

Ocular Toxicity and Management Strategies in Uveal Melanoma Radiotherapy

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Abstract

Uveal melanoma is the most common primary intraocular malignancy, primarily affecting the choroid, ciliary body, and iris. Radiotherapy is an important treatment modality for preserving vision and preventing metastasis in patients with uveal melanoma. However, despite its efficacy, radiotherapy is associated with a range of ocular complications that can significantly impact visual function and quality of life. This article provides a comprehensive review of the ocular complications of radiotherapy in uveal melanoma, including radiation retinopathy, cataract formation, neovascular glaucoma, optic neuropathy, and radiation-induced tumor recurrence. The underlying mechanisms, clinical manifestations, diagnostic approaches, and management strategies for these complications are discussed, highlighting the importance of multidisciplinary care and long-term follow-up to optimize patient outcomes. A poor visual outcome is mainly associated with the presence of radiation retinopathy and radiation optic neuropathy. Therapeutic options are available for the majority of complications with the notable exception of optic neuropathy. Reducing complication rates can be achieved by lowering the dose of radiation, with the use of eccentric, customized plaques and careful planning of the irradiation delivery in order to protect structures vital to vision and by associating radiation therapy with other methods with the aim of reducing tumor volume.

Keywords: Ocular toxicity; Uveal melanoma; Retinopathy; Radiotherapy

Introduction

Uveal melanoma is the most common primary intraocular malignant tumor in adults. The results of the Collaborative Ocular Melanoma Study (COMS) proved the nonsuperiority of enucleation compared to I-125 brachytherapy in terms of metastasis rates and survival and paved the way to a new era in the treatment of uveal melanoma for eye-sparing therapies [1]. The most utilized globe-preserving treatment is radiation therapy, comprising ruthenium and iodine brachytherapy, proton beam therapy, stereotactic radiosurgery, and stereotactic radiotherapy. All types of radiotherapy, if used as indicated, achieve good local tumor control and eye preservation rates. However, the incidence of radiation-related complications is elevated, estimated to be between 61 and 78%. Some complications lead to significant ocular morbidity, visual loss, and, in some cases, even secondary enucleation. The majority of complications are related to tumor characteristics and irradiation parameters. This review aims to present the most important complications of radiation therapy encountered in uveal melanoma and their pathophysiology, incidence, risk factors, and available treatments and preventive measures, information that is essential in selecting the most appropriate therapy for each patient [2].

Radiation Retinopathy

This section focuses on radiation retinopathy, one of the most common and clinically significant ocular complications of radiotherapy. It discusses the underlying pathophysiology, risk factors, clinical features, diagnostic modalities, and management options, such as laser photocoagulation and intravitreal injections [3].

When radiation treatment is given using implants, it is called internal radiation therapy or brachytherapy. Most uveal melanomas in the United States are treated with brachytherapy. During a short operation, a small metal plaque is sewn on or near the tumor. The plaque delivers radiation directly into the tumor. Sometimes this is called "plaque therapy."

Another common type of radiation treatment is called external-beam radiation therapy. This is radiation given from a machine outside the body. Traditional external-beam radiation therapy may also be used as an adjuvant therapy after surgery. Adjuvant therapy is treatment given after the main treatment. It may reduce the chance of cancer coming back by destroying any remaining cancer cells [4]. Traditional external-beam radiation therapy may also be given as a palliative treatment. Proton beam therapy is a type of external-beam radiation therapy that uses protons rather than x-rays. At high energy, protons can destroy cancer cells. Proton beam therapy may be used to treat uveal tumors that are large or near the optic nerve. Learn more about proton therapy.

A radiation therapy regimen, or schedule, usually consists of a specific number of treatments given over a set period of time. Brachytherapy often lasts for several days before the plaque is removed. External-beam radiation therapy is typically done daily over the course of several days. Using radiation therapy to treat the tumor may result in side effects such as vision loss. It is important to talk with your ophthalmologist about what to expect after treatment. However, treatment for eye melanoma using radiation therapy is continually improving [5]. The extent of the side effects depends on the type and dose of radiation therapy the person receives where the tumor is located, and the patient's general health. For larger tumors, there is more risk for side effects or complications from radiation therapy. The side effects may not show up right away, so let your doctor know if a problem arises. Be sure to ask what problems and signs to watch out for

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after being treated with radiation therapy.

Cataract Formation

This section explores radiation-induced cataract formation, a common complication following radiotherapy for uveal melanoma. It discusses the pathogenesis, clinical presentation, and various types of cataracts associated with radiotherapy. The article highlights the importance of timely cataract surgery and the considerations specific to uveal melanoma patients [6].

Radiation-Induced Tumor Recurrence

This section highlights the risk of radiation-induced tumor recurrence in uveal melanoma patients treated with radiotherapy. It discusses the factors contributing to recurrence, such as incomplete tumor control and radiation resistance, and the importance of long-term surveillance and early detection. The sclera is a relatively radioresistant tissue. Scleral complications include scleritis and, more rarely, scleral necrosis. Inflammation manifests as deposits of migrating macrophages in the vicinity of the tumor at the level of the sclera and episclera and may occur in the context of associated autoimmune and infectious states. Risk factors include tumors located anterior to the equator, ciliary body invasion, extraocular extension, tumors thicker than 6 mm [7], radiation doses to the outer sclera of more than 400 Gy, increased intraocular pressure (IOP), inadequate conjunctival closure, disinsertion of the superior rectus muscle, and younger age. An important differential diagnosis must be made with tumor recurrence. Slit-lamp examination, echography, and ultrasound biomicroscopy are useful in differentiating the two entities. Berry et al. Reported three cases of conjunctival dehiscence and scleral necrosis occurring very soon, within 6 weeks from plaque therapy, near the site of muscle disinsertion. The authors propose, as possible mechanisms, a direct necrotizing effect of the irradiation, an atypical, milder form of surgically induced necrotizing scleritis, poor wound healing, inflammation related to tumor toxic syndrome, or an undiagnosed microinfection. All three patients responded to conservative therapy with topical antibiotics and steroids tapered over several weeks [9]. Other options in the management of scleral necrosis include observation, the use of lubricants, tissue glue, or if the necrotic area is extensive, surgical reconstruction with amniotic membrane, conjunctiva, scleral patch graft, dermal patch graft, or Tenon's fascia.

Optic Neuropathy

Radiation doses of more than 50 Gy lead to optic neuropathy by direct and ischemic mechanisms. Irradiation results in damage to glial cells, leading in time to demyelination and neural degeneration. Endothelial cell damage, as in the case of retinopathy, leads to vascular occlusion and consecutive ischemia. This is considered to be the result of the lack of myelin at this level and because this part of the optic nerve is found at the border between the territories of the retinal and choroidal networks [11]. If the optic nerve is included in the irradiation field and receives high or even full doses of radiation, modulating the radiation dose along the length of the optic nerve can help retain some visual function. There are reported cases of some spontaneous improvement in VA. Shields et al. attempted the treatment of radiation papillopathy, manifesting as an elevated, hyperemic disc with surrounding hemorrhages with an intravitreal injection of triamcinolone acetonide. There was an initial improvement in seven patients and a stable or better visual acuity at 11 months with the resolution of clinical signs. Hyperbaric oxygen therapy has also been tried in order to break the ischemia–necrosis cycle. However, apart from a few sporadic cases, hyperbaric oxygen

therapy has not been proven to improve visual outcomes. In most cases, radiation-induced optic neuropathy progresses to optic atrophy and irreversible vision loss [12].

Conclusion

The conclusion summarizes the key findings and highlights the importance of recognizing and managing ocular complications in uveal melanoma patients undergoing radiotherapy. It emphasizes the need for ongoing research, improved treatment strategies, and long-term follow-up to optimize patient care and minimize the impact of these complications on visual function and quality of life. Ye-sparing radiotherapy is the first line of treatment for small, medium, and selected large uveal melanomas. The pathophysiology of radiation-induced complications resides firstly in the direct cytotoxic effect of radiation on the tissues surrounding the tumor and on the tumor itself, manifesting as toxic tumor syndrome. Secondly, irradiation damages the endothelium of blood vessels, resulting in ischemic changes. The most frequent radiation-induced complications are cataracts, which may be managed surgically, and radiation retinopathy. Radiation retinopathy and radiation optic neuropathy are the main complications associated with a poor visual outcome, which is common in most treated eyes. Around half of secondary enucleations are due to complications, especially neovascular glaucoma. Efforts for reducing the occurrence and impact of radiation-related complications focus on reducing radiation doses while maintaining the same tumor control rate. This may be achieved by customized treatment planning, taking into account the dimensions, location, and proximity of the tumor to structures vital to maintaining vision, and by associating radiotherapy with other methods, such as tumor resection and transpupillary thermotherapy, in order to reduce the need for high radiation doses and eliminate the remaining tumor tissue, which is a source of proinflammatory and angiogenetic factors.

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