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ONCOLOGY

23-mm iodine-125 plaque for uveal melanoma: benefit of vitrectomy and silicone oil on visual acuity

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Abstract
Purpose To review outcomes in mostly large uveal melanoma treated with a 23-mm-diameter iodine-125 plaque, the largest size available at our center, and the influence of vitrectomy and silicone oil 1000 centistokes for radiation attenuation.
Methods A one-to-one matched case–control comparison was performed. Case patients were treated with a 23-mm-diameter iodine-125 plaque and vitrectomy with silicone oil 1000-cSt placement. Control cases, treated with 23-mm plaque alone, were matched to cases with respect to tumor size and distance from tumor apex to optic nerve and fovea. Postoperative complications, visual acuity and metastasis were reviewed.
Results Twenty case patients with uveal melanoma treated with a 23-mm plaque were identified. The final logMAR vision was 0.83 in case patients and 2.06 in control patients ($P = 0.0064$); the change from pre-treatment to last follow-up logMAR vision was 0.70 in cases and 1.62 in controls ($P = 0.019$). Of good vision outcomes, 65 % of cases and 25 % of controls achieved vision ≥20/200 ($P = 0.025$). Of poor vision outcomes, 35 % of cases and 80 % of controls achieved vision <20/200 ($P = 0.0053$), and 5 % of cases and 35 % of controls achieved "light perception" or "no light perception" vision ($P = 0.044$). Thirty-nine of the 40 eyes (98 %) achieved local tumor control. Metastasis occurred in 15 % of cases and 45 % of controls ($P = 0.082$).
Conclusions Iodine-125 brachytherapy for mostly large uveal melanoma is effective in achieving local tumor control. Furthermore, combining brachytherapy with vitrectomy and silicone oil 1000-cSt for radiation attenuation significantly improves vision over the use of plaque alone.

Keywords Uveal melanoma · Choroidal melanoma · Ocular melanoma · Vitrectomy · Silicone oil · Radiation retinopathy

Introduction

Melanoma arising from the choroid and ciliary body is the most common primary intraocular cancer in adults [1]. Iodine-125 is most frequently used as the source of radiation for local brachytherapy treatment of uveal melanoma in North America, and its effectiveness was established by the Collaborative Ocular Melanoma Study (COMS) [2–4].

The management of patients with large uveal melanoma remains challenging. Prognosis for the patient is poor, as large tumor size is strongly associated with a higher risk of systemic metastasis [4, 5]. The COMS defined "large melanoma" as a tumor with greatest basal dimension greater than 16 mm, and tumor height greater than 10 mm [5]. Concerns for attempting globe-salvaging measures for these large tumors include higher rates of local treatment failure, and significant complications of radiation such as neovascular glaucoma and exudative retinal detachment, resulting in a high likelihood of visual loss with no light perception vision.

Radiation retinopathy associated with brachytherapy is the cause of vision worse than 20/200 in nearly half of all eyes by 3 years following treatment [6]. Although there

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continues to be interest in the use of intravitreal anti-VEGF agents and steroids, no successful treatment for radiation retinopathy has been reported in a randomized clinical trial [7]. An entirely novel method of addressing radiation retinopathy is the use of silicone oil 1000 centistokes as a vitreous substitute. Oliver et al. demonstrated that silicone oil 1000-cSt has the capacity to attenuate the radiation exposure from iodine-125 to non-tumor ocular tissue by approximately 50-60 % [8]. Our center also reported the clinical benefit of combined vitrectomy and silicone oil placement at the time of brachytherapy compared to iodine-125 brachytherapy alone for successfully reducing macular edema and clinical macular abnormalities associated with radiation retinopathy at 2 years [9]. This has now become a standard treatment option at our center.

We sought to describe our experience in treating uveal melanomas with our largest available brachytherapy plaque (23-mm diameter), and to evaluate the effect of vitrectomy and silicone oil for radiation attenuation on visual acuity in this cohort.

Materials and methods

The study was performed in accordance with the United States Health Insurance Portability and Accountability Act (HIPAA) of 1996, and was approved by the Office of the Human Research Protection Program (institutional review board) of the University of California, Los Angeles.

From January 1, 2005, to October 31, 2014, all patients who had been diagnosed with uveal melanoma and treated using a 23-mm-diameter iodine-125 plaque were identified. Inclusion criteria for cases were that the patient was treated for uveal melanoma with iodine-125 plaque brachytherapy alone or iodine-125 brachytherapy in combination with vitrectomy and silicone oil 1000-cSt placement, and there was a minimum follow-up of one year. The clinical charts were reviewed for baseline patient and tumor demographic information and for surgical details of the brachytherapy treatment. Clinical outcomes including eye retention, local treatment failure, complications, visual acuity, and development of metastasis were recorded.

The prescribed radiation dose was calculated in the same manner as the COMS, i.e. 85 Gy to tumor apex, with a dose rate of approximately 0.5 Gy/hr. We followed the methodology outlined by Task Group 43 of the American Association of Physicists in Medicine. [10] In brief, iodine-125 seeds were modeled as point sources, and water equivalence of the methyl methacrylate used to cement the seeds to the gold plaque was assumed. The margin of plaque coverage beyond the tumor in this cohort of 23-mm-diameter plaques ranged from 0.5 mm to 5.5 mm. At our center, we feel that extra coverage beyond the greatest basal dimension of ciliary body involving melanomas, when possible, may help to minimize local treatment failure.

Details of the brachytherapy plaque placement procedure have been described elsewhere [11–13]. Briefly, fundus examination was performed on the affected eye, followed by monitored anesthesia care with retrobulbar anesthesia. A 360-degree conjunctival peritomy was performed, followed by isolation of the four rectus muscles with 2-0 silk suture. Transpupillary transillumination was used to mark the anterior border of the tumor. If the rectus muscles or their insertion interfered with placement of the plaque on the sclera, they were dis-inserted and hung back. Fine needle aspiration biopsy for cytopathology and molecular prognostication was performed via a transscleral approach. The position of the plaque in relation to the tumor was optimized with ultrasonography, as we previously reported [14].

Details of silicone oil placement with vitrectomy have been reported previously [9]. In cases of combined plaque and silicone oil placement, concomitant phacoemulsification with intraocular lens placement was performed at the outset of the case in all phakic patients from December 2012 onwards, prior to plaque placement and vitrectomy. This was performed for three main reasons: 1) more complete vitreous removal, allowing more silicone oil placement; 2) more thorough future silicone oil removal (no crystalline lens and minimal vitreous for oil to be lodged in); 3) maximized vision and convenience for patients, resulting in one fewer surgical procedure. A 23-gauge pars plana vitrectomy was performed after the position of the plaque was optimized by ultrasonography, with trocars placed into bare sclera at a 90-degree angle. Vitrectomy included elevation and dissection of the posterior hyaloid to the vitreous base. Once a thorough vitrectomy was completed, an air–fluid exchange was performed, followed by silicone oil 1000-cSt infusion for as complete a fill as possible. No drainage retinotomy was made. At the time of plaque removal, the silicone oil was removed, unless there was serous retinal detachment. In such cases, the silicone oil was removed at a later date following resolution of the serous retinal detachment.

Patients were evaluated postoperatively according to a standardized protocol. Follow-up visits were scheduled at 1 week, 1 month, 3 months, and 6 months after brachytherapy, and every 6 months thereafter. Starting at 3 months, A- and B-scan ultrasonography was performed at each visit to evaluate tumor response to brachytherapy. Patients and their medical oncologists were recommended to have biannual systemic evaluation for metastatic disease, which included liver function testing and abdominal imaging by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or combined positron emission tomography-CT.

Recorded best vision by Snellen visual acuity was converted to logMAR visual equivalent for analyses. Chi-square and Fisher's exact tests were used for statistical analyses.

Results

Twenty case patients who received iodine-125 brachytherapy with a 23-mm-maximal-diameter plaque in combination with vitrectomy and silicone oil 1000-cSt met the inclusion criteria. Twenty control patients were matched for tumor height, tumor greatest basal dimension, tumor apex distance from optic nerve and fovea, and duration of follow-up. The comparison of baseline characteristics between case patients and control patients is presented in Table 1. The distribution and comparison of tumor size between cases and controls according to the American Joint Committee on Cancer staging system are shown in Table 2. No patient had metastatic disease at initial presentation.

Ocular retention and local treatment failure

Of this cohort of 40 patients, 39 (98 %) patients had retained their eye at last follow-up. There were two cases of local treatment failure in this series that occurred in the group with iodine-125 plaque alone. Case 1 was a papillary uveal melanoma with height 7.70 mm and greatest basal dimension of 16.7 mm. The treated tumor demonstrated increasing height by ultrasonography at 13 months following iodine-125 plaque treatment, and was re-plaqued with a 23-mm-diameter notched plaque, which resulted in tumor regression. Case 2 was a ciliary body melanoma with height of 10.8 mm height and greatest basal dimension of 21.3 mm. The treated tumor demonstrated increasing tumor height at 14 months following treatment, and the eye was enucleated.

Ocular complications

Ocular complications are listed in Table 3. One patient developed neovascular glaucoma and was treated with periodic intravitreal bevacizumab. Glaucoma that developed in the case patient was treated with tube shunt; of the two patients that developed glaucoma in the control group, one was treated with topical anti-hypertensive medication, and the other was treated with a tube shunt. The three instances of retinal detachment that occurred in the cases were treated with vitrectomy resulting in retinal reattachment; two cases were rhegmatogenous in etiology, and the third resulted from progressive subretinal fibrosis.

Visual acuity

The comparison of logMAR visual acuity outcomes in cases and controls is presented in Table 4. Comparisons of percentages of patients with good and poor vision subgroups are detailed in Fig. 1.

Final lens status

Lens status at last follow-up is detailed in Table 5. In the control patients who remained phakic, the presence of a visually significant cataract was documented. The 3 cases with visually significant cataract were each recorded as 3+

Table 1 Baseline characteristics between case patients and control patients

	Case patients (SiOil) n = 20	Control patients (no SiOil) n = 20	*P* value
Follow-up, months (SD)	19.4 (6.2) [range, 12.2–36.7]	22.5 (11.8) [range, 12.0–56.2]	0.7250
Age, years (SD)	60.6 (9.68)	64.2 (14.5)	0.5075
Diabetes mellitus (%)	1 (5)	2 (10)	1.0
Phakic (%)	18 (90)	13 (65)	0.1274
Other macular disease (%)*	2 (10)	1 (5)	1.0
Tumor > 50 % in macula (%)	1 (5)	1 (5)	1.0
Tumor > 50 % in ciliary body (%)	9 (45)	9 (45)	1.0
Tumor height, mm (SD)	7.8 (2.7)	7.9 (2.1)	0.8498
Tumor GBD, mm (SD)	16.4 (1.7)	17.5 (1.8)	0.0458
Distance from apex to fovea, mm (SD)	12.6 (2.9)	12.5 (4.3)	0.3862
Distance from apex to optic nerve, mm (SD)	11.6 (4.1)	13.4 (6.1)	0.3268

Abbreviations: SiOil = silicone oil, n = number, SD = standard deviation, GBD = greatest basal dimension

*Two patients with macular pucker both 20/30 vision (cases); one exudative age-related macular degeneration with 20/50 vision (control)

Table 2 AJCC tumor staging distribution of cases and controls

	Case patients (SiOil) n = 20	Control patients (no SiOil) n = 20
T1	0	0
T2	4	0
T3	13	12
T4	3	8

($P = 0.056$)

Abbreviations: AJCC = American Joint Committee of Cancer, SiOil = silicone oil, n = number, T = tumor

Table 3 Ocular complications in cases and controls

	Case patients (SiOil) n = 20	Control patients (no SiOil) n = 20
Neovascular glaucoma	1	0
Non-neovascular glaucoma	1	2
Corneal opacity	0	2
Retinal detachment	3	0

Abbreviations: SiOil = silicone oil, n = number

nuclear sclerosis with 4+ posterior subcapsular cataract, and none precluded a view of the fundus. The corresponding final visual acuities were 20/70, counting fingers and no light perception.[1]

Chromosome 3 status and metastatic outcome

Chromosome 3 status and metastatic outcome are detailed in Table 6.

Discussion

We have demonstrated a local tumor control rate of 98 % using a 23-mm-diameter iodine-125 plaque to treat eyes with mostly large uveal melanoma and with greatest basal diameter up to 21 mm. Additionally, we have demonstrated significant visual benefit in eyes that underwent both iodine-125 brachytherapy in combination with vitrectomy and silicone oil 1000-cSt for radiation attenuation.

The treatment of large uveal melanoma as defined by the COMS is usually enucleation [5]. However, our report supports the use of brachytherapy as an excellent globe-sparing option. We attribute our success in achieving tumor control in these challenging cases to intraoperative ultrasonography. Although most centers do not confirm optimal plaque placement with intraoperative ultrasonography, we and others have reported that ultrasound-guided plaque placement may contribute to an extremely low rate of local treatment failure [14–18]. In the treatment of tumors with a large greatest basal diameter, we feel that intraoperative ultrasonography is imperative to ensure that the plaque adequately covers the margins of the tumor.

The data in this series demonstrate a visual benefit of vitrectomy and silicone oil, and provide further evidence of the attenuating effect of silicone oil 1000-cSt, which we first reported in 2010 [8]. We subsequently reported the 2-year results of our first cohort of 20 patients in a similar case–control matched series, which revealed that there was less macular edema by ocular coherence tomography (OCT) and fewer clinical macular abnormalities. However, there was only a trend toward better vision in the silicone oil group [9]. Unlike the previous clinical report, where the tumors treated were smaller (average tumor height 5.0 mm), the results in this manuscript reflect data from only uveal melanomas treated with our largest-sized 23-mm iodine-125 plaques, which represent treatment of the largest-sized tumors. Therefore, these patients required maximal doses of radiation for local tumor control. For silicone oil to have a clinically meaningful radiation-attenuating effect on vision, we expected to see it in this "high-dose" cohort and within a relatively short period of follow-up, as we indeed demonstrated. silicone oil 1000-cSt, therefore, may still improve vision in patients with smaller tumors; however, the time to realize a clinically significant difference in vision compared to eyes with plaque alone may require longer follow-up.

Management of the lens was a major difference between the cases and controls, with the majority of cases rendered pseudophakic at the time of plaque vitrectomy and silicone oil, and all cases pseudophakic at last follow-up. It is conceivable that a mature or white cataract could result in a treatable exaggeration of the difference in visual outcome between the two groups. Although only 11 (55 %) of the controls were pseudophakic at last follow-up, none of the remaining phakic patients had fundus-obscuring dense cataract. Of the three controls with "visually significant cataract" (recorded each

Table 4 Vision: baseline, final, change from baseline in cases and controls

	Case patients (SiOil) n = 20	Control patients (no SiOil) n = 20	*P* value
Baseline logMAR (SD) [Snellen equivalent]	0.16 (0.21) [20/29]	0.54 (0.59) [20/69]	0.0149
Final logMAR (SD) [Snellen equivalent]	0.83 (0.86) [20/135]	2.06 (1.4) [20/2296]	0.0064
Change from baseline logMAR (SD)	0.70 (0.85)	1.62 (1.49)	0.0195

Abbreviations: SiOil = silicone oil, n = number

[1] The patient with 20/70 vision and visually significant cataract eventually had cataract surgery with vision best corrected to 20/30; the patient with counting fingers vision did not have cataract surgery and developed metastatic disease

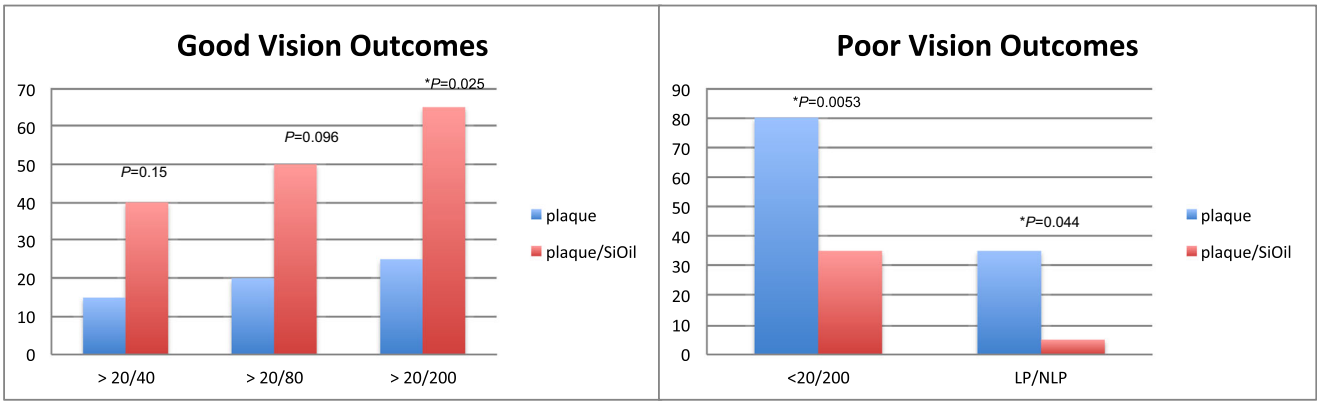

Fig. 1 Graph demonstrating rates of good vision outcome and poor vision outcome subgroups in case patients compared to controls. SiOil = silicone oil, LP = light perception, NLP = no light perception

as 3+ nuclear sclerosis and 4+ posterior subcapsular cataract), the final visual acuity was "no light perception", "counting fingers" and 20/70.

Others have reported on outcomes of globe-sparing treatment for large uveal melanoma, which constituted the majority of our cohort. Shields et al., in a series of 344 patients with large uveal melanoma treated with iodine-125 brachytherapy, reported an ocular retention rate of 76 %, which was somewhat lower than our rate of 98 %; vision > 20/200 was 43 %, which was lower than our silicone oil group, where 65 % achieved this outcome [19]. Pusaari et al. reported a series of 97 patients with large uveal melanoma treated with iodine-125, noting an ocular retention rate of 89 % and vision > 20/200 in only 42 % [20]. Semenova and Finger reported on a series of 47 patients with stage T3 and T4 uveal melanoma who were treated with Palladium-103 brachytherapy, with an 89 % ocular retention rate and vision > 20/200 achieved by 53 % of the patients in their series [21]. Some of the differences may be explained by a difference in technique (lack of ultrasound guided plaque confirmation), different radioisotope, variable rates of follow-up, and perhaps an overall larger size of tumors in their series. Among series of patients where proton beam radiotherapy was used to treat large uveal melanomas, the ocular retention rates were below 75 %, and vision > 20/200 ranged from 25 to 49 % [22–24]. Perhaps brachytherapy for the treatment of large uveal melanoma is more favorable than proton beam treatment with respect to globe salvage and vision outcome [25].

The strengths of this report include its data derived from a single center, where two retinal surgeons (TAM and CAM) performed all procedures using a similar technique, and the excellent patient follow-up. An additional strength is the value of using a one-to-one matched case–control analysis to help evaluate the effect of silicone oil 1000-cSt attenuation. Reporting the outcomes of a novel technique in the setting of a rare and variable disease is challenging at best. However, we feel that the data may be best interpreted when compared with data from a matched control group as reported here.

The relative weaknesses of this report include the retrospective nature of the data that are presented and the relatively small cohort of patients. The ideal study would be a prospective randomized trial. However, given our previously published evidence demonstrating benefit in eyes that had undergone vitrectomy and silicone oil placement, we did not feel that randomizing patients would be ethical. Additionally, the cohort of case patients that had undergone vitrectomy with silicone oil were treated more recently than patients in the control group, and a more aggressive approach for surgical management of ocular complications such as retinal detachment might have been the case compared to patients traditionally treated with brachytherapy alone in the relatively distant past. Finally, this cohort had a relatively short follow-up

Table 5 Final lens status in cases and controls

	Case patients (SiOil) n = 20	Control patients (no SiOil) n = 20
Phakic (%)	0	9 (45)
Vis sig cataract (%)	0	3 (15)*
Pseudophakic (%)	20 (100)	11 (55)

Abbreviations: SiOil = silicone oil, n = number, Vis sig = visually significant

* All 3 control patients with visually significant cataract were recorded as "3+ nuclear sclerosis, 4+ posterior subcapsular cataract" and had final visual acuity of counting fingers, no light perception and 20/70

Table 6 Metastatic outcome and chromosome 3 status in cases and controls

	Case patients (SiOil) n = 20	Control patients (no SiOil) n = 20	*P* value
Metastasis (%)	3 (15)	9 (45)	0.0824
Monosomy 3 (%)	9 (47)	11 (65)	0.3351

Abbreviations: SiOil = silicone oil, n = number

period; longer follow-up might have demonstrated more vision-altering complications associated with radiation. However, patients with large uveal melanoma tend to suffer earlier metastasis, and therefore we believe that an average 20-month follow-up for this cohort was appropriate for patients at high risk for metastasis and for our analyses.

Conclusions

In summary, we report a 98 % rate of ocular retention following the use of a 23-mm-diameter iodine-125 plaque in the treatment of mostly large uveal melanoma. Furthermore, the use of vitrectomy and silicone oil 1000-cSt as a vitreous substitute for radiation attenuation resulted in significantly better vision and fewer poor vision outcomes compared to conventional brachytherapy alone. The use of silicone oil 1000-cSt may be considered as an option for maximizing vision in the treatment of larger-sized uveal melanoma.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

For this type of study, formal consent is not required.

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