Complications and adverse events of plaque brachytherapy for ocular melanoma

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Abstract

Plaque brachytherapy is a well-accepted modality to manage selected cases of ocular melanoma. Although this modality provides validated oncologic and quality of life benefits, severe complications and adverse events can occur. This article reviews complications and adverse events of plaque brachytherapy, including scleral necrosis, strabismus, cataract, glaucoma, and retinopathies as well as management of these conditions. For practicing oncologists and ophthalmologists, these complications are important to understand, identify, and treat. Additionally, an understanding of common complications of brachytherapy should influence the decision of pursuing it as a treatment option.

Key words: ocular melanoma, plaque brachytherapy, complications, adverse events.

Purpose

In 2016, an estimated 2,810 new cases of primary intraocular tumors were diagnosed, having led to 280 deaths nationwide [1]. The most common primary intraocular tumor is uveal melanoma, also known as ocular melanoma. This neoplasm can be located in various parts of the uvea, including the choroid (90%), ciliary body (7%), and iris (2%) [2]. The metastatic potential and overall prognosis of uveal melanoma can be predicted by tumor size [2], histology, and genetics [3,4]. Regarding treatment, the Collaborative Ocular Melanoma Study (COMS) trials conducted in the 1980s-1990s have helped pave the way for treatment paradigms that focus on preserving vision, instead of eye removal. Treatment for ocular melanoma is largely dictated by tumor size. Traditionally, the majority of small ocular melanomas (1.5-2.4 mm height and 5-16 mm diameter) are observed [5], medium ocular melanomas (2.5-10 mm apical height and < 16 mm diameter) are treated with plaque brachytherapy [6], and large ocular melanomas (> 10 mm apical height 16 mm diameter) can selectively be treated with brachytherapy or removal of the eye [7]. In 2014, the guidelines by the American Brachytherapy Society changed to reflect the AJCC system, with AJCC T1, T2, T3, and T4a-d uveal melanoma stages applicable for treatment with plaque brachytherapy. Exceptions to brachytherapy included patients with blind painful eyes, extraocular extension, and those with limited light perception [8].

Brachytherapy is a radiation therapy modality in which a radioactive implant (most commonly 125I, 103Pd, or 106Ru) is sutured onto the eyeball. This implant delivers radiation (generally, 70-100 Gy prescribed to the tumor apex, regardless of isotope [8]) to the area of interest and attempts to minimize the risk to the surrounding ocular structures. After a defined period of time when the applicator is in contact with the target tissue, the implant is removed, and the patient is subsequently clinically monitored for a recurrence. The American Brachytherapy Society and the Interventional Radiotherapy Active Teaching School have published guidelines on the utilization of brachytherapy for ocular melanoma [8,9]. Clinical data has shown that brachytherapy has tremendous efficacy in reducing tumor recurrence risk [10,11]. Particle therapy is another (newer) radiation modality that refers to heavy particles (such as protons, helium ions, and carbon ions) directed to deliver tumoricidal radiation doses to the target [12,13,14]. Particle therapy can be used to treat any part of the eye, unlike brachytherapy, where anatomical location may limit plaque placement.

For practicing ophthalmologists and oncologists, it is crucial to know the potential ocular complications of both ocular melanoma and plaque brachytherapy. First, it can serve to better counsel patients regarding the risks and benefits of this procedure. Next, having a roadmap of the complications and their relative frequencies can guide physicians in treatment of patients that present for...
post-procedural appointments. It may also help in identifying patients that may have an unacceptably high-risk of vision complications with brachytherapy; those patients can be advised to consider an alternative form of therapy with a similar rate of survival [15].

**Radiation retinopathy**

In many ways, radiation retinopathy is similar to diabetic retinopathy in terms of the effects on the choroidal layer. Radiation retinopathy starts as a non-proliferative occlusive vasculopathy that can progress to vision loss through variable ischemic necrosis [16,17]. Non-proliferative changes to the retina are nearly universal after exposure of the retina to radiation. A study of 46 eyes after $^{125}$I brachytherapy showed occlusion of the choriocapillaris in every eye, and occlusion of small and large vessels in 96% of eyes. Choroid vascular remodeling and aneurysmal changes were seen less commonly, in 35% and 15% of eyes, respectively [18]. In some eyes, proliferative radiation retinopathy occurs when growth factor production feeds the production of weaker, incompetent blood vessels in a process known as angiogenesis. This is seen in 5.8% of eyes at 5 years and 7% of eyes at 10 years [19]. Sagoo et al. indicated a 75% chance of developing non-proliferative retinopathy and a 32% chance of proliferative retinopathy in patients who had received plaque placement for juxtapupillary choroidal melanomas [19]. In general, the factors that increase the likelihood of developing radiation retinopathy include comorbidities such as diabetes or hypertension, high radiation dose, and proximity of the tumor to the foveola [17]. Retinopathy is most commonly managed by panretinal photocoagulation (70%), vitrectomy (21%), and observation (17%) [20].

**Radiation-induced cataract**

Radiation-induced cataract is perhaps the most common complication after radiation therapy. On a molecular level, radiation accelerates cataract formation through multiple mechanisms that damage the optically-clear lens cells. Microwave and ionizing radiation deform heat labile enzymes, damage cellular DNA, and physically destroy lens cells through thermoelastic expansion [21]. The rate of cataract formation is highly variable, because it is dependent on multiple variables such as anterior tumor location, greater tumor height, increased patient age, and radiation dose to the lens [22]. A COMS trial illustrated a direct relationship between cumulative radiation dose and incidence of cataracts. At 5-year follow-up, a cumulative dose of ≥ 24 Gy was associated with a 92% cataract incidence, as compared to 88%, 86%, and 65% with doses 16-23.9 Gy, 12-15.9 Gy, and < 12 Gy, respectively [23]. Tumor size and location also greatly influence cataract risk. From the aforementioned study, the risk of cataract was 85% for anterior tumors and 17% for posterior tumors. This difference can easily be explained by the anatomic proximity of the lens to the brachytherapy plaque in anteriorly-situated disease [23]. The influence of tumor size is also intuitive, as tumor size determines the plaque size. Of note, the rate of cataract development in proton beam therapy is similar to the rate of cataract development in radiation therapy. Seibel et al. indicated that 74.3% of patients developed cataract from proton beam therapy, which did not differ from plaque radiotherapy [24]. As far as treatment is concerned, it is important to consider that 95% of patients report improvement in post-operative visual acuity after cataract surgeries, following development of a radiation-induced cataract [25]. Presently, there is no evidence to suggest that prior history of radiation meaningfully alters the safety or efficacy of cataract surgery.

**Radiation maculopathy**

Radiation maculopathy is a radiation retinopathy specific to the macula, and comprises of similar mechanisms as discussed above. Tumor location, tumor thickness, tumor volume, and radiation dose to the fovea have been identified by several studies as important risk factors for radiation maculopathy [26,27]. It is important to understand these risk factors because the extent of radiation maculopathy is directly correlated with visual acuity outcomes [28]. Studies have shown that radiation maculopathy occurs in 25% of patients at an average of 31 months after radiation [29]. Of note, in cases where the optic nerve is affected instead of the macula, radiation optic neuropathy develops. Radiation optic neuropathy is observed in 14% of $^{125}$I brachytherapy cases and 8% of $^{106}$Ru brachytherapy cases, although the particular isotope does not impact this incidence as much as tumor location. It is also more commonly seen with posterior pole tumors and tumors that have thickness of 3-8 mm [30].

Anti-VEGF intravitreal therapy is effective in treating radiation maculopathy. It leads to reduction of pathology in the macula such as retinal hemorrhages, cotton-wool spots, and retinal edema, with relatively few side effects [31]. In addition, intravitreal dexamethasone implants can decrease foveal thickness and lead to significant improvements in maculopathy [32,33]. The usage of silicone oil during brachytherapy has led to fewer abnormal maculae, lower central macular thickness, and better final visual acuity [34].

Another notable subset of radiation maculopathy is cystoid macular edema. The tumor in itself plays a large role in its development, with 54% of eyes having cystoid macular edema even before commencing brachytherapy. However, larger tumor size and the presence of prior sub-retinal fluid have a tendency to further develop cystoid macular edema after radiation [35]. A study of these eyes found increased levels of VEGF and cytokines, making intravitreal bevacizumab a natural fit for treatment. Indeed, bevacizumab injections have decreased macular edema, clinically evident radiation maculopathy, and vision loss in this population [36]. The effects can be immediate, with one study finding that 4 injections of bevacizumab decreased macular edema in 56% of eyes and improved corrected visual acuity in 42% of the treated eyes in 4-6 months [37].
Secondary glaucoma

Uveal melanoma treated by radiation can commonly lead to secondary glaucoma in 2-15% of cases. The specific mechanism has been better studied in proton beam therapy, and appears to be related to neovascular glaucoma. Tumor necrosis leads to secretion of angiogenic factors, release of inflammatory stimuli, and retinal ischemia [38]. These cause secondary neovascular glaucoma that is usually refractory to intraocular pressure-reducing agents. The tumor mass itself may limit the ability of the surgeon to perform filtration surgeries such as trabeculectomy. Intravitreal administration of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab has been an effective therapy in reducing pain, intraocular pressure, and the need for enucleation. A small investigation by Nagendra and colleagues showed that bevacizumab decreased neovascularization in 9 of 12 eyes, and reduced intraocular pressure in 8 of 12 eyes [39]. Trans-scleral cyclophotocoagulation, which consists of using optic energy to destroy the ciliary body, has been shown to be a useful treatment as well [40]. In a small study of 27 eyes, cyclophotocoagulation decreased intraocular pressure from 40 mmHg to 28 mmHg in one year, and to 23 mmHg in two years [41]. However, the prognosis continues to be very poor for these eyes, as Shields et al. found that neovascular glaucoma was the second most common reason for enucleation in these patients after tumor recurrence [41].

Vitreous hemorrhage and retinal detachment

Because 90% of uveal melanomas are located in the choroid, vitreous hemorrhage and retinal detachment can often be caused by the tumor. Poor adhesion between the retina and sclera resulting from tumor mass effect is a relatively common cause of vitreous hemorrhage and retinal detachment. Tumor necrosis is also a common cause of vitreous hemorrhage. Radiation reduces the tumor size, and thus would generally decrease the possibility of the immediate risk of vitreous hemorrhage or retinal detachment. However, radiation does impact the surrounding retina and retinal blood vessels, and can lead to ischemia and neovascularization [38]. As ischemia and neovascularization increase, the risk of vitreous hemorrhage and retinal detachment also increase. In the ocular melanoma population, the incidence of vitreous hemorrhage ranges from 4.1% at one year to 15.1% at five years to 18.6% at ten years, whereas retinal detachment occurs in 1-2% of patients following I^125 plaque brachytherapy [42,43]. Risk factors for vitreous hemorrhage include pre-existing diabetic retinopathy, shorter tumor distance to the optic disc, greater initial tumor thickness, and break in the Bruch’s membrane [44].

There are multiple treatment options for these conditions. For smaller exudative retinal detachments, intraoperative triamcinolone acetonide induces regression in 69% of cases, but it is associated with a side effect of steroid-induced cataract in 12% of cases [45]. Vitreous hemorrhage directly caused by the tumor itself can be treated with pars plana vitrectomy without an increased risk of intraocular, local, orbital, or systemic dissemination of the tumor [46,47]. Although with prompt surgical management, many patients can achieve improved visual outcomes, non-operative management is also possible [48]. Houston et al. conducted a retrospective study, which showed that 73% patients who had received the bevacizumab treatment regimen had resolution of exudative retinal detachment by 4 months [49].

Extra-ocular muscles

A study of 20 patients by Sener et al. has shown that the majority of patients develop some degree of strabismus after brachytherapy. Only 8 of the 20 had orthophoria or “straight” eyes. Nine had exotropia, one had hypertropia, and two had both [50]. One reason is the direct damage that muscle fibers undergo from plaque placement. For instance, the dissection of the conjunctiva and Tenon’s capsule required for plaque placement can disrupt extra-ocular muscles. In addition, mechanical stretching of the plaque may lead to ischemia of the underlying blood vessels and sarcomeric rearrangement of the muscle. This can lead to anatomical disruption of the extraocular muscle insertion sites that would weaken the ability to rotate the eye [50]. In addition to damage to plaque placement, the extraocular muscles also undergo damage from radiation exposure. While sometimes not macroscopically visible and harder to estimate, the COMS group determined that radiation plaques situated over extra-ocular muscles showed ultrastructural radiation-induced changes on electron microscopy.

It should be noted, however, that not all series document high incidences of strabismus; Dawson and colleagues reported just a 1.7% incidence over 8 years in 929 patients [51]. Of note, treatment with surgery, prisms, or botulinum toxin injection resulted in satisfactory outcomes thereafter.

Scleral necrosis

Because the sclera is avascular and hypocellular, scleral necrosis is an uncommon complication of radiation. The phenomenon was first described in the 1950s among patients presenting with dry eye, pain, and foreign body sensation after ocular irradiation [52]. Studies have described both necrotizing effects from radiation (direct) or local ischemic inflammation (indirect) as possible mechanisms for scleral necrosis. Radiation is the most important risk factor for scleral necrosis, with doses greater than 15 Gy demonstrating visible damage to the sclera [53]. Tumor thickness, ciliary body involvement, and high intraocular pressures have all also been implicated in increasing scleral necrosis, with tumor thickness playing a particularly important role. Kalikki et al. showed that the incidence of scleral necrosis was <1% for tumors < 3 mm thick, 1% for tumors 3-8 mm thick, and 5% for > 8 mm thick tumors [53]. Scleral necrosis presents at an average of 70 months after treatment [54]. In studies with larger cohorts, treatments such as scleral patches, conjunctival flaps, or enucleation have been utilized [55]. The most dangerous complication of scleral necrosis is scleral perforation, which occurs in 4% of cases. This is managed
similarly to an open globe injury, requiring an immediate trip to the operating room and suturing to reform the globe [53].

Conclusions

The COMS trials have paved the way for vision preserving therapies, such as plaque brachytherapy, to become standard of care in ocular melanoma patients. While very effective in treating the tumor, radiation presents several side effects to the numerous anatomical structures of the eye. The most common of these include strabismus, cataracts, glaucoma, vitreous hemorrhage, retinal detachment, radiation retinopathy, radiation maculopathy, and scleral necrosis. Although a summary and incidences thereof are presented in Table 1, it cannot be understated that complication rates heavily depend on the particular tumor location. In brief, strabismus is a common complication that results from damage to the extraocular muscles. This occurs both as a result of stretching of the extraocular muscles for plaque placement as well as damage to these fibers from radiation. Cataracts happen as radiation damages the free-radical scavenger mechanisms that keep the lens clear. These can be removed by standard cataract surgery. The release of inflammatory mediators, angiogenesis, and retinal ischemia can lead to a neovascular glaucoma that is refractory to therapy. Vitreous hemorrhage and retinal detachment can either occur from mass effect by the tumor or secondary to proliferative radiation retinopathy; vitrectomy is usually required. Radiation retinopathy and maculopathy occur through similar mechanisms as diabetic retinopathy, and usually respond well to intravitreal bevacizumab. Scleral necrosis is a rarer complication that is caused by inflammation and subsequent damage to scleral tissue. In addition to ophthalmologists, oncologists should also aggressively examine patients for these conditions following brachytherapy, as timely identification and treatment can lead to better ocular outcomes.

Disclosure

Authors report no conflict of interest.

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