Educational Article

Original paper

Complications and adverse events of plaque brachytherapy for ocular melanoma

Krishi V. Peddada, MD[1], Roshun Sangani, BS[1], Hari Menon, BS[2], Vivek Verma, MD[3]

[1]Department of Ophthalmology, Drexel University College of Medicine, Philadelphia, PA, United States, [2]University of Arizona College of Medicine – Phoenix, Phoenix, AZ, United States, [3]Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA, United States

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.

J Contemp Brachytherapy 2019; 11, 4: 392–397
DOI: https://doi.org/10.5114/jcb.2019.87407

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 ^{125}I, ^{103}Pd, or ^{106}Ru) 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

Address for correspondence: Vivek Verma, MD, Department of Radiation Oncology, Allegheny General Hospital, 320 E. North Ave., Pittsburgh, PA 15212, United States, phone: +1 412 359 3400, fax: +1 412 359 3171, ✉ e-mail: vivek333@gmail.com

Received: 30.01.2019
Accepted: 19.06.2019
Published: 29.08.2019

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 choroid 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 Nagendran 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 ^{125}I 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. Kaliki *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

Table 1. Summary table

Ophthalmologic complications from plaque radiotherapy
• Plaque brachytherapy has become the mainstay of treatment for choroidal melanoma after the Collaborative Ocular Melanoma Study (COMS) publications. An understanding of the common complications of therapy and treatments is required for those providers that treat these patients.
• Radiation retinopathy is most commonly associated with high radiation dose, proximity of tumor to the macula, and comorbidities such as diabetes or hypertension. The risk of this varies greatly by location, from 5-6% in tumors with less proximity to near 100% in tumors located on the macula. The most common treatments are panretinal photocoagulation, vitrectomy, and observation.
• Radiation damages the enzymes that protect the lens, leading to cataract formation. This occurs in 65-90% in anterior tumors and 15-20% for posterior tumors. Patients respond well to standard cataract surgery.
• Neovascular glaucoma (2-15% in most series) can potentially result from melanoma-induced angiogenic factors along with retinal ischemia from irradiation. These cases are difficult to manage and refractory to most therapy.
• Vitreous hemorrhage (5-year risk ~15%) and retinal detachment (1-2%) are generally secondary to the tumor itself, but may also occur due to proliferative radiation retinopathy. Vitrectomy is required for treatment.
• Radiation plaque placement can disrupt extraocular muscle insertion sites and the blood supply to the extraocular muscles (< 5% incidence in modern series). The radiation itself can also damage the muscle fibers at an ultrastructural level, leading to strabismus. Patient may require extraocular muscle recessions and resections to straighten the eyes.
• Necrotizing effects of radiation therapy and local inflammation can lead to necrosis of the sclera, an outer coating of the eye. This occurs in 5% or less of patients.

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.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66: 7-30.
2. Shields CL, Manalac J, Das C et al. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. *Curr Opin Ophthalmol* 2014; 25: 177-185.
3. Medina CA, Biscotti CV, Singh N et al. Diagnostic cytologic features of uveal melanoma. *Ophthalmology* 2015; 122: 1580-1584.
4. Shields JA, Shields CL. Management of posterior uveal melanoma: past, present, and future: the 2014 Charles L. Schepens lecture. *Ophthalmology* 2015; 122: 414-428.
5. Collaborative Ocular Melanoma Study Group. Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol* 1997; 115: 886-893.
6. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. *Arch Ophthalmol* 2006; 124: 1684-1693.
7. Hawkins BS. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. *Am J Ophthalmol* 2004; 138: 936-951.
8. American Brachytherapy Society - Ophthalmic Oncology Task Force; Simpson ER, Gallie B, Laperrierre N et al. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy* 2014; 13: 1-14.
9. Tagliaferri L, Pagliara MM, Boldrini L et al. INTERACTS (INTErventional Radiotherapy ACtive Teaching School) guidelines for quality assurance in choroidal melanoma interventional radiotherapy (brachytherapy) procedures. *J Contemp Brachytherapy* 2017; 3: 287-295.
10. Badiyan, SN, Rao RC, Apicelli AC et al. Outcomes of iodine-125 plaque brachytherapy for uveal melanoma with intraoperative ultrasonography and supplemental transpupillary thermotherapy. *Int J Radiat Oncol Biol Phys* 2014; 88: 801-805.
11. Kowal J, Markiewicz A, Dębicka-Kumela M et al. Outcomes of I-125 brachytherapy for uveal melanomas depending on irradiation dose applied to the tumor apex – a single institution study. *J Contemp Brachytherapy* 2018; 10: 532-541.

12. Verma V, Mehta MP. Clinical outcomes of proton radiotherapy for uveal melanoma. *Clin Oncol (R Coll Radiol)* 2016; 28: e17-27.
13. Verma V, Rwigema JM, Malyapa RS et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiother Oncol* 2017; 125: 21-30.
14. Mishra KK, Quivey JM, Daftari IK. Long-term results of the UCSF-LBNL randomized trial: charged particle with helium ion versus iodine-125 plaque therapy for choroidal and ciliary body melanoma. *Int J Radiat Oncol Biol Phys* 2015; 92: 376-383.
15. Rao YJ, Sein J, Badiyan S et al. Patterns of care and survival outcomes after treatment for uveal melanoma in the post-COMS era (2004-2013): a surveillance, epidemiology, and end results analysis. *J Contemp Brachytherapy* 2017; 5: 453-465.
16. Krema H, Xu W, Payne D et al. Factors predictive of radiation retinopathy post (125)Iodine brachytherapy for uveal melanoma. *Can J Ophthalmol* 2011; 46: 158-163.
17. Gündüz K, Shields CL, Shields JA et al. Radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. *Arch Ophthalmol* 1999; 117: 609-614.
18. Pilotto E, Vujosevic S, De Belvis V et al. Long-term choroidal vascular changes after iodine brachytherapy versus transpupillary thermotherapy for choroidal melanoma. *Eur J Ophthalmol* 2009; 19: 646-653.
19. Sagoo MS, Shields CL, Emrich J et al. Plaque radiotherapy for juxtapapillary choroidal melanoma: treatment complications and visual outcomes in 650 consecutive cases. *JAMA Ophthalmol* 2014; 132: 697-702.
20. Bianciotto C, Shields CL, Pirondini C et al. Proliferative radiation retinopathy after plaque radiotherapy for uveal melanoma. *Ophthalmology* 2010; 117: 1005-1012.
21. Lipman RM, Tripathi BJ, Tripathi RC. Cataracts induced by microwave and ionizing radiation. *Surv Ophthalmol* 1988; 33: 200-210.
22. Finger PT, Chin KJ, Yu GP et al. Risk factors for cataract after palladium-103 ophthalmic plaque radiation therapy. *Int J Radiat Oncol Biol Phys* 2011; 80: 800-806.
23. Collaborative Ocular Melanoma Study Group. Incidence of cataract and outcomes after cataract surgery in the first 5 years after iodine 125 brachytherapy in the Collaborative Ocular Melanoma Study: COMS Report No. 27. *Ophthalmology* 2007; 114: 1363-1371.
24. Seibel I, Cordini D, Hager A et al. Cataract development in patients treated with proton beam therapy for uveal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2016; 254: 1625-1630.
25. Wachtlin J, Bechrakis NE, Schueler AO et al. Phacoemulsification following treatment of choroidal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2000; 238: 942-948.
26. McCannel TA. Post-brachytherapy tumor endoresection for treatment of toxic maculopathy in choroidal melanoma. *Eye* 2013; 27: 984-988.
27. Tagliaferri L, Pagliara MM, Masciocchi C et al. Nomogram for predicting radiation maculopathy in patients treated with Ruthenium-106 plaque brachytherapy for uveal melanoma. *J Contemp Brachytherapy* 2017; 9: 540-547.
28. Miguel D, Frutos-Baraja JM, López-Lara F et al. Visual outcome after posterior uveal melanoma episcleral brachytherapy including radiobiological doses. *J Contemp Brachytherapy* 2018; 10: 123-131.
29. Pagliara MM, Tagliaferri L, Azario L et al. Ruthenium brachytherapy for uveal melanomas: Factors affecting the development of radiation complications. *J Contemp Brachytherapy* 2018; 17: 432-438.
30. Mills MD, Harbour JW. Lipid exudation following plaque radiotherapy for posterior uveal melanoma. *Am J Ophthalmol* 2006; 141: 594-595.
31. Finger PT, Chin KJ, Semenova EA. Intravitreal anti-VEGF therapy for macular radiation retinopathy: a 10-year study. *Eur J Ophthalmol* 2016; 26: 60-66.
32. Caminal JM, Flores-Moreno I, Arias L et al. Intravitreal dexamethasone implant for radiation maculopathy secondary to plaque brachytherpay in chorodial melanoma. *Retina* 2015; 35: 1890-1897.
33. Bui KM, Chow CC, Mieler MF. Treatment of recalcitrant radiation maculopathy using intravitreal dexamethasone (Ozurdex) implant. *Retin Cases Brief Rep* 2014; 8: 167-170.
34. McCannel TA, McCannel CA. Iodine 125 brachytherapy with vitrectomy and silicone oil in the treatment of uveal melanoma: 1-to-1 matched case-control series. *Int J Radiat Oncol Biol Phys* 2014; 89: 347-352.
35. Mashayekhi A, Schonbach E, Shields CL et al. Early subclinical macular edema in eyes with uveal melanoma: association with future cystoid macular edema. *Ophthalmology* 2015; 122: 1023-1029.
36. Shah SU, Shields CL, Bianciotto CG et al. Intravitreal bevacizumab at 4-month intervals for prevention of macular edema after plaque radiotherapy of uveal melanoma. *Ophthalmology* 2014; 121: 269-275.
37. Mashayekhi A, Rojanaporn D, Al-Dahmash S et al. Monthly intravitreal bevacizumab for macular edema after iodine-125 plaque radiotherapy of uveal melanoma. *Eur J Ophthalmol* 2014; 24: 228-234.
38. Gragoudas ES, Seddon JM, Egan K et al. Long-term results of proton beam irradiated uveal melanomas. *Ophthalmology* 1987; 94: 349-353.
39. Nagendran ST, Finger PT. Anti-VEGF intravitreal bevacizumab for radiation-associated neovascular glaucoma. *Ophthalmic Surg Lasers Imaging Retina* 2015; 46: 201-207.
40. Piirtola A, Puska P, Kivela T. Red laser cyclophotocoagulation in the treatment of secondary glaucoma in eyes with uveal melanoma. *J Glaucoma* 2014; 23: 50-55.
41. Shields CL, Shields JA, Karlsson U et al. Reasons for enucleation after plaque radiotherapy for posterior uveal melanoma. Clinical findings. *Ophthalmology* 1989; 96: 919-923.
42. Chia SN, Smith HB, Hammer HM et al. Incidence and indications for pars plana vitrectomy following the treatment of posterior uveal melanomas in Scotland. *Eye* 2015; 29: 748-756.
43. Beykin G, Pe'er J, Hemo Y et al. Pars plana vitrectomy to repair retinal detachment following brachytherapy for uveal melanoma. *Br J Ophthalmol* 2013; 97: 1534-1537.
44. Bianciotto C, Shields CL, Pirondini C et al. Vitreous hemorrhage after plaque radiotherapy for uveal melanoma. *Retina* 2012; 32: 1156-1164.
45. Parrozzani R, Pilotto E, Dario A et al. Intravitreal triamcinolone versus intravitreal bevacizumab in the treatment of exudative retinal detachment secondary to posterior uveal melanoma. *Am J Ophthalmol* 2013; 155: 127-133.e2.
46. Lonngi M, Houston SK, Murray TG et al. Microincisional vitrectomy for retinal detachment in I-125 brachytherapy-treated patients with posterior uveal malignant melanoma. *Clin Ophthalmol* 2013; 7: 427-435.
47. Bansal AS, Bianciotto CG, Maguire JI et al. Safety of pars plana vitrectomy in eyes with plaque-irradiated posterior uveal melanoma. *Arch Ophthalmol* 2012; 130: 1285-1290.
48. Gibran SK, Kapoor KG. Management of exudative retinal detachment in choroidal melanoma. *Clin Exp Ophthalmol* 2009; 37: 654-659.
49. Houston S, Shah NV, Decatur C et al. Intravitreal bevacizumab combined with plaque brachytherapy reduces melanoma tumor volume and enhances resolution of exudative detachment. *Clin Ophthalmol 2013;* 7: 193-198.

50. Sener EC, Kiratli H, Gedik S et al. Ocular motility disturbances after episcleral plaque brachytherapy for uveal melanoma. *J AAPOS* 2004; 8: 38-45.
51. Dawson E, Sagoo MS, Mehta JS et al. Strabismus in adults with uveal melanoma following episcleral plaque brachytherapy. *J AAPOS* 2007; 11: 584-588.
52. Jones IS, Reese AB. Focal scleral necrosis; a late sequel of irradiation. *AMA Arch Ophthalmol* 1953; 49: 633-636.
53. Kaliki S, Shields CL, Rojanaporn D et al. Scleral necrosis after plaque radiotherapy of uveal melanoma: a case-control study. *Ophthalmology* 2013; 120: 1004-1011.
54. Radin PP, Lumbroso-Le Rouic L, Levy-Gabriel C et al. Scleral necrosis after radiation therapy for uveal melanomas: report of 23 cases. *Graefes Arch Clin Exp Ophthalmol* 2008; 246: 1731-1736.
55. Chaudhry IA, Liu M, Shamsi FA et al. Corneoscleral necrosis after episcleral Au-198 brachytherapy of uveal melanoma. *Retina* 2009; 29: 73-79.