Low-dose brachytherapy strategies to treat uveal melanoma: is less more?

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Practice points

- The Collaborative Ocular Melanoma Study (COMS) established radiation dose for choroidal melanoma is 85 Gray to the tumor apex or 5 mm inner sclera, whichever greater.
- While appropriate survival and local tumor control has been realized by the COMS protocol, there continue to be significant clinical challenges from radiation toxicity.
- Low-dose brachytherapy studies have demonstrated COMS-equivalent local and distant tumor control with reduced radiation complications.
- Intraoperative ultrasound may aid in correct identification of intraoperative placement of the radiation plaque.
- Adjuvant therapies such as transpupillary thermotherapy and anti-VEGF pharmacotherapy may provide additional tumor control or enhance visual outcome, but further studies are needed to better assess these adjuvant measures.

The Collaborative Ocular Melanoma Study (COMS) has established equivalency of globe salvaging brachytherapy compared with enucleation in terms of survival for medium-sized choroidal melanoma. The radiation dose protocol followed by the COMS was 85 Gray to a prescription point of the tumor apex or 5 mm inner sclera; whichever was greater. While the COMS realized appropriate local and distant tumor control rates, ocular morbidity due to radiation complications remains a significant clinical challenge. Recent studies challenge the COMS radiation dose paradigm by demonstrating similar tumor control by utilizing lower radiation doses that are associated with reduced radiation toxicity. Improved operative techniques including intraoperative ultrasound can aid to obtain adequate radiation delivery to the tumor by ensuring optimal plaque position. Adjuvant transpupillary thermotherapy, intravitreal anti-VEGF and posterior sub-Tenon steroids may further enhance outcome by providing additional tumor control and/or facilitating visual recovery.

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Choroidal melanoma is the most common intraocular malignant tumor in adults [1]. The mean age adjusted incidence of choroidal melanoma of 5.1 per 1 million has remained stable between 1973 and 2008 [1]. Historically, treatment for choroidal melanoma has been enucleation. However, to enhance patient outcome and enable globe salvage, ophthalmologists ventured for more sophisticated

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therapies. In the 1970s, reports by Zimmerman and McLean sparked a debate about whether enucleation may actually increase the chance for metastasis. They have observed that mortality rates prior to enucleation were low, but rose sharply following enucleation and hypothesized a dissemination of malignant cells to the blood stream during enucleation and/or weakening of the host's immune response as a consequence of removing the main tumor [2,3]. This and other reports have led to heightened interest in alternative therapies for choroidal melanoma. As such, episcleral plaque brachytherapy using high-energy isotope Cobalt-60 was used by Stallard in England in the 1960s with encouraging results [4]. Lower energy isotopes such as Iridium-122, Iodine-125 [5], Palladium-103 and Ruthenium-106 [6], which is a beta-emitter, have been popularized in the following years [7]. Due to its availability and easy shielding by gold, Iodine-125 is the most commonly used radioisotope in the USA today [8]. With only few studies available limited by short follow-up time, many physicians at the time were concerned about patient safety of conservative treatments. Addressing these concerns, the Collaborative Ocular Melanoma Study (COMS), a multi-center international study conducted in North America, was initiated. The three arms of the study have subsequently established the standard of modern choroidal melanoma treatment in many countries:

- Globe sparing therapy with episcleral plaque Iodine-125 brachytherapy provides equivalent survival when compared with enucleation for medium choroidal melanomas (2.5–10 mm apical height, 16 mm largest basal dimension) [9];
- Enucleation alone provides equivalent survival, compared with enucleation plus external beam irradiation, for large choroidal melanomas (>10 mm apical height or >16 mm basal dimension) [10];
- A third observational arm described the natural history of small choroidal melanoma (1.0–3.0 mm in apical height and 5.0–16.0 mm in largest basal dimension) [11]. Tumors enlarged in 31% by 5 years to medium size requiring treatment [11]; but risk for metastasis associated death was low [12].

The 5-year all-cause mortality for medium choroidal melanoma was 19% both for brachytherapy

and enucleation, while melanoma-related mortality was 9 and 10% in each arm, respectively [13]. Local failure rate (tumor recurrence) in the COMS brachytherapy trial was 9%. The aggregate of these studies provided clinical guidelines favoring globe sparing radiotherapy techniques when appropriate rather than enucleation.

However, the results of brachytherapy came at the cost of significant radiation toxicity and associated complications. Forty-nine percent of enrolled patients lost 6 or more lines on the Snellen visual acuity chart at 3-year follow-up due to radiation complications such as retinopathy, maculopathy and optic neuropathy [14]. The COMS reported 91.5% prevalence among enrolled patients with signs of radiation retinopathy on fluorescein angiography (FA) at 5 years following brachytherapy. Proliferative radiation retinopathy, accounted by neovascularization of the disk (NVD), was present in 5.2% of patients [15]. Optic neuropathy (accounted by any optic disk edema, hemorrhage and/or pallor) was present in 27.4% at 5 years in the COMS brachytherapy trial [15]. In addition, there was a 12.5% secondary enucleation rate [16]. The COMS quality-of-life study revealed that patients in the brachytherapy arm had some early visual advantages over patients treated with enucleation such as driving and peripheral vision [17]. However, both the enucleation and brachytherapy patients reported significantly increased difficulties with visual tasks following treatment [17]. Of interest, ocular pain only improved in the enucleation arm, but not in the brachytherapy arm [17].

In conclusion, while appropriate local tumor control is realized with the current treatment as established by the COMS, there exists significant treatment-associated ocular morbidity due to radiation complications. Improving the vision related outcome following plaque brachytherapy treatment may involve two general strategies. First is reduction of radiation dosing to the tumor and surrounding tissues while still maintaining excellent local tumor control. Second is to use adjuvant therapies to reduce degree of radiation retinopathy.

Low-dose brachytherapy reduces complications

Per design of COMS, choroidal melanomas with apical height 5 mm or greater were prescribed 85 Gray (Gy) to the tumor apex height, whereas the prescription point was 5 mm to

inner sclera for melanomas of 2.5–4.9 mm apical height [9]. This radiation dose was chosen based on expert opinion and the available data at the time. Consequently, apex prescription dose of the smaller medium-sized choroidal melanomas have exceeded 85 Gy (Figure 1) as determined by dose–distance relationship.

More recently, promising studies were published investigating lower radiation doses for choroidal melanoma (Table 1). Gragoudas *et al.* published a prospective randomized trial of 190 patients receiving 50 versus 70 Cobaltgray (cgy) prescribed to the tumor apex using proton beam radiation [19]. The authors reported no significant difference in 5-year rate of tumor recurrence, metastasis and proportion of patients retaining visual acuity better than 20/200 among the higher and lower radiation dose. Whereas radiation maculopathy rates were also not significantly different between the groups, there was a trend toward fewer cases with optic neuropathy in the 50 cgy compared with 70 cgy group and there was significantly less visual field loss in the lower dose group [19].

Saconn *et al.* published their retrospective series of patients receiving a median dose of 62.5 Gy radiation by Iodine-125 brachytherapy for medium-sized choroidal melanoma [21]. Distant failure, local failure as well secondary enucleation rate compared very similarly to the anecdotal COMS data, where as unfavorable

visual acuity results (Snellen visual acuity of 20/200 or worse as well as loss of 6 or more Snellen lines) outperformed the COMS dataset. Rates of radiation complications were not reported in this study [21].

Murray *et al.* reported a retrospective Iodine-125 brachytherapy series of 95 patients with small and medium-sized choroidal melanoma <5 mm apical height receiving either 85 Gy to the actual tumor apex point or 5 mm to the inner sclera [22]. While all cause mortality, local failure and secondary enucleation were very low, results did not differ between the two groups at 10-year follow-up. Visual acuity results also were equivalent, but the authors found a statistically significant lower rate in radiation retinopathy as well as overall pooled radiation complications in the group that received a lower radiation dose by prescription to actual tumor apex strategy [22]. The authors state that visual acuity may have been preserved due to aggressive treatment of radiation complications [22].

Vonk *et al.* published similar results on prescribing 85 Gy via I-125 plaque to the tumor apex regardless of tumor height [23]. In their series, 67 of 76 cases with tumor height less than 5 mm had radiation dose prescription to the actual tumor height, while nine cases had a prescription point at 5 mm inner sclera. The study also included 41 eyes with tumors >5 mm height that were treated according to the regular COMS

Figure 1. Example of radiation dose calculations using different prescription strategies. (A) 85 Gy to the tumor apex of 5 mm and (B) 85 Gy to 5 mm inner sclera, as prescribed in the Collaborative Ocular Melanoma Study. (C) 85 Gy to the actual tumor apex of 2.5 mm, (D) 70 Gy to the actual tumor apex of 2.5 mm. Dose calculation data taken from [18].

All data in figure: for 12-mm basal diameter tumor, using 16-mm round plaque.

Study	Year	Comment	Subjects (n)	Study type	Dose	All cause mortality	Distant failure	Local failure	Secondary enucleation	VA	Radiation retinopathy	Radiation papillopathy	Ref.
COMS	1986–1998	Medium-sized tumors	657	I-125, prospective	85 Gy to apex height or 5 mm inner sclera	19% at 5 years; 35% at 10 years; 43% at 12 years	10% at 5 years; 18% at 10 years; 21% at 12 years	9% at 5 years	12.5% at 5 years	Median VA 20/125 at 3 years 34% <20/40; 45% >20/200 [†]	84.4% at 2 years, 91.2% at 5 years NVD: 3.4% at 2 years, 5.2% at 5 years	11.2% at 2 years, 27.4% at 5 years	[13–15,20]
Gragoudas <i>et al.</i>	1989–1994	Medium-sized tumors within 4DDM of macula or optic disk	190	Protons, prospective	50–70 cgy	NA	7–8% at 5 years	2–3% at 5 years	4–5% at 5 years	Median VA 20/100–160 at 5 years [‡]	40–75% at radiation maculopathy at 5 years	58–77% at 5 years	[19]
Sacconi <i>et al.</i>	1990–2004	Medium-sized tumors	62	I-125, retrospective	63.5 Gy median dose	21% at 5 years	10% at 5 years	9% at 5 years	12% at 5 years	≥20/200: 16% at 3 years, 22% at 5 years [§]	NA	NA	[21]
Murray <i>et al.</i>	1991–1998	Tumors between 1.5 and 5 mm apex height [¶]	55	I-125, retrospective	85 Gy to specific apex height	1% at 10 years	1% at 10 years	2% at 10 years	0.4% at 10 years	≤20/40: 52% at 2 years; ≤20/200: 31% at 2 years	20% at 10 years	20% at 1 year	[22]
Vonk <i>et al.</i>	1990–2010	Medium-sized tumors	116	I-125, retrospective	Variable, majority with 85 Gy to specific apex height			2.8% at 3 years, 4.7% at 5 and 10 years [¶]	5.7% at 3 years, 9.8% at 5 and 10 years [¶]	>20/200: 22.3% at 3 years, 40.7% at 5 years, 64.1% at 10 years [¶]	NA	NA	[23]
Perez <i>et al.</i>	1988–2010	Medium-sized tumors	190	I-125, retrospective	63–85 Gy to specific apex height	16% at 5 years ^{††}	10% at 5 years ^{††}	9% at 5 years ^{††}	7% at 5 years ^{§§}	Mean VA 20/160 ^{††}	Dose dependent	Dose dependent	[18]

[†]COMS: Loss of six lines VA of Snellen letters were 18% at 1 year, 34% at 2 years, 49% at 3 years.

[‡]Gragoudas: No significant difference in 5-year rate of tumor recurrence, metastasis and proportion of patients retaining VA better than 20/200.

[§]Sacconi: Loss of six or more lines of Snellen VA was 10% at 3 years and 16% at 5 years.

[¶]Murray: This study compared dose prescription to the actual tumor apex versus 5 mm inner sclera: in this table only data on actual tumor apex dosing presented. There was no significant difference between the dosing strategies for survival, distant failure and local failure. There was significantly less radiation retinopathy and pooled overall radiation complications in the dosing to actual apex group.

^{¶¶}Vonk: Outcomes represent estimates based on survival curves. Median follow-up was 2.63 years.

^{††}Perez: No significant difference between different radiation dose quartiles and overall survival, distant failure and local failure between radiation dose quartiles.

^{§§}Perez: VA loss as well as loss ≥3 lines of Snellen acuity was positively related to both increasing 5 mm and apex dose.

^{§§§}Perez: On univariate and multivariate analysis, higher dose to tumor apex, to 5 mm prescription point and to sclera were all associated to enucleation.

cgy: Cobaltgray; COMS: Collaborative Ocular Melanoma Study; DDM: Disk diameter; I-125: Iodine-125; NA: Not available; NVD: Neovascularization of the disk; VA: Visual acuity.

algorithm of 85 Gy to the tumor apex. With this strategy, the overall average dose to 5 mm inner sclera was reduced to 62.4 Gy. Results of this study have to be viewed with caution due to the very short median follow-up time of 2.63 years. Estimated local control rates as well as globe preservation rates at 5 years were similar to the COMS data, where as retention of visual acuity <20/200 compared favorably [23]. The paper does not include a subanalysis of tumors less than 5-mm apical height. Further results with longer follow-up of this patient cohort will be important to correctly interpret the results.

Finally, our group recently reported the largest study to date on lower dose radiation Iodine-125 brachytherapy for COMS medium-sized choroidal melanoma [18]. One-hundred-and-ninety patients at our center between 1988 and 2010 had received radiation doses between 63 and >89 Gy to the tumor apical height. Plaque types included circular (66%), notched (23%) and ciliary (11%). The decision to treat to an apical dose below 85 Gy was based on treatment practice, which has evolved over two decades at Duke. Stratifying patients into quartiles by radiation dose (<69, 69–81, 81–89, >89 Gy), there was no difference in overall survival, local failure or distant failure, whereas overall pooled endpoints compared similarly to the COMS data [18]. The overall 5-year actuarial freedom of distant failure rate was 90% and the 5-year overall survival rate was 84%. The overall 5-year local failure rate was 9%. However, the study demonstrated better visual acuity outcomes and less treatment complications in tumors treated with lower dose brachytherapy. In detail, general visual acuity loss as well as loss ≥ 3 lines of Snellen acuity was positively related to both increasing 5-mm dose and apex dose. Final visual acuity outcome $\leq 20/200$ was associated to increasing 5-mm radiation dose. The crude enucleation rates by increasing 5-mm dose quartiles were significantly higher in the increased dosage quartiles [18]. On univariate and multivariate analysis, higher dose to tumor apex, to 5-mm prescription point and to sclera were all associated to enucleation. The risk of any treatment complication (radiation retinopathy, optic neuropathy, cataract, neovascular glaucoma and keratopathy) was associated with both increasing apex and 5-mm dose, while the most common complications were cataract formation and radiation retinopathy. In addition to higher radiation dose, greater tumor height was also

associated with time to radiation complication on univariate and multivariate analysis [18].

In conclusion, the five aforementioned studies show favorable functional ocular outcomes due to reduced toxicity by lower radiation doses without diminished tumor control. Our study suggests that radiation doses as low as 69 Gy delivered via Iodine-125 episcleral plaque may be sufficient to achieve COMS-equivalent tumor control. Using protons, Gragoudas even showed success using 50 cgy, which in many instances of medium-sized melanomas <5 mm would approximately cut radiation dose prescribed by the COMS algorithm in half.

We hypothesize that especially smaller medium-sized tumors (2.5–4.9 mm apical height) may benefit the most from lower dose radiation strategies, since they are essentially overtreated compared with their >5 mm apical height counterparts as a consequence of the COMS protocol. Currently at Duke, we utilize low-dose radiation strategies with approximately 70 Gy to the tumor apex point, irrespective of tumor apical height.

Intraoperative ultrasound ensures treatment accuracy

Some studies have suggested there may be increased mortality in patients with recurrent tumors after brachytherapy [24–26]. Inaccurate intraoperative plaque placement with subsequent subtherapeutic radiation dose is a preventable iatrogenic factor that may at least play a partial role in tumor recurrence. Intraoperative ultrasound allows for proper plaque localization and immediate correction of poorly positioned plaques [27]. Plaque repositioning can be helpful in cases of plaque tilt away from the sclera, noncoverage of at least one tumor margin or suboptimal centration [28]. If plaque placement remains suboptimal, as may be the case for surgically difficult to access posteriorly or juxtapapillary located tumors, increasing the prescription point 0.5–1 mm may help to prevent subsequent treatment failures [29]. A recent large series demonstrated a need for plaque repositioning as high as 37%, even by experienced surgeons [30]. However, another study demonstrated that requirement for plaque repositioning may become less frequent with increasing surgeon experience, associated with a learning curve [31]. Even after initial correct placement, plaque tilt is not infrequently identified at the time of plaque removal 4–5 days after original insertion [32].

Risk factors for subsequent plaque tilt identified at the time of removal are posterior and juxtapapillary tumor location, notched plaque and episcleral hematoma formation [32]. To prevent treatment failure due to insufficient radiation doses when plaque tilt is identified postoperatively before removal, plaques can be left longer and/or adjuvant therapy such as transpupillary thermotherapy (TTT) may be performed [32]. There is data to suggest that centers using intraoperative ultrasound-guided plaque repositioning may have more optimal outcomes including lower tumor recurrence rates [18,22,29]. Given that plaque tilt is often identified at the time of removal despite initial correct plaque placement as identified by ultrasound without increased local recurrence rates [32], some experts question whether there is a true benefit for intraoperative ultrasound at the time of plaque placement.

At our center, we routinely perform intraoperative ultrasound for both plaque insertion and removal.

Adjuvant therapy enhances control & reduces retinopathy

While low-dose radiotherapy may reduce radiation complications with an overall equivalent failure rate compared with traditional radiation doses, ensuring tumor control is of paramount importance. There are adjuvant therapies that may provide additional tumor control as well as help ease radiation complications. Adjuvant therapies may play an increasing role to provide best possible outcomes. We hypothesize that some adjuvant therapies such as transpupillary thermotherapy or photodynamic therapy may be especially helpful, but are not limited to tumors with high-risk features for recurrence such as ones with posterior or juxtapapillary location. Intravitreal anti-VEGF and periocular steroid therapy are commonly applied to reduce radiation-associated complications.

Laser

• Transpupillary thermotherapy laser

Laser has been used to treat choroidal melanomas since the 1960s when Meyer-Schwickerath used lenses to collimate the sun's light onto choroidal melanoma [33]. This was followed by xenon arc and argon laser photocoagulation, that were more advanced but still carried significant side effects that could lead to tractional retinal detachment or vascular occlusion, whereas local tumor recurrence was also common [34,35]. In 1995, Osterhuis

introduced TTT as a new treatment for choroidal melanoma. TTT delivers energy via a near infrared diode laser to produce intratumoral local hyperthermia at 45°C (photocoagulation occurs at 65°C) producing tissue necrosis up to a depth of 3.9 mm (photocoagulation is limited to 1.0 mm depth). Initially, TTT was evaluated as rescue therapy for tumors that had failed ruthenium plaque brachytherapy, simultaneous to ruthenium brachytherapy and also as primary therapy for small tumors with juxtapapillary location [36]. Subsequently, primary therapy for small choroidal melanomas has been mostly discouraged due to high rate of tumor recurrence and may only play a role in a small subset of patients [37,38], but adjuvant TTT to radiation has gained increasing interest. Combined TTT and episcleral plaque brachytherapy is referred to as 'sandwich procedure' [35]. As radiation doses from the episcleral plaque decreases with distance to the sclera and may reach insufficient doses at the apical tumor, the tumor surface is treated via TTT through the pupil. In an effort to increase tumor control in their patients, the Shields group found excellent tumor control with 3% local recurrence and 12% distant failure after immediate plus delayed adjuvant TTT (initial session at plaque removal, with two subsequent sessions at 4-month intervals). In addition to this, juxtapapillary tumors, which notoriously have a worse prognosis, recurred in only 2.5% [39]. In The Netherlands, where TTT was originally introduced, delayed adjuvant TTT (either one or two sessions occurring 2 months after brachytherapy) following Ru-106 was employed for choroidal tumors (apical height ≥ 3 mm). Peripheral tumors that could not be reached by TTT received higher radiation doses. Overall the study demonstrates encouraging tumor control of 96.1% at 5 years, however all recurrences were in the group that received TTT which also more commonly exhibited risk factors for recurrence such as juxtapapillary or posterior location. It is unclear if the recurrence rate in these cases was affected by TTT [40]. Yarovoy reported a matched controlled series of patients either receiving Ru-196 brachytherapy with simultaneous adjuvant TTT or mono radiation therapy with Ru-106. In this series, adjuvant TTT resulted in lower 5-year tumor recurrence rate (96 vs 83%, $p < 0.034$), higher globe preservation (98 vs 87%, $p < 0.024$) and recurrence-free survival rates (89 vs 67%, $p < 0.017$) [41]. Recently, a Korean group reported mixed results on adjuvant TTT for larger choroidal melanomas [42].

Badiyan *et al.* used delayed adjuvant TTT (initial session at plaque removal, subsequently additional one or two sessions at 3-month intervals in select patients until tumor control achieved) following I-192 brachytherapy in 72 high-risk patients (of 526 total patients) with plaque tilt >1 mm, juxta-papillary tumor location, slow tumor regression, slow exudative retinal detachment resolution or in cases of local tumor recurrence. While actual TTT results are not presented separately, the authors achieved excellent control rate of juxta-papillary tumors of 96.5% at 5 years. In addition to possibly providing improved tumor control, TTT may play a role in reduction of exudate retinal detachment, but to our knowledge, no controlled data for this are available [29,43]. One should note that TTT is associated to treatment-related complications such as macular ischemia and epiretinal membrane formation, which was noted in 18% and 8% in the Shields study, respectively [39]. Additional complications can include rhegmatogenous retinal detachment in rare cases [44]. We think that there are encouraging data to use adjuvant TTT, especially for high-risk patients, but optimal patient selection, treatment parameters and timing for the treatment have yet to be determined.

• Photodynamic therapy

Photodynamic therapy (PDT) using verteporfin as photosensitizer activated by argon 692 nm wavelength laser was described as experimental therapy for choroidal melanoma in rabbits [45], but subsequently has gained much more acceptance for the treatment of choroidal neovascularization. It has been used as salvage therapy in four patients with choroidal melanoma that failed previous therapy with I-125 brachytherapy and TTT. Tumor control was achieved in one case, whereas continued growth was present in the remaining ones with need for enucleation in two patients [46]. Shields *et al.* reported a case of complete tumor control with PDT that was commenced after previously failed brachytherapy in a patient with amelanotic choroidal melanoma [47]. Rundle reported on 18 cases with posterior uveal melanoma (mean tumor thickness 1.92 mm, range: 0.5–4.0 mm) treated with multidose PDT alone. After a median follow-up of 28 months, tumor regression was noted in 16 cases (83%), while two cases required proton beam therapy. While follow-up is short, this represents encouraging data. Studies with longer-term follow-up are needed to determine

whether high rates of late recurrence arise as witnessed with TTT when used as primary monotherapy [48]. Note that there is consideration that TTT may have low efficiency in amelanotic tumors due to reduced energy absorption and subsequent less thermal release. Adjuvant PDT may play a role in these selected patients, but we do not employ this in our clinical practice to this date.

Pharmacotherapy

• Periocular triamcinolone

Periocular triamcinolone may serve the purpose to prevent immediate radiation complications such as macular edema, which may occur in at least up to 70% of patients following plaque brachytherapy, in addition to help generally with postoperative inflammation. Shields *et al.* evaluated periocular triamcinolone administered at the time of plaque placement in addition to 4 and 8 months in a randomized clinical trial. The authors found lower rates of macular edema (detected by optical coherence tomography [OCT]) as well as reduced moderate to severe to vision loss. There was no statistically significant increase in intraocular pressure >21 mmHg or cataract formation [49]. We feel that periocular steroids at the time of surgery should play a role in the adjuvant treatment of choroidal melanoma. Currently, at Duke we administer 40 mg posterior sub-Tenon triamcinolone at the time of plaque removal.

• Anti-VEGF

Bevacizumab is recombinant humanized full-length antibody to VEGF that was originally designed and subsequently US FDA approved for the systemic tumor angiogenesis inhibition of colon carcinoma.

Few studies have evaluated adjuvant bevacizumab for the treatment of choroidal melanoma. A pilot study showed that systemic intravenously administered 10 mg/kg bevacizumab may be used in the treatment of exudate retinal detachments following brachytherapy for choroidal melanoma [50]. Houston and Murray studied adjuvant intravitreal bevacizumab administered at the time of plaque removal. They found encouraging results for tumor control, visual acuity and enhanced resolution of exudative retinal detachment [51]. The authors hypothesize that timing of anti-VEGF administration may be crucial given some experimental data pointing toward increased resistance to radiation in hypoxic tumor cells [51]. The study did not have a control

group and results need to be viewed with caution. Prophylactic intravitreal bevacizumab was shown to reduce incidence of anterior segment neovascularization after proton therapy [52].

To date, there is insufficient data to determine whether adjuvant bevacizumab may provide additional tumor control, but there are reports on other solid tumors such as colon carcinoma or glioblastoma benefitting from the effect on tumor angiogenesis inhibition by VEGF antibodies. As a cautionary tale, Newman *et al.* reported three patients with choroidal melanoma initially misdiagnosed having neovascular choroidal membranes treated with intravitreal bevacizumab and found no evidence of tumor control [53].

At Duke, we adapted the use of intravitreal 1.25 mg/0.05 ml bevacizumab injection at the time of plaque removal and see encouraging results in earlier resolution of exudative retinal detachment, which is one of the main determinants contributing to poor visual acuity [54]. Long-term follow-up and additional studies are needed to determine the potential benefits on VEGF inhibition for choroidal melanoma.

Conclusion

The COMS has established safety and efficiency of eye preserving brachytherapy for medium-sized choroidal melanomas. While appropriate survival rates have been realized, radiation treatment is associated with significant morbidity due to radiation complications. Available studies provide encouraging data that radiation doses below the COMS algorithm of 85 Gy to the tumor apex or 5 mm to inner sclera, whichever greater, achieve

equivalent local and distant tumor control with improved functional ocular outcomes. Adjuvant therapies such as TTT, periocular triamcinolone and intravitreal anti-VEGF medications will play an expanded role in the future management of choroidal melanoma. Our current approach at Duke consists of low-dose (approximately) 70 Gy apex dose via I-125 brachytherapy, transvitreal biopsy for genetic and histologic studies at the time of plaque insertion and posterior sub-Tenon 40 mg triamcinolone administration in addition to intravitreal 1.25 mg/0.05 ml bevacizumab administration at the time of plaque removal.

Future perspective

With the increased use of molecular predictive testing, clinicians treating ocular melanoma will have more confidence counseling patients on survival prognosis. This implies a greater need for better visual outcomes from globe sparing radiation strategies. Doses at least as low as 69 Gy may be feasible to achieve appropriate tumor control rates. We think that a multicenter low-dose brachytherapy (prescribed to the tumor apex) trial for medium-sized choroidal melanoma would be desirable to further validate this strategy.

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