Editorial Commentary

Overview of late complications of radiation therapy in uveal melanoma

Andrew J. Wong[1], Amy C. Schefler[2,3], Bin S. Teh[3]

[1]Department of Radiation Oncology, The University of Texas Medical Branch, Galveston, TX, USA; [2]Retina Consultants of Houston, Houston, TX, USA; [3]Department of Radiation Oncology, Houston Methodist Hospital, Houston, TX, USA

Correspondence to: Bin S. Teh, MD, FACR, FASTRO, FACRO. Department of Radiation Oncology, Houston Methodist Hospital, Cancer Center, Institute for Academic Medicine, Research Institute, Weill Cornell Medicine, Houston, TX, USA. Email: bteh@houstonmethodist.org.

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Introduction

Traditionally, the local treatment of uveal melanoma was primarily managed with enucleation. The treatment paradigm shifted to radiotherapy after a series of Collaborative Ocular Melanoma Study (COMS) trials established eye plaque brachytherapy as a standard treatment option, demonstrating no significant difference in outcome metrics while preserving the globe and visual function. In addition to eye plaque brachytherapy, external beam radiotherapies such as fractionated and stereotactic radiosurgery with photon therapy, as well as proton-based therapies, are used in the treatment of uveal melanoma.

Radiotherapy is an essential component to treating uveal melanoma. For small tumors, radiotherapy is indicated for small tumors with significant growth after conservative management. For medium-sized tumors, eye plaque brachytherapy (standard treatment approach) and proton therapy are treatment options. For large-sized tumors, proton therapy is an option. Radiotherapy can also be utilized in the locally recurrent and palliative settings.

Although radiotherapy for uveal melanoma can achieve excellent tumor control while sparing the globe, it can also lead to several late complications that deteriorate patient quality of life. It is critical to have an understanding of the late toxicities from radiation therapy when treating uveal melanoma. Providers must be able to counsel their patients appropriately so that the patient can evaluate the long-term risks and impact to quality of life associated with radiotherapy to the eye. Also, providers from the radiation oncology team need to incorporate this knowledge during radiation treatment planning and evaluation to reduce such late toxicities.

We discuss the most common late toxicities (radiation retinopathy, cataract, maculopathy, secondary glaucoma) including pathophysiology, rates, risk factors, and management. Also briefly discussed sequela including visual acuity and secondary enucleation as a consequence of late toxicities. We also discuss emerging radiotherapy measures that can potentially decrease late radiation toxicity.

Late complications

Radiation retinopathy

Radiation retinopathy is one of the most frequent complications following radiation. It is a progressive, occlusive vasculopathy characterized by radiation-induced endothelial damage in the retinal vessels. Clinically, its appearance is characterized by cotton wool spots, hard exudates, teleangiectases, microaneurysms, neovascularization, vitreous hemorrhage, and macular edema. In addition to nonproliferative radiation retinopathy, retinal neovascularization can develop following treatment leading to proliferative radiation retinopathy. If untreated, radiation retinopathy can lead to profound and often irreversible vision loss. The rate of radiation retinopathy following eye plaque brachytherapy is 43% at 5 years (1). An increased incidence and earlier onset of radiation retinopathy may be observed following

external radiotherapy. Risk factors for radiation retinopathy include young age, comorbid diabetes or hypertension (in proliferative variant), proximity of tumor margin or higher dose to optic disc or foveola, tumor limited to choroid/posterior tumor location, and high radiation dose to tumor base (1-3). Radiation retinopathy may be managed with observation, corticosteroids, photocoagulation, photodynamic therapy, vitrectomy, and intravitreal injections of anti-vascular endothelial growth factor, although currently there are no optimal treatments (2,4-6).

Cataracts

Secondary cataracts from irradiation is one of the more common late toxicities. The lens is particularly susceptible to radiation-induced injury, with cataractogenesis noted to occur at doses as low as 4 Gy when fractionated, or 2 Gy as a single dose (7). Ionizing radiation deforms lens fibers, leading to debris accumulation in the sub-capsular region which compromises the formerly optically-clear lens cells (6). A COMS trial described the rate of radiation-induced cataracts as 83% at 5 years following treatment with Iodine-125 (I-125) brachytherapy (8). The timeline at which cataracts form is highly variable, dependent on numerous patient, tumor, and treatment related factors. Important risk factors for cataract formation post-radiotherapy include patient age, tumor location, tumor dimension, and radiation dose to lens. Given the relative anterior location of the lens within the globe, cataractogenesis risk is greater for anterior tumors. Larger tumor height is also associated with increased cataract risk. Notably, dose to lens has been cited as the most significant risk factor to cataractogenesis, with cumulative radiation dose directly related to increased incidence of cataracts (8). Radiation-induced cataracts can be treated as standard with cataract surgery, which can confer improvement or stability in visual acuity in a majority of patients (8). It is recommended waiting for least 6–12 months post-brachytherapy before considering cataract surgery.

Maculopathy and optic neuropathy

Radiation maculopathy is a subset of radiation retinopathy specific to the macula. Optic neuropathy develops in cases where the optic nerve is affected. Tumor location, tumor thickness, tumor volume, and radiation dose and distance to the fovea have been identified as important risk factors for radiation maculopathy (9,10). Optic neuropathy is most likely to develop if the dose received by optic nerve exceeds 50 Gy (6). Rates of radiation maculopathy and optic neuropathy vary in the literature and are largely impacted by the aforementioned factors. Untreated radiation maculopathy and optic neuropathy often result in poor visual acuity. Anti–vascular endothelial growth factor (anti-VEGF) agents and intravitreal dexamethasone implants have been cited as effective therapies for radiation maculopathy (11,12). The optimal treatment for optic neuropathy has yet to be defined, but encouraging results have been reported with anti-angiogenic agents (6,13).

Secondary glaucoma

Secondary glaucoma can develop following radiotherapy to uveal melanoma in 2–19% of cases (14,15). The pathophysiology involves radiation-induced tumor necrosis leading to inflammatory stimuli, retinal ischemia, angiogenic factor release, increased intraocular pressure, as well as persistent exudative retinal detachment (6,14). Tumor size, iris location and ciliary body involvement are cited as risk factors for secondary glaucoma (15-17). Treatment options include anti-angiogenic agents such as intra-cameral bevacizumab, intraocular steroids, transpupillary thermotherapy, photodynamic therapy, endoresection, or transscleral local resection (6,18).

Neovascular glaucoma can result from radiation damage to the iris and resultant ischemia-induced proliferation of vessels. It is more commonly seen with treatment of anterior segment tumors and tumors with larger thickness. Although many other ocular complications following radiotherapy primarily affect vision, neovascular glaucoma may lead to a painful and blind eye requiring enucleation.

Other late complications

Other less common late complications from radiotherapy include dry eye, strabismus, and scleral necrosis. Dry eye and keratitis are managed symptomatically with topical lubricants. Strabismus can develop as an extraocular muscle alteration following radiotherapy may require surgical correction for persistent symptoms that severely impact quality of life. Scleral necrosis is a very rare complication that may necessitate surgical patching for progressive cases.

Sequalae as a consequence of late complications

Visual acuity following radiotherapy to uveal melanoma

The main toxicities associated with decreased visual acuity are retinopathy, maculopathy, cataract, neovascular glaucoma, and nerve atrophy. Risk factors for loss of visual acuity following plaque brachytherapy include initial visual acuity, apical height, plaque size, juxtapapillary localization, distance/dose to macula, disc and nerve, subretinal fluid, tumor associated retinal detachment (19,20). Visual acuity is most effectively preserved in eyes with small tumors outside a radius of 5 mm from the optic disc and foveola (20). The COMS No. 16 study reported that 43% to 49% of patients treated with brachytherapy experienced substantial vision loss (defined as loss of ≥6 lines of visual acuity or visual acuity 20/200 or worse) within 3 years of treatment (21). Anti-VEGF agents have been studied and cited to improve vision outcomes, but how to optimally use these agents to prevent vision loss is still under investigation. A study has suggested that early and repetitive treatments are key contributors towards optimal long-term visual outcomes (22).

Secondary enucleation

Per the COMS No. 19 trial, the actuarial estimate for enucleation rate after I-125 plaque brachytherapy was 12.5%. Treatment failure was the most common cause of secondary enucleation within 3 years of treatment, and ocular pain (commonly associated with uncontrolled neovascular glaucoma) was the most common reason beyond 3 years post-treatment. Risk factors for secondary enucleation were greater tumor thickness, closer proximity of the posterior tumor border to the foveal avascular zone, and poorer baseline visual acuity in the affected eye (23).

Radiotherapy approaches to mitigate late radiation toxicity

When planning the radiotherapy approach, there are several potential avenues that may mitigate late radiation toxicity that have been proposed, including dose de-escalation and staged/fractionated radiotherapy.

Dose de-escalation may lead to better visual outcomes without compromising tumor control, especially with smaller tumors. 85 Gy has been the standard dose prescription for I-125 plaque brachytherapy as it was the minimum dose prescribed in COMS report No. 19, which had compared I-125 plaque brachytherapy with enucleation for patients with medium-sized tumors. Perez *et al.* reported their analysis of dose on disease control and visual outcomes with I-125 plaques and suggested a dose to tumor apex <85 Gy especially for tumors <5 mm in height (21). Kheir *et al.* reported on their single institution experience of treating patients with I-125 brachytherapy with 63 Gy to the target volume which included tumor with 2mm circumferential margin and the apex height of the tumor. Their preliminary results suggest effective disease control and favorable visual acuity outcomes (24).

Staged/fractionated radiotherapy in select settings may also help reduce late toxicity. Chevli *et al.* reported on a novel staged eye plaque brachytherapy approach in which patients underwent 2 separate iodone-125 plaque insertions three months apart with a cumulative prescription dose to 90 Gy. The approach was developed for patients with large uveal melanoma lesions which would have otherwise required enucleation due to toxicity from a single eye plaque insertion. At 1–2 years post-treatment, they report the patients to have continued tumor shrinkage with good visual acuity and minimal radiation toxicity (25).

Although several of the studies are single institution, with small number of patients, and/or retrospective in nature, they encourage further investigation with larger, prospective studies towards these approaches as potential avenues to reduce late toxicity.

Conclusions

Common late complications following radiotherapy to uveal melanoma include radiation retinopathy, cataract, maculopathy and secondary glaucoma. Compromised visual acuity and secondary enucleation are possible sequalae from radiation-related toxicities. An understanding of common complications should factor into deciding the appropriate radiotherapy modality and in customizing the treatment plan to minimize toxicities.

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