 Gy, and corneal ulceration after 60 Gy.[14] Late corneal toxicities are seen due to stem cell loss after delivery of larger doses.[12]

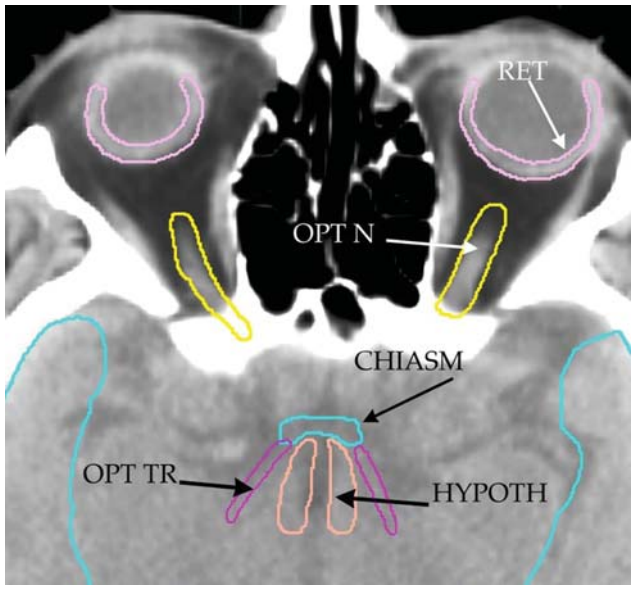

Fig. 3 This image shows retinas (RET) and the optic nerves (OPT N). The optic tracts (OPT TR) extend posteriorly from the chiasm. The hypothalamus (HYPOTH) is located on either side of the third ventricle. The anterior temporal lobes are shown in the most lateral portion of the brain. (Figure is provided courtesy of Dr. Barbara Fullerton.)

Optic Nerves, Optic Chiasm, and Optic Tracts

The optic nerves leave the posterior edge of the globe and join the chiasm (►**Fig. 4**) that is superior to the pituitary gland and anterior to the infundibular stalk (95% of cases).

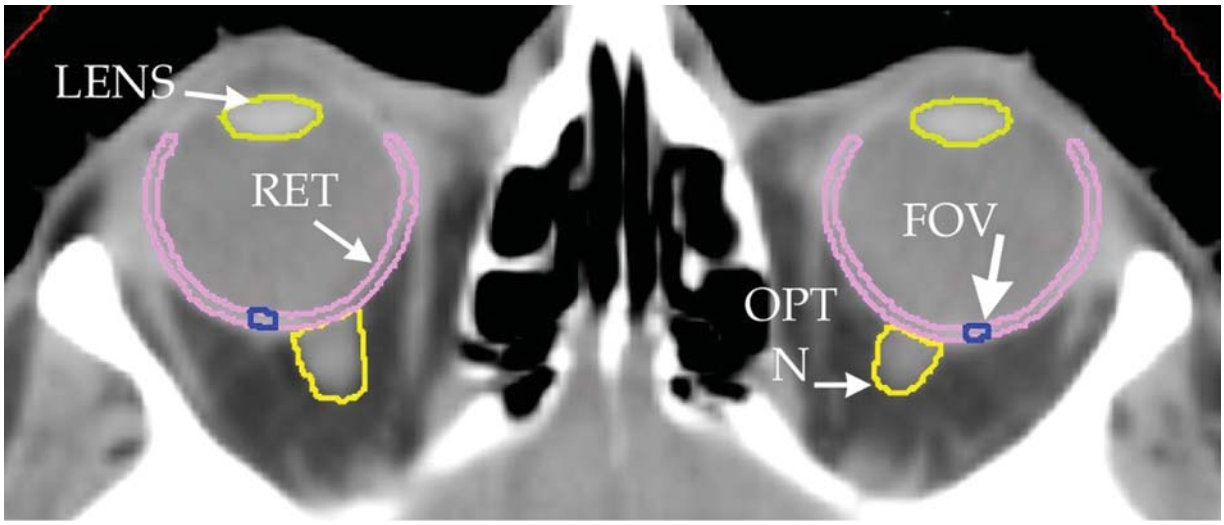

Fig. 2 Axial slice from a planning CT. The lens is shown as well as the retina (RET) and its fovea (FOV). The retina contour, more easily seen in the CT than in the MR scan, includes the retina, the choroid, and the sclera. The fovea is indicated just lateral to the optic disk, the region where the optic nerve (OPT N) exits the globe. (Figure is provided courtesy of Dr. Barbara Fullerton.)

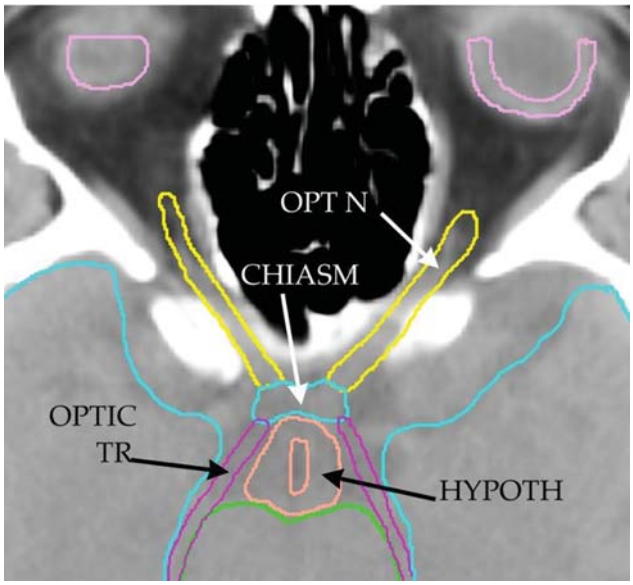

Fig. 4 This image shows the optic nerves (OPT N) extending through the optic canal medial to the anterior clinoid processes to join the chiasm. The optic tracts (OPT TR) extend posteriorly from the chiasm to the lateral geniculate nucleus of the thalamus. The hypothalamus is wider at this level than in ►**Fig. 3**. The third ventricle is located at the center of the hypothalamus. (Figure is provided courtesy of Dr. Barbara Fullerton.)

The optic tracts can be in danger of receiving a high dose of radiation, and so they are sometimes contoured as well, but the dose constraint is not well established.

Radiation-induced optic neuropathy can manifest as visual acuity loss or visual field loss depending on the area of the optic pathway affected. Again, it is critical to think about how visual loss will manifest and impact a patient's day-to-day life. Though many series report maximum dose tolerance, more recent series describe a dose/volume relationship.[15,16] If the maximum dose to the optic nerve remains below 54 to 55 Gy, radiation-induced optic injury is rare, but it is best to keep below 50 Gy if possible and as low as reasonably possible. Additional organs that may be impacted by radiation for orbital tumors include the hypothalamus, pituitary gland, temporal lobes, and hippocampi. The hormones affected are dependent on the dose delivered and area of the pituitary axis receiving RT. Radiation of the temporal lobes and hippocampi can cause a decline in neurocognitive function, particularly for young children. The impact is variable and dependent on dose and volume.

Case Examples of Orbital Tumors

Optic Glioma

Background

Optic pathway gliomas (OPG), also known as optic pathway juvenile pilocytic astrocytoma, as this is nearly always the pathology of these tumors when they are biopsied, represent 5% of pediatric CNS tumors and account for approximately 1 to 2% of all orbital tumors.[17–19] These low-grade tumors are subdivided into optic nerve gliomas (ONGs), chiasmatic gliomas, and hypothalamic gliomas.[20] Often these tumors involve more than one of these locations and it is impossible to know the true location of origin (i.e., chiasm or hypothalamus). OPG has its clinical onset during the first decade of life and it has a strong association with the tumor predisposition syndrome neurofibromatosis type 1 (NF1).[21] In contrast to sporadic OPG, which has a more aggressive behavior, NF1-associated OPG has an earlier onset and a less severe clinical course and even spontaneous regression.

ONG is an important diagnostic consideration in any young child presenting with sudden vision loss. Proptosis is often discrete but may be severe and associated with incomplete occlusion of the eyelid, and complications such as corneal ulceration (►**Fig. 5**). Some ONGs are asymptomatic and can be incidental findings on routine orbital MRI screening in NF1 patients. In the early stages, fundus examination may reveal a swollen optic disc. Patients with chiasmal tumor usually present with decreased visual acuity and temporal field defects, while the clinical course of hypothalamic tumors includes nystagmus, visual field deficits, impaired visual acuity, and increased intracranial pressure.[22,23]

Management

The management of OPGs is a subject of controversy. Biopsy is rarely necessary today, as brain and orbit MRI are the gold standard neuroimaging examination to confirm the diagnosis of OPG. Given that these tumors may have a benign course in children and therapeutic interventions are of greater consequence in younger patients, children who are asymptomatic or with NF1 are generally managed with observation and close follow-up, whereas adults are managed more aggressively. Asymptomatic lesions are usually left untreated and followed with serial examinations evaluating for the visual acuity, pupillary reaction, visual fields, and color vision of both eyes. Unilateral ONGs in patients with absent or impaired vision with no chiasmatic involvement are also considered ideal for maximal safe resection as curative treatment.

Systemic cytotoxic regimens including vincristine/carboplatin (VC) combination chemotherapy[24]; thioguanine, procarbazine, lomustine, and vincristine[25]; and single-agent vinblastine[26,27] have been the mainstay of treatment in children with progressive NF1-OPG without threatened vision, leading to an excellent overall survival, and satisfactory long-

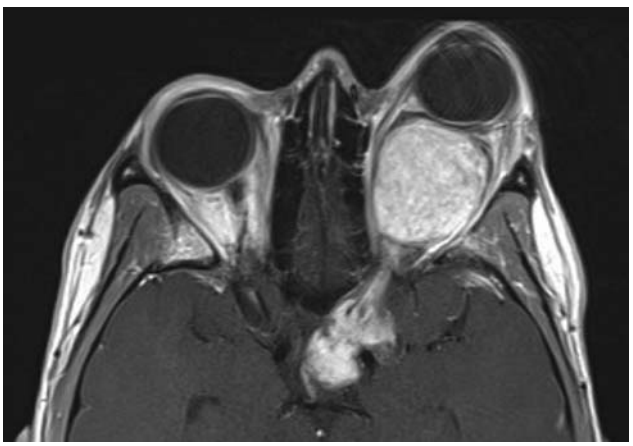

Fig. 5 MRI image of a progressive optic pathway glioma causing significant proptosis in a 19-year-old patient.

term tumor control. Treatment duration may vary between 12 and 18 months, according to two largest prospective trials in the United States and Europe, but with similar results in terms of 5-year progression-free survival (PFS) of 69 and 71%, respectively. For children without NF1, chemotherapy is often used, but progression and the need for an additional therapy such as radiation are more likely. Targeted agents are actively being researched for OPG and include MEK inhibitors, such as trametinib and selumetinib,[28,29] and V600E BRAF inhibitors such as vemurafenib and dabrafenib.[30,31]

The role of radiation for low-grade gliomas has been much disputed due to the high control rates and long potential timeline for the development of late toxicities. The use of effective systemic treatment means that radiotherapy can be delayed or reserved for chemotherapy failures. Many children, who are not good candidates for surgery, will ultimately require radiation to achieve local control of the tumor (►**Fig. 6**). Radiation doses range from 45 to 54 Gy, in 1.8 Gy per fraction, with lower doses being preferred for younger patients.[32,33] It should also be noted that OPGs represent a special case of low-grade glioma and often require conformal treatment due to threatened vision. The response rate of OPGs with visual symptoms is remarkable, with greater than 75% having either stabilization or improvement in vision with radiotherapy.[34] Long-term survival rates have been reported to be as high as 80 to 100%.[23,33,35] Radiation provides a definitive treatment for local control but carries risks of neuroendocrine dysfunction, neurocognitive effects, and second malignancy. Given the long-term survival rates, avoidance of toxicity is critical. However, it is also important that these tumors are treated early enough to avoid additional visual loss and other impairments that may occur due to tumor progression.[36] Though systemic agents are effective, they rarely offer durable control of tumor for patients without NF1.

In conclusion, radiotherapy is potentially curative in 80 to 90% of OPGs. However, given the risk of late toxicities, radiation is often used in older children and adults or after progression following multiple chemotherapy or targeted therapy schemes or when vision is threatened for younger children.

Ocular Melanoma

Background

Ocular melanoma is the most common primary intraocular malignancy of adulthood, with 1,500 to 2,000 cases per year in the United States.[17,18,37–39] It arises from melanocytes located in conjunctival membrane and uveal tract of the eye.[40] Ocular melanomas comprise 3 to 5% of all melanomas, of which 85% are uveal, 5% are conjunctival, and 10% are other. Incidence of ocular melanomas is increasing with age, with a peak in seventh and eighth decades of life. Males have been affected more than females, while rates are 8 to 10 times higher among Caucasians compared with black people.[38] Several risk factors have been identified, including the fair skin and the presence of light eyes, dysplastic nevus syndrome, and mutations in the tumor-suppressor gene *BAP1*.[41–43] The role of sun exposure as a risk factor for ocular melanomas is not well defined.

The most common initial symptom of uveal melanoma is blurred vision followed by visual field deficit, photopsia, eye irritation and pain, pressure, and metamorphosia[44]; however, up to 30% of the patients may remain asymptomatic for a long period and sometimes the diagnosis is made incidentally on a retinal exam. Tumor enlargement can cause secondary retinal detachment with consequent visual loss. The diagnosis of ocular melanoma can be primarily established by ophthalmic examination alone.[45] Despite that, specialized ocular imagings, including ultrasonography, fluorescein angiography, and optical

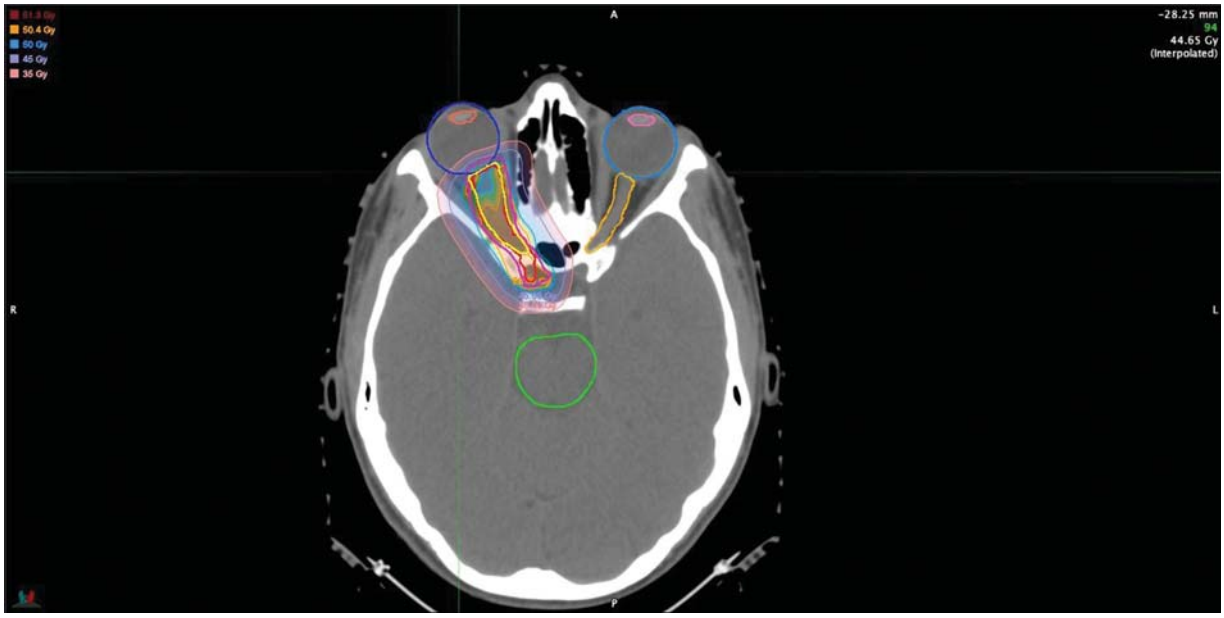

Fig. 6 Pencil beam scanning for optic glioma. A 13-year-old female patient with right optic pathway glioma treated with proton radiation therapy to a total dose of 50.4 Gy (RBE)/28 fractions. The prechiasmatic location of the tumor and its small size made it anatomically very amenable to proton radiation therapy with excellent sparing of nearby normal tissue.

coherence tomography, are often performed for further characterization. Moreover, fine-needle aspiration biopsy is gaining ground in diagnostic process due to advancements in the use of cytogenetics and molecular profile for prognostication.[46]

Management

Generally, the management of ocular melanomas can be divided into eye-sparing therapy and exenteration. Globe-preserving therapy can be further classified into radiation, laser, and resection. According to the Collaborative Ocular Melanoma Studies (COMS), the majority of primary ocular melanomas are treated with plaque radiotherapy.

Small uveal melanomas with a height of less than 3 mm and a diameter of less than 16 mm can often be differentiated from choroidal nevi only through serial observation. Within 5 years, only 30% exhibit progression.[47] There is no apparent loss of survival or decrease in vision with close follow-up of small lesions. Medium-sized melanomas with a height of less than 8 mm and a diameter of less than 16 mm can be treated with I-125 brachytherapy (minimum tumor dose of 85 Gy) and proton radiotherapy (►**Figs. 7–10**) with eye preservation or enucleation, Interestingly, no difference in mortality has been observed between patients with medium-sized melanomas treated with brachytherapy versus enucleation.[48] Furthermore, high-dose radiation therapy for uveal melanomas has shown comparable survival outcomes to those of surgery. In fact, proton therapy has become the gold standard of care for this type of tumor, whereas stereotactic radiosurgery and fractionated stereotactic radiation therapy are considered safe and effective treatment techniques as well.[10,49] Larger nonresectable masses with a height of more than 8 mm and a diameter of more than 16 mm can also be treated by radiation modalities or enucleation.[50]

Randomized trials by Gragoudas et al[51] in patients with uveal melanomas treated with proton therapy of 50 Gy (RBE) versus 70 Gy (RBE) in five fractions failed to show difference in ocular toxicity or 5-year local control. Overall, 5-year local control and 15-year local control for proton therapy were 97 and 95%, respectively.[52] Nowadays, typical proton dose prescribed for uveal melanomas is 50 Gy (RBE)—70 Gy (RBE) in five fractions depending on the size of the lesion and the proximity to the optic disk and fovea with smaller lesions close to critical optic structures receiving a lower dose and larger lesions receiving a higher dose. For most choroidal melanomas, PRT requires the placement of fiducial clips in the operating room to allow for X-ray imaging for planning and daily setup (►**Figs. 8** and **9**). Four clips are placed around the tumor if possible or in close proximity if the location of the tumor makes it impossible to surround the entire tumor with clips (i.e., if it is very posterior and

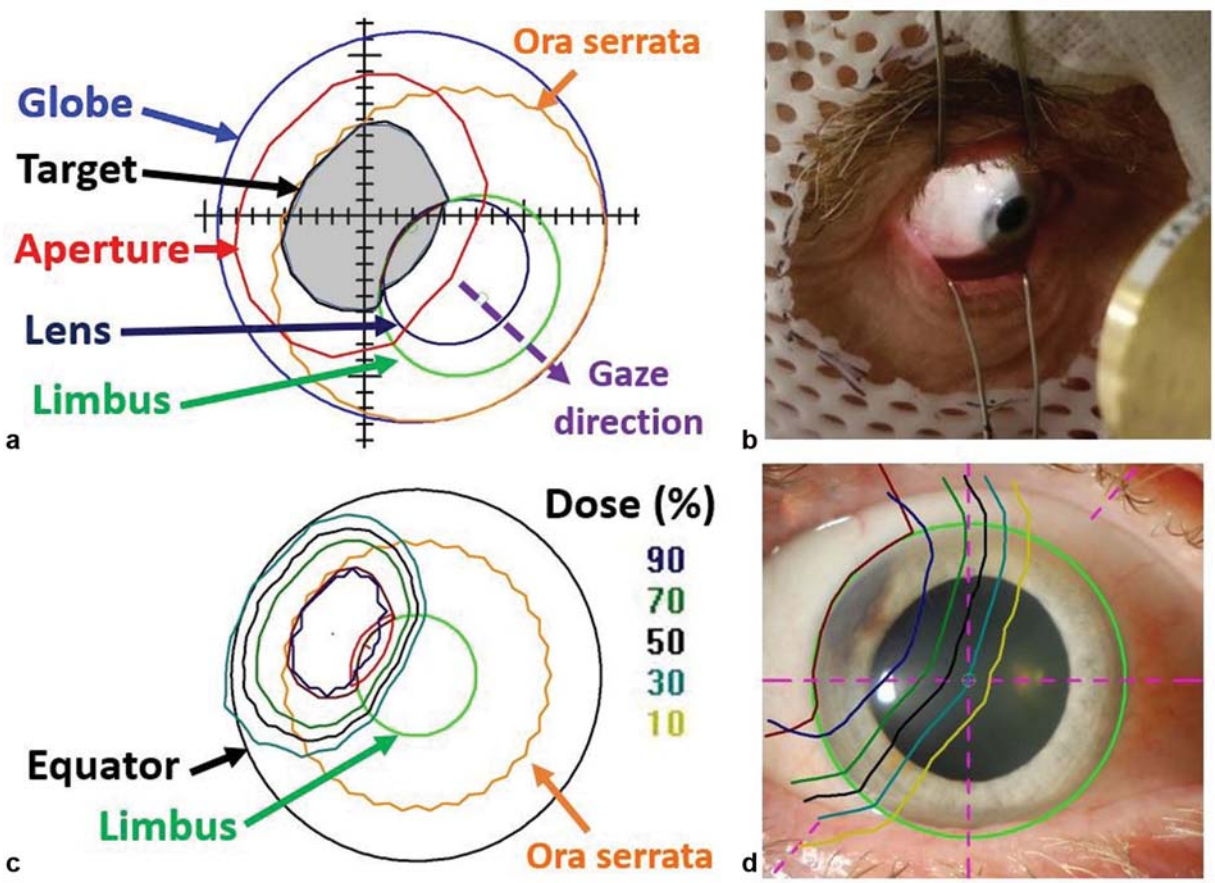

Fig. 7 Treatment of iridociliary melanoma: (**a**) the beam's eye view of the model shows the structures of the globe, projection of the target for the selected gaze direction, and the beam aperture including a 2– to 3-mm margin; (**b**) the field is set up based on the light projection through the beam aperture, without fiducial markers; (**c**) the planned dose distribution on the surface of the cornea and sclera, in polar view; and (**d**) the surface dose distribution overlaid on the photo of the cornea. (Figure is provided courtesy of Dr. Alexei Trofimov.)

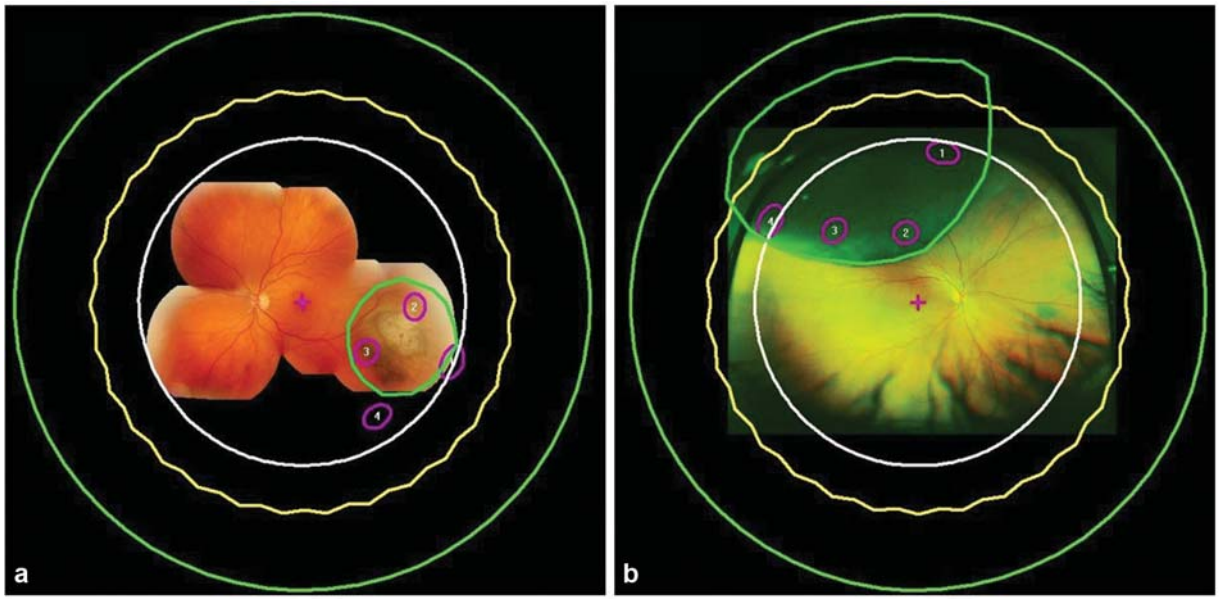

Fig. 8 The polar projection of the eye fundus overlaid with (**a**) a mosaic of narrow-angle photos, and (**b**) wide-angle photo. The target is defined based on the position of four fiducial markers, with the aid of fundus photos. (Figure is provided courtesy of Dr. Alexei Trofimov.)

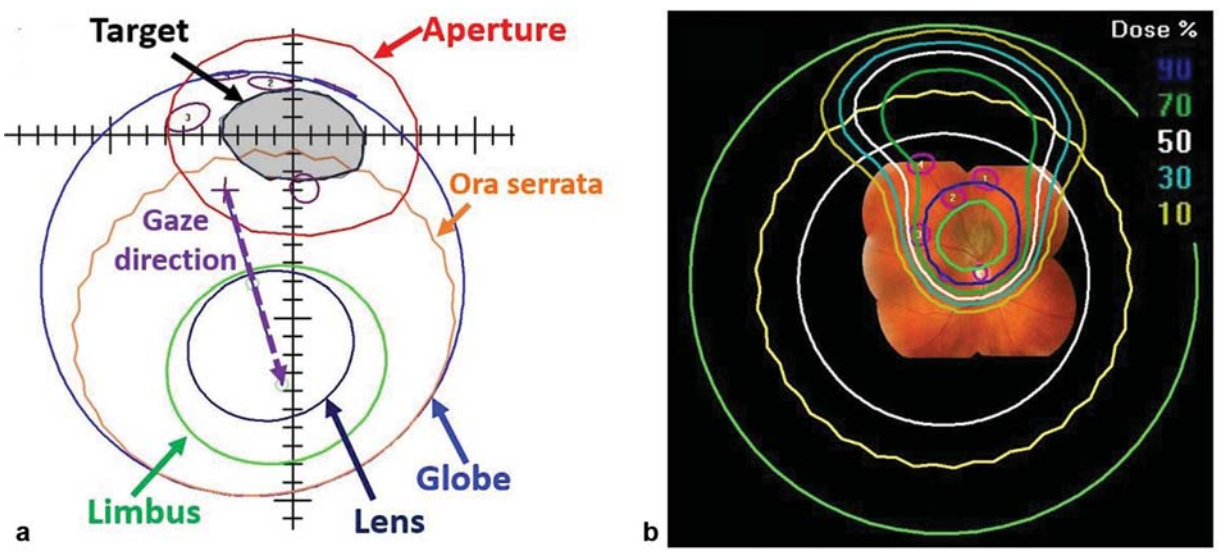

Fig. 9 Treatment of choroidal melanoma: (**a**) the beam's eye view of the model shows the structures of the globe, projection of the target for the selected gaze direction, the beam aperture including a 3-mm margin, and location of four fiducial markers (tantalum rings); (**b**) the dose distribution is shown on the polar projection of the fundus, overlaid with the photo-mosaic. (Figure is provided courtesy of Dr. Alexei Trofimov.)

adjacent to the optic nerve). Tumors involving the iris or ciliary body may be visualized and therefore they do not require fiducial markers (►**Fig. 7**). Proton therapy for this indication is typically delivered with the patient in a sitting position with their gaze fixed on a light, but some centers do deliver proton RT for ocular melanoma in the supine position with a gantry.

Despite the excellent local control outcomes, complications following the completion of radiation treatment are quite common. Radiation retinopathy is seen in 43% of the patients treated with episcleral plaque, followed by optic atrophy, cystoid macular edema, cataracts, vitreous hemorrhage, neovascular glaucoma, central retinal vein occlusion, and secondary strabismus.[53] Proton beam radiation for ocular melanomas has been associated with increased anterior complications from entrance beam including epiphora, dry eye syndrome, lash loss, cataract, telangiectasias, maculopathy, retinopathy, and optic neuropathy. Therefore, several novel approaches, including therapeutics targeting the tissue factor and driving genetic event, are vigorously developed.

Regarding posttreatment follow-up, ocular ultrasound and fundus images every 3 to 6 months initially, then manually, are recommended. Several surveillance scans and tests, including chest X-ray, abdominal imaging, and liver function tests, should be performed annually. Unfortunately, COMS medium and large

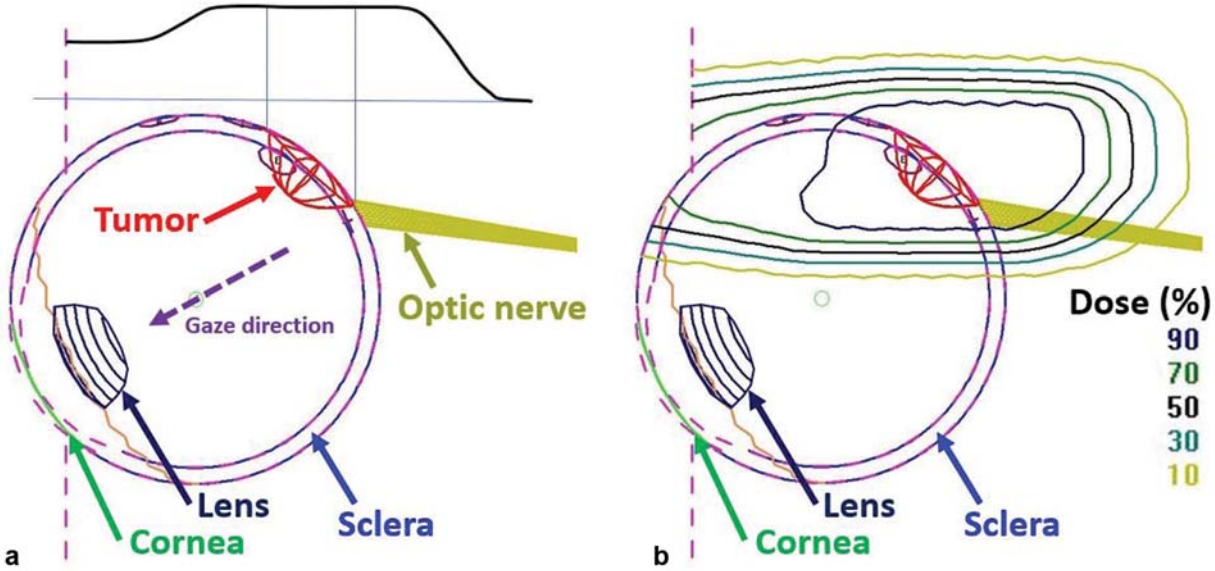

Fig. 10 A cross-section of the eye model shows the position of the target and structures of the globe for the selected gaze direction: (**a**) the required range and modulation width of the spread-out Bragg peak are determined based on the target depth and dimensions, with added anterior and posterior margins of 3–4 mm; (**b**) the corresponding sagittal dose distribution. (Figure is provided courtesy of Dr. Alexei Trofimov.)

trials have found a metastatic melanoma rate at 5 years to be 25% and at 10 years to be 34%, with most common metastatic sites including liver (90%), lung (30%), and bone (20%).[54,55]

To sum up, radiation treatment can control ocular melanomas and at the same time preserve the vision as well as the globe. Nevertheless, the radiation doses required are above the tolerance doses of the adjacent normal structures. Therefore, correspondingly adjusted techniques and radiation planning are necessary, while new agents that modify gene expression and epigenetics will hopefully lead to improved outcomes.

Orbital and Adnexal Lymphoma

Background

Orbital and adnexal lymphomas are very rare tumors which usually arise from the orbit, followed by conjunctiva, lacrimal gland, and eyelids. The most common types of orbital lymphomas primarily affect the older population.[17,18,56] Gender-wise, there is a female predominance among the most frequent types of this malignancy. Most of the orbital lymphomas involve the superior part of the orbit behind the orbital spectrum, while more than 40% show involvement of the lacrimal gland. With respect to pathology, the vast majority of these lymphomas are of B-cell origin, of which extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the most common subtype, followed by diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma.[57] Orbital lymphomas can be unilateral or bilateral with less than 20% of the cases presenting with bilateral orbital involvement.

The clinical manifestations of the disease present a wide variety with proptosis being its most common clinical sign. Other frequently reported symptoms include swelling, palpable mass, eye irritation, decreased eye motility, diplopia, and vision changes. B-symptoms (night sweats, fever, or weight loss) are common in patients with B cell lymphoma.[58] The duration of symptoms varies between weeks to several months with the high-grade lymphomas having the shortest as well as the most aggressive clinical course.

The diagnosis of an orbital lymphoma is based on imaging studies, including CT and MRI to identify the size and the location of the tumor, followed by biopsy-proven histopathological confirmation. After histological classification, a bone marrow biopsy and a full body PET/CT or MRI should be performed for complete staging workup.

Management

There are a variety of treatment options employed for achieving local and systemic control of ocular lymphoid tumors. Observation, surgery, antibiotics, steroids, radiation therapy, chemotherapy, and immunotherapy have been recommended as a treatment strategy for these neoplasms.[59–63]

External beam radiotherapy (EBRT) is the primary treatment of choice for localized, low-grade lymphomas. Target volume usually includes the entire orbit for patients with any intraorbital involvement, while for superficial small lesions confined to the conjunctiva or the eyelid, target volume includes only the tumor plus a small margin (►**Fig. 11**). Partial orbital irradiation is contraindicated due to intraorbital recurrences outside the target volume or the area of the orbit that received lower dose. Typical doses for orbital lymphomas are 25 to 35 Gy in 1.8 or 2 Gy per fraction. Five-year local control rates of more than 80% with doses under 30 Gy and 100% with higher doses have been reported in multiple single-institution studies.[64–66] Long-term follow-up of these patients is demanded though, as extraorbital metastases can be seen in even the lowest grade tumors.

The excellent local control rates are true for low-grade lymphomas, but distant metastases can often be seen in

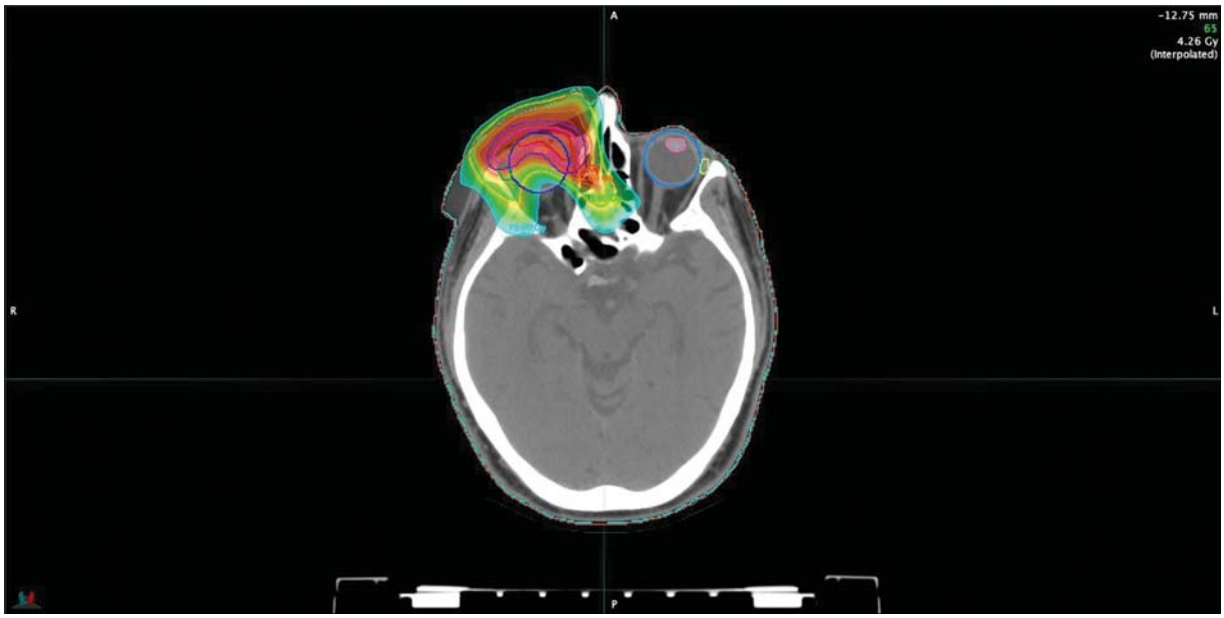

Fig. 11 Volumetric modulated arc therapy plan for right conjunctival MALT lymphoma treated with conventional radiation therapy to a total dose of 24 Gy/12 fractions.

patients with intermediate- and high-grade tumors. Therefore, treatment for advanced disease should include induction chemotherapy, followed by consolidative radiation to a total dose of 30 Gy in a hypofractionated scheme to palliate symptoms and to achieve temporary local control.

Given that radiation is useful for only the local disease and may cause side effects, newer treatments with immunotherapy such as the chimeric monoclonal antibody rituximab have recently gained popularity in the treatment of B-cell lymphomas.

Overall, lymphoid tumors of the orbit are treated with radiation therapy, chemotherapy, and immunotherapy agents. Radiotherapy plays a crucial role in the treatment of localized disease, whereas systemic treatment should be used if extraocular lymphoma is present. This may be supplemented with adjuvant radiation if ocular regression is subtotal. Continual monitoring for systemic relapse is required. Further studies on the pathogenesis of these tumors are needed to better understand their biology and to design the optimal treatment protocol for advanced disease.

Retinoblastoma

Background

Retinoblastoma is the most common intraocular malignancy in childhood, with an incidence of one new case in 15,000 to 20,000 live births.[17,18,67] There is no racial or gender predilection for the incidence of this tumor. It occurs most often in children younger than 2 years. Approximately 60% of tumors are sporadic and unilateral, while 40% are familial caused by germinal mutation in the *RB-1* gene.[68] The hereditary form of retinoblastoma has a high propensity for bilateral disease and subsequent malignancies.[69] A child with heritable retinoblastoma has an increased risk of a pineal tumor in the brain as well as other types of cancer such as lung cancer, bladder cancer, or melanoma in later years. In case of hereditary retinoblastoma, the risk of transmission is 50%, while in case of unilateral, nonfamilial retinoblastoma, the risk of transmission is 5%. Thus, genetic counseling and regular follow-up exams are important aspects in the management of retinoblastoma.

The clinical presentation of retinoblastoma depends on the stage of disease. Leukocoria is the most common presenting symptom of retinoblastoma (►**Fig. 12**), followed by strabismus, iris rubeosis, eye pain, proptosis, and loss of vision. Atypical symptoms of retinoblastoma include iris rubeosis, hypopyon, hyphema, vitreous hemorrhage, and orbital cellulitis. However, some patients may remain asymptomatic. Tumors develop in the retina and tend to grow into or along the optic nerve. Cerebrospinal fluid (CSF) dissemination and even systemic metastasis may occur in very advanced cases, which is rare in developed countries. A child with suspected retinoblastoma requires a complete ophthalmic examination under general anesthesia including a binophthalmoscopic funduscopy with a B-scan ultrasonography. MRI is considered the imaging modality of choice to assess for the local extension. CSF and bone marrow biopsy is indicated only in very advanced cases.

Survival rates for retinoblastoma patients are very high, with a cure rate of 95% in industrialized countries, due to early diagnoses and advances in local therapy.[70] Staging systems are not based on survival rates, but on eye preservation as this disease has such a high rate of cure. The International

Fig. 12 A child with leukocoria due to retinoblastoma of the left side.

Classification for Retinoblastoma groups patients as follows: *Group A*: small tumors confined to retina, < 3 mm, at least 2 DD from fovea and 1 DD from optic nerve, no vitreous seeding or retinal detachment; *Group B*: all remaining discrete tumors confined to the retina, no subretinal or vitreous seeding, no retinal detachment > 5 mm from tumor base, no subretinal fluid beyond 3 mm from tumor; *Group C*: local subretinal seeding or fine vitreous seeding < 2 DD from tumor, no retinal detachment > 5 mm from tumor base; *Group D*: diffuse disease with significant vitreous or subretinal seeding or "snowballs" or tumor masses, subretinal fluid involving up to total retinal detachment; *Group E*: tumor touching lens, tumor anterior to anterior vitreous face involving ciliary body or anterior segment, diffuse infiltrating, neovascular glaucoma, opaque media from hemorrhage, tumor necrosis with aseptic orbital cellulitis, phthisis bulbi.

Current treatment modalities aim to preserve the visual function and minimize complications, which are the main cause of morbidity and mortality.

Management

The management of retinoblastoma needs a multidisciplinary team approach including an ophthalmologist, a radiation oncologist, a medical oncologist, and a geneticist. The treatment strategy is based on the stage of disease, the laterality and the location of the tumor, and the extension of the disease.

Historically, radiation was first line, and often definitive, treatment for retinoblastoma.[71–73] Long-term eye preservation rates range from 50 to 100% in multiple large series.[71,72,74] However, with the advent of effective chemoreduction regimens as well as the fear of radiation-induced side effects, the use of RT has largely been avoided. Radiation is generally reserved for disease refractory to alternative therapies (cryotherapy, laser photocoagulation/thermotherapy, intra-arterial chemotherapy, and systemic therapy) in an eye with useful vision, while enucleation is advised if it is thought that there is no meaningful visual potential. Nonetheless, radiation is still very effective both applied as an episcleral plaque and as en EBRT and is generally used as a part of a multimodality approach for patients with residual localized disease following other focal therapy or for metastatic disease. Specifically, for unilateral, small tumors, episcleral plaque brachytherapy is an excellent means of obtaining local control. A variety of radionuclides have been used with comparable efficacy, although I-125 is the most commonly used. For bilateral and multifocal tumors, EBRT can still offer a cure with optimal visual outcome, with proton RT representing the most conformal of all available modalities.[75,76]

Radiotherapy is indicated for Group C and D tumors. Radiation also often plays a role in the treatment of more advanced tumor in conjunction with chemotherapy, sometimes based on response to chemotherapy. For very advanced tumors, radiation may be indicated following enucleation or orbital exenteration, with the most common postsurgical indication being a positive optic nerve margin following enucleation. With respect to radiation doses, most patients are treated with EBRT to a total dose of 45 Gy in 1.8 Gy per fraction. Trials have examined slightly lower doses of 36 Gy, but data are very limited for this reduced dose. For the rare patient with CSF dissemination with incomplete response to chemotherapy, craniospinal irradiation (CSI) to 23.4 Gy is recommended if less than 5 years of age or 36 Gy if greater than 5 years of age. Residual spine, cranial, and/or pineal sites will receive 36, 45, or 50.4 Gy, respectively. ►**Fig. 13** shows a proton RT plan for a

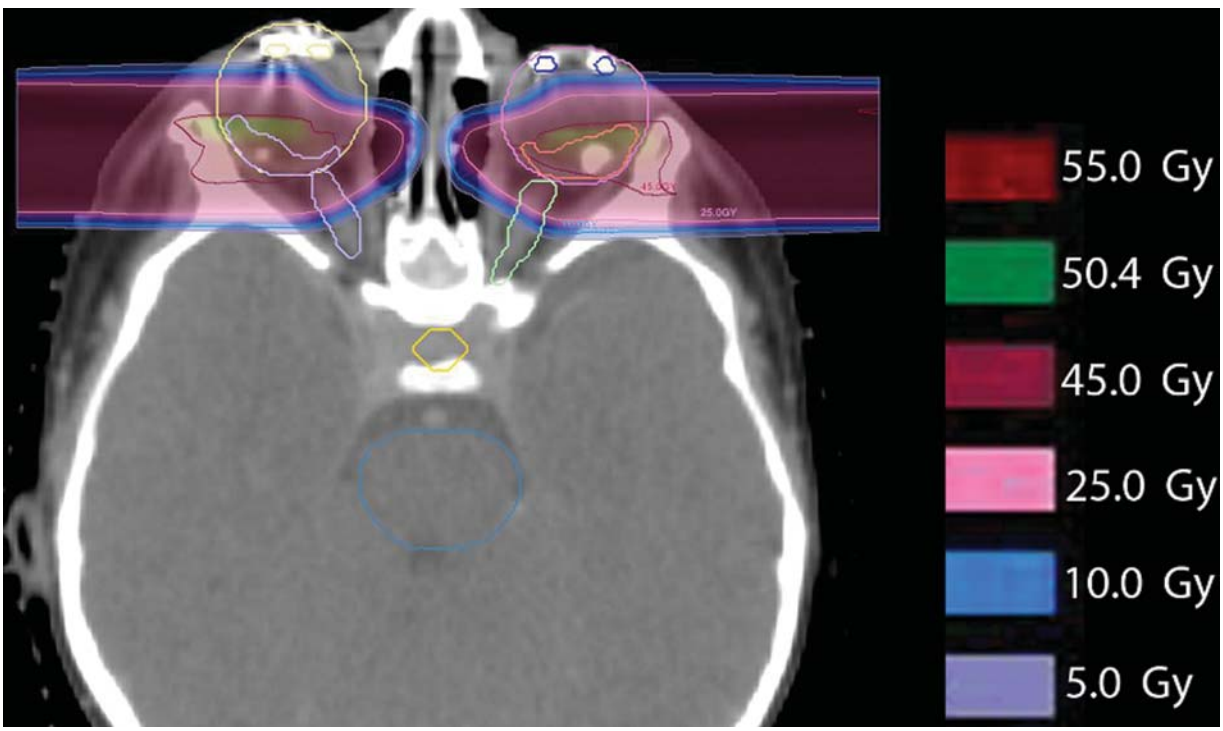

Fig. 13 Representative proton radiotherapy plan in a patient with bilateral disease. Clinical target volume is confined to the tumor in the posterior retina. Protons provide excellent sparing of tissues outside the target area.

patient with bilateral hereditary retinoblastoma treated at the Massachusetts General Hospital to 45 Gy (RBE). Protons reduce exposure of tissue at risk for a radiation-induced malignancy and avoid severe bony growth abnormalities.[72,77,78]

Despite the fact that retinoblastoma is highly sensitive to radiation and radiotherapy provides a definitive treatment for many tumors refractory to focal and systemic therapy, the late effects of radiation, especially the high incidence of secondary malignancies, continue to be the subject of controversy. However, many of the estimates of radiation-induced tumors are based on the outcomes of patients treated in a different era of radiation.[69,79,80] Recent studies on proton RT for retinoblastoma have found a low rate of secondary malignancy supporting the consideration of protons for appropriately selected patients. The risk of RT-related sarcomas is statistically elevated at doses as low as 5 Gy and increases with additional dose. Besides secondary tumors, late effects include bony hypoplasia around the orbit, retinopathy, xerophthalmia, and prosthesis contracture.[81–83]

As previously mentioned, the cure rates of retinoblastoma have dramatically improved over the past decades due to the parallel advancements in ophthalmic diagnostic methods and the development of interdisciplinary treatment strategies as well as regular follow-ups. With recent advances in RT techniques, such as proton RT and IMRT, radiation can be safely delivered with reduced dose to adjacent normal structures, minimizing the risk for severe late toxicities.

Orbital Rhabdomyosarcoma

Background

Rhabdomyosarcoma (RMS) is a rare childhood malignant tumor with an estimated 250 to 350 new cases per year.[17,18,84,85] Orbital RMSs comprise 10% of all pediatric RMS. Primary orbital RMS has been reported from birth to the seventh decade, with 90% occurring before the age of 16 years. There is a slight male-to-female predisposition.

RMS can primarily involve the orbit, eyelid, conjunctiva, and, rarely, the uveal tract. Very rarely, RMS can metastasize to the orbit from distant sites (lung, bone, liver, chest) lowering significantly the chance for cure. Overwhelming however, the majority of ophthalmic RMSs arises from the orbit and remains confined to the orbit and has a very favorable prognosis. Orbital RMSs have been observed many years after orbital irradiation for retinoblastoma.[86]

RMS is divided into four histopathological subgroups: embryonal, alveolar, pleomorphic, and botyroid.[87] The histologic features have been shown to influence long-term prognosis. Embryonal RMS is the most common subtype seen in the orbit and generally has the most favorable prognosis, while alveolar RMS is the least common variety and carries the worst prognosis.

Patients with primary orbital RMS most often present with rapid onset of unilateral proptosis and globe displacement. Furthermore, patients may report a history of worsening eyelid swelling, redness or drooping, ophthalmoplegia, or a palpable mass. Orbital pain is less common presenting symptoms ranging from 10 to 20%. A history of trauma is sometimes associated with the clinical presentation of the tumor, which may confound the diagnosis.

The differential diagnosis of orbital RMS includes orbital cellulitis, nonspecific orbital inflammation (pseudotumor), capillary hemangioma, lymphoma, and other childhood orbital tumors. Imaging studying can help with the differentiation. The tumor usually shows enhancement with contrast material. Suspected orbital RMS should be managed by a systemic evaluation to exclude metastatic disease, followed by tumor biopsy with histopathologic confirmation of the diagnosis.

Management

Guidelines regarding treatment approach for RMS depend on risk group stratification. The most commonly used staging classification system has been introduced by the Intergroup Rhabdomyosarcoma Studies (IRS).[85,88–90] There are four different groups which are based on histology, site, stage, and the presence or absence of metastatic disease, with orbit being a favorable site. The intensity of chemotherapy and the use of surgery and/or radiotherapy vary among high-, intermediate-, and low-risk groups.

Prior to the IRS studies, complete excision, often with orbital exenteration, was the primary treatment modality. With primarily surgical management, survival was generally low, with 3-year survival rates often quoted in the 30 to 40% range. Nowadays, with current standard of care consisting of vincristine and actinomycin D chemotherapy and definitive radiation therapy, the cure rates at 10 years are in excess of 85%.[91–93] Group I patients are treated with chemotherapy (vincristine + actinomycin D) without radiation. Group II patients are treated with chemotherapy (vincristine + actinomycin D) and a reduced dose of 41.4 Gy conventional fractionated irradiation. Group III patients—the most frequent group—are treated with chemotherapy (vincristine + actinomycin D + cyclophosphamide or vincristine + actinomycin D + ifosfamide or vincristine + actinomycin D + etoposide) and 50.4 Gy. In patients with low-risk RMS, which includes group III orbital RMS, reduced doses of radiation (45.0 Gy) have been used (►**Fig. 14**); however, outcomes were inferior for orbital RMS patients when dose was reduced to 45 Gy in combination with a reduced dose of cyclophosphamide. On ARST 0331, a high rate of local failure observed with 45 Gy for patients who did not achieve a complete response (CR) to chemotherapy.[94] Current children's oncology group (COG) recommendations are to give 50.4 Gy for patients with orbital RMS that do not have a complete response. Group IV patients by definition have metastatic disease and therefore are treated only with palliative regimens.

Regarding radiation therapy, care should be taken to limit the dose and volume of orbital bone treated, especially in young children at risk for facial hypoplasia, and for this reason as well as for other sensitive nearby structures, PRT is often utilized. If possible, the lens and corneal surface should be blocked to protect the anterior segment and dose to the lacrimal gland should be minimized. If going to doses higher than 45 Gy, the retina receiving $>$ 45 Gy should be minimized.

To conclude, the modern therapeutic regimens for orbital RMS offer a 90% survival rate. Although the goal of combined

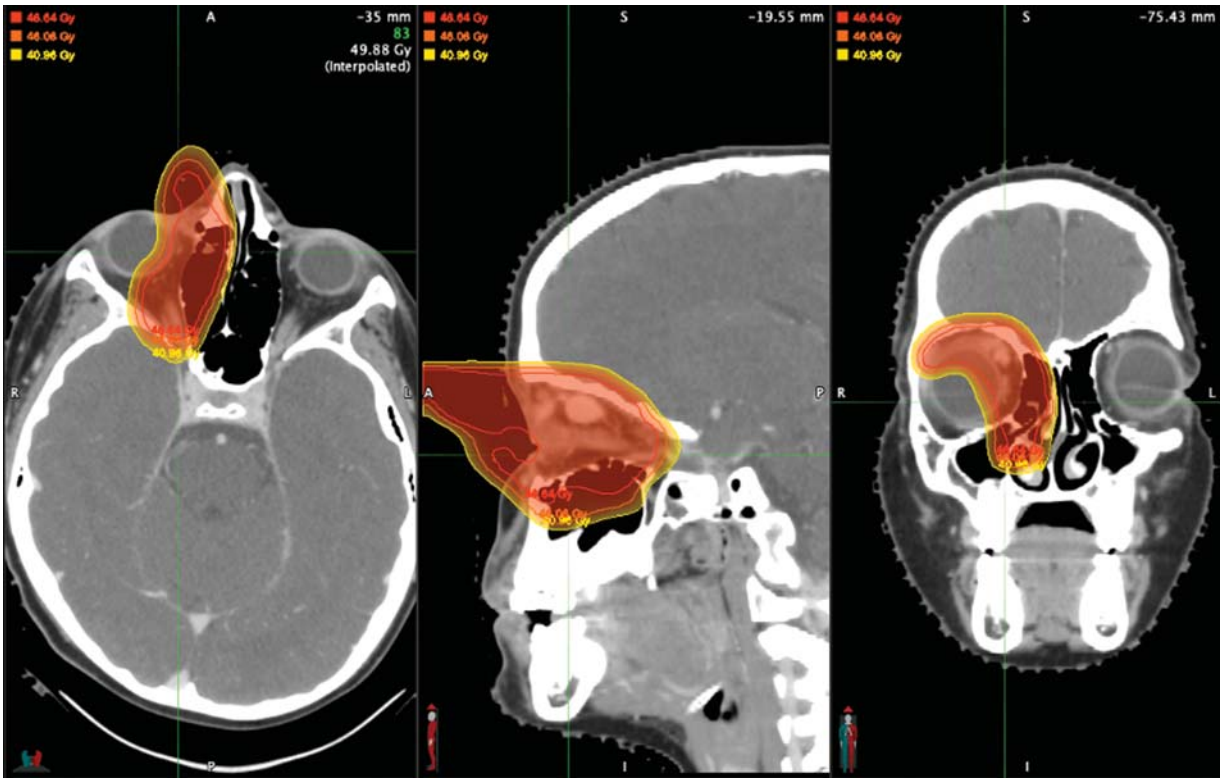

Fig. 14 Passive-scattering proton therapy for orbital rhabdomyosarcoma. A 9-year-old female with embryonal RMS of right orbit, group III, stage I, s/p resection biopsy of the mass and VAC chemotherapy per protocol ARST0331 followed by adjuvant proton radiation to a total dose of 45 Gy (RBE)/27 fractions with cone down to 48.8 Gy (RBE) to gross residual disease.

modality therapy for orbital RMS is both to cure and preserve organ function, the latter is often compromised.[95,96] Radiation treatment is typically associated with late ocular toxicities such as cataract, orbital hypoplasia, enophthalmos, and chronic keratitis. Many patients suffer from decreased vision in the treated eye, and rarely orbital exenteration may be required for a complication of treatment.

Lacrimal Gland Tumors

Background

Lacrimal gland tumors constitute less than 15% of all orbital tumors. Lesions of the lacrimal gland can be divided into epithelial and nonepithelial lesions.[37,97,98] Nonepithelial tumors include dacryoadenitis, lymphoid tumors, and other mesenchymal masses such as dermoid cysts and cavernous hemangiomas. Among the epithelial neoplasms of the lacrimal gland, pleomorphic adenoma is the most frequent, followed by malignant neoplasms such as adenoid cystic carcinoma (ACC), pleomorphic adenocarcinoma, and other rare entities.[99] Pleomorphic adenomas are addressed with surgery alone, but ACCs and other mixed malignancies are treated with surgical resection followed by chemotherapy and external beam radiation therapy.[100,101] The estimated rate of mortality at 5-year follow-up is 50% regardless of the form of the treatment. ACC, which is the focus of this article, is the second most common malignant epithelial neoplasm of the lacrimal gland, accounting for approximately 60% of the cases.

Lacrimal gland tumors can present in any age and affect equally both men and women. Epithelial neoplasms are mostly seen in middle-age patients. Particularly, ACC follows a bimodal age distribution with the first peak occurring at 10 to 20 years of age and the second peak in the fourth decade of life. Lymphomas and adenocarcinomas of the lacrimal gland typically present in older patients. The classic presentation of all lacrimal gland tumors includes facial asymmetry due to displacement of the eyeball, diplopia, ptosis, exophthalmos, enlargement of the lacrimal gland, and limited ocular motility. Pain is a cardinal symptom for ACC and adenocarcinoma but uncommon for other types of lacrimal gland tumors with the exception of dacryoadenitis. The duration of symptoms varies between 1 and 2 years for benign tumors, whereas the malignant tumors have a more aggressive clinical course lasting for approximately 6 months.

Imaging characteristics are very useful in establishing a preoperative diagnosis of a lacrimal gland mass. Contrast-enhanced CT is necessary for evaluating a pleomorphic adenoma, whereas MRI can reveal the early peripheral nerve and extraocular muscle invasion of ACC. Although these tools are helpful for the diagnostic process, the final diagnosis can only be established after histological evaluation of a biopsy.

Regarding the histologic subtype of ACC, it has been suggested that pathology is an important prognostic factor for survival. Particularly, the basaloid (solid) type has the most aggressive behavior and is associated with poorer prognosis, in contrast to the cribriform or the tubular type.[102]

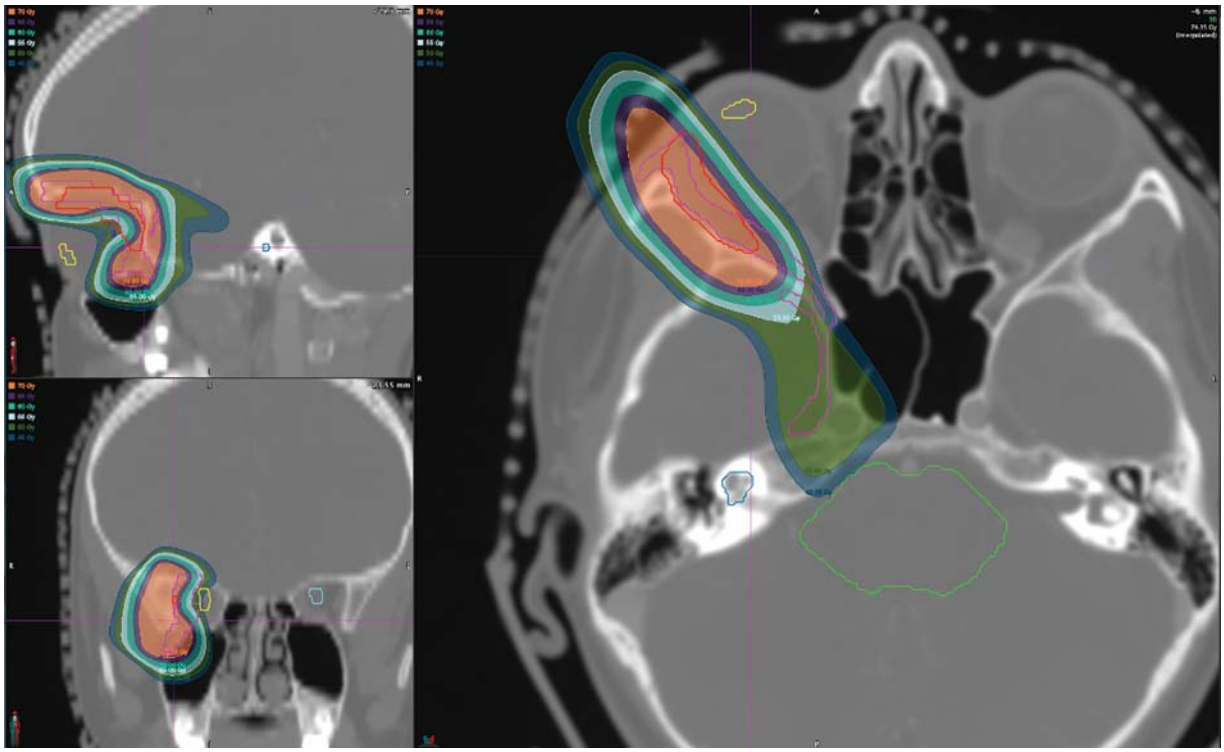

Fig. 15 Composite proton radiotherapy plan for adenoid cystic carcinoma (ACC) of lacrimal gland. A 12-year-old patient with ACC, cribriform type, of right lacrimal gland, s/p pre-op RT to a total dose of 20 Gy (RBE)/10 fractions, en block resection of the tumor followed by post-op RT to a total dose of 54 Gy (RBE)/30 fractions. The accumulative dose to the tumor bed is 74 Gy (RBE). The fifth nerve is tracked and a dose of 54 Gy (RBE) was prescribed.

Management

As mentioned earlier, the prognosis of benign tumors of the lacrimal gland is very good. If the tumor is gross totally resected, no further intervention is indicated; however, if there is tumor disruption, long-term follow-up is recommended because of the risk of recurrence and malignant transformation. On the other hand, malignant epithelial lacrimal gland tumors have a much worse biological behavior and, consequently, a dismal prognosis.

ACC's reported recurrence rates are up to 70%, with 10-year survival rates being between 20 and 30%.[103] The relatively high mortality associated with ACC of the lacrimal gland has been associated with the difficulty to obtain negative surgical margins due to its tendency for perineural invasion, with extension to the periosteum and the adjacent bone. In addition, ACC is relatively resistant to radiation and known systemic treatment agents.

The optimal treatment strategy for ACC of the lacrimal gland remains controversial. Most recent studies advocate globe-preserving surgery followed by proton beam radiation or IMRT with concurrent platinum-based chemotherapy.[104–106] Our institution has a large experience with high-dose proton therapy to a total dose of 72 to 76 Gy in standard fractionation of 2 Gy per fraction following eye-sparing surgery for ACC of lacrimal gland (►**Fig. 15**). Due to the propensity of perineural spread, the fifth nerve is tracked and included to a lower dose (54–56 Gy [RBE]). This approach avoids the morbidities of a more extensive surgery and offers good visual outcome as well as satisfying cosmetic result. Postoperative radiation has been associated with moderate toxicities including radiation retinopathy, dry-eye syndrome, cataract formation, and unilateral ptosis. Moreover, studies of brachytherapy boosts to the tumor bed along with complete irradiation of the orbit have allowed for eye preservation. Still others believe that orbital exenteration can achieve better local control, and possibly better long-term survival. Last but not least, neutron and carbon-ion radiation therapy has been used for this fatal disease.

The rare nature of these tumors eliminates the possibility of performing randomized control trials to determine the comparative merits of the different treatment approaches, and clinical practice patterns are mostly based on anecdotal experience. Undoubtedly, various therapies, such as proton therapy with PBS technique, IMRT, and intra-arterial cytoreductive chemotherapy,[107] were undertaken to minimize radiation-induced complications and improve survival outcomes. Future efforts might concentrate on targeted biological therapies to prevent distant metastases.

Summary

Radiation therapy is a valuable treatment modality that provides excellent local control with vision and eye preservation for several benign and malignant orbital tumors. Advances in both diagnostic radiology and radiation modalities and techniques in combination with a better understanding of ocular malignancies allow for better disease control and fewer side effects enabling patient survival with a good quality of life. While current treatment

recommendations are still based on a tumor's location, size, and histology, future therapies will likely be dictated by genomic analyses that define the biological behavior of a specific tumor. This information will also likely reveal molecular mutations for which targeted agents may be used as a sole therapy or in conjunction with local therapies such as radiation to allow for lower doses of radiation or better local control. New forms of radiation, such as intensity-modulated proton therapy using PBS technique and carbon ion therapy, are becoming increasingly available allowing more patients to receive highly precise and targeted treatments with little excess tissue receiving radiation. We hope that future treatments will include lower dose and even smaller target volumes combined with less toxic biological agents.

Conflict of Interest
None declared.

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