Practice Patterns for the Treatment of Uveal Melanoma with Iodine-125 Plaque Brachytherapy: Ocular Oncology Study Consortium Report 5

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Keywords

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Abstract

Background: Treatment planning for I-125 plaque therapy for uveal melanoma has advanced significantly since the Collaborative Ocular Melanoma Study trial, with more widely available image-guided planning and improved dosimetry. **Objective:** We evaluated real-world practice patterns for I-125 plaque brachytherapy in the United States by studying practice patterns at centers that comprise the Ocular Oncology Study Consortium (OOSC). **Methods:** The OOSC database and responses to a treatment practice survey were eval-

uated. The database contains treatment information from 9 institutions. Patients included in the database were treated between 2010 and 2014. The survey was conducted in 2018 and current treatment planning methods and prescriptions were queried. **Results:** Examination of the OOSC database revealed that average doses to critical structures were highly consistent, with the exception of one institution. Survey responses indicated that most centers followed published guidelines regarding dose and prescription point. Dose rate ranged from 51 to 118 cGy/h. As of 2018, most institutions use pre-loaded plaques and fundus photographs and/or computed tomography or magnetic resonance imaging in planning. **Conclusions:** While there were differences in dosimetric practices, overall agreement in plaque brachytherapy

practices was high among OOSC institutions. Clinical margins and planning systems were similar among institutions, while prescription dose, dose rates, and dosimetry varied.

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Introduction

Uveal melanoma is the most common primary intraocular tumor in adults [1]. It is a vision- and life-threatening cancer. The pivotal Collaborative Ocular Melanoma Study (COMS) trial for medium-sized uveal melanomas established plaque brachytherapy as an eye-sparing treatment with survival outcomes similar to enucleation [2]. Since the initiation of the COMS trial, use of plaque brachytherapy has increased from 1.8% in 1973–1975 to 62.5% in 2006–2008 with a corresponding decrease in treatment with enucleation from 93.8 to 28.3% over that same interval [1].

Plaque brachytherapy is now the most widely used treatment modality for uveal melanoma. COMS published its protocol guidelines in 1993 [3]. The American Brachytherapy Society (ABS) and American Association of Physicists in Medicine (AAPM) have released several updated recommendations since that time, expanding the indications for treatment with plaque brachytherapy beyond those initially evaluated in the COMS trial [4, 5]. The 2014 ABS guidelines endorse treatment of most melanomas of the choroid, iris, and ciliary body with plaque brachytherapy with the exception of tumors with gross orbital extension and painful eyes with no light perception [4]. Dose calculations per AAPM Task Group 129 (TG-129) are recommended under the ABS guidelines. Though TG-129 supports the use of material heterogeneity corrections, integrated plaque localization and image guidance, and individual seed Monte Carlo based dosimetry for eye plaques, it did not recommend their use for treatment planning calculations as no such FDA approved treatment planning system exists to date [5].

Current guidelines acknowledge pending questions regarding ideal prescription dose and dose rate, plaque size selection, and efficacy of notched and slotted plaques in preventing underdosing of juxtapapillary and circum-papillary tumors. Several publications have questioned the radiation therapy prescription dose and dose point [5–13]. Moreover, strict adherence to a planning treatment volume (PTV) with a 2–3 mm circumferential margin has been called into question. Experimental modeling and in vivo imaging for location verification indicate that 2–3 mm may be inadequate for tumors with large uncer-

tainties in size or difficult plaque placement [7, 13–18]. Generally, studies advocate for a larger PTV. This must be balanced with the risk for vision complications associated with an increase in dose to normal tissues. Due to these lingering uncertainties and a lag between recommendations and updated planning technology, actual treatment practices vary between institutions.

Given the heterogeneity reported in the literature, we sought to ascertain real-world practice patterns for I-125 plaque brachytherapy. We examined the previously established Ocular Oncology Study Consortium (OOSC) database and conducted a questionnaire-based survey of OOSC centers regarding current plaque brachytherapy methods for treatment of uveal melanoma. The consortium was initially created to examine treatment response based on gene expression profile (GEP) class. GEP allows for the classification of primary uveal melanomas into Class 1A (low metastatic risk), Class 1B (intermediate risk) and Class 2 (high risk) [19, 20]. We have previously demonstrated that Class 1 tumors respond faster to radiation therapy as seen by a decrease in tumor height, described practice patterns with regard to tumor biopsy technique, and correlated GEP with American Joint Commission on Cancer Staging [21, 22]. Here we report practice patterns for patients treated for uveal melanoma with I-125 plaque brachytherapy who concurrently underwent fine-needle aspirate biopsy for GEP testing of the melanoma, as well as current practice patterns at OOSC institutions as determined by a 2018 survey.

Material and Methods

Data Acquisition

This study analyzed data from 9 institutions in the OOSC: Duke Eye Center (coordinating center), Oregon Health and Science University/Casey Eye Institute, University of Miami/Bascom Palmer Eye Institute, University of Southern California/USC Roski Eye Institute, Smilow Cancer Center at Yale-New Haven Hospital, University of Michigan, Colorado Retina Associates/Rocky Vista University, Retina Specialists of Michigan, and Houston/Blanton Eye Institute at Houston Methodist Hospital. The OOSC database has been described in detail previously [21]. It is a multi-institutional retrospective database of patients with melanoma of the choroid or ciliary body. Eligible patients had a documented preoperative clinical diagnosis of uveal melanoma, underwent tumor biopsy for GEP testing immediately prior to treatment, and had at least 3 months of follow-up. GEP testing was reported between January 1, 2010 and June 30, 2014. Data are stored in a password-protected, encrypted Research Electronic Data Capture database. The current study includes only patients treated with I-125 plaque brachytherapy. Institutional Review Board approval was obtained at each participating institution.

Table 1. Treatment parameters for subjects included in the OOSC database. Rx/given is the ratio of prescribed dose to delivered dose

	Institution									
	Total	A	B	C	D	E	F	G	H	I
<i>Doses</i>										
Apex dose rate, cGy/h	85±25 (43–186)	77±11 (68–110)	61±11 (43–92)	114±4 (111–118)	79±11 (56–95)	111±30 (88–186)	93±15 (89–168)	69±17 (51–90)	60±11 (51–77)	82±15 (73–99)
Apex, Gy	93±21 (66–201)	79±5 (69–86)	123±32 (85–201)	80±8 (66–101)	100±13 (83–151)	Not reported	85±0 (all 85 Gy)	94±17 (85–129)	95±12 (84–126)	85±0.5 (84–87)
Apex Rx/given	1.11	1.13	1.45	0.94	1.18	Not reported	1.00	1.11	1.12	1.00
Optic nerve, Gy	39±28 (5–156)	Not reported	35±23 (6–101)	40±26 (5–111)	40±25 (8–100)	Not reported	29±17 (7–89)	41±31 (15–89)	85±42 (27–156)	Not reported
Fovea, Gy	55±47 (6–263)	Not reported	61±59 (6–263)	51±36 (7–147)	60±49 (8–195)	Not reported	36±23 (7–109)	40±28 (17–106)	94±43 (25–155)	Not reported
Lens, Gy	23±20 (5–134)	Not reported	22±18 (8–85)	22±14 (7–55)	27±20 (5–100)	Not reported	19±20 (5–134)	19±20 (5–134)	35±34 (13–109)	Not reported
<i>Margins, mm</i>										
Clinical margin	2.9±1.0 (0–6.4)	3.3±1.0 (1.2–6.2)	3.7±1.0 (0.8–5.5)	2.4±0.4 (1.8–3.4)	3.3±1.0 (2–6.4)	2.6±1 (1.0–5.0)	2.1±0.6 (0–4.5)	4.0±1.7 (0.3–5.5)	2.6±0.7 (1–3.6)	2.3±0.3 (1.6–3.3)
No notch	2.7±0.9 (0.3–6.2)	3.1±0.9 (1.2–6.2)	3.4±0.9 (0.8–4.5)	2.4±0.4 (1.8–3.2)	3.2±0.8 (2–5.3)	2.3±0.8 (1–3.5)	2.1±0.5 (1–4.5)	3.1±2.0 (0.3–4.9)	2.6±0.7 (1–3.3)	2.3±0.3 (1.6–3.3)
Notch	3.3±1.3 (0–6.4)	3.6±1.2 (2–5.8)	4.1±1.0 (2.3–5.5)	2.6±0.5 (2.2–3.4)	4.5±1.5 (2.7–6.4)	2.8±1.1 (2–5)	2.1±0.8 (0–3.5)	4.6±1.0 (3.0–5.5)	2.6±0.7 (1.5–3.6)	2.6±0.1 (2.5–2.8)

OOSC, Ocular Oncology Study Consortium.

For the retrospective study of treatment methods, only subjects with posterior uveal melanomas involving the ciliary body and/or choroid were included, as treatment considerations for iris tumors differ substantially, particularly with regards to calculating the clinical margin. Not all fields were complete for all patients. Only patients with all data needed for the particular question were included in that analysis. Of 428 possible subjects, 375 had information regarding whether a plaque was notched or non-notched, 334 had plaque size information, and 418 had fine-needle aspirate biopsy results. The number of subjects for further analysis within those groups was limited by available information. The total number of subjects included in analyses was 406. The average number of patients included per institution was 45.2 with a standard deviation of 20.2. The median number of patients included per institution was 50.

All OOSC institutions were asked to participate in the survey portion of this study, and a representative from radiation oncology or radiation physics at each institution completed a questionnaire regarding current and past treatment planning practices. Questions addressed planning methods, dosimetry, plaque selection, prescription, and imaging.

Data Analysis

The clinical margin was defined as the difference between the tumor basal diameter and the PTV and was calculated as follows: (plaque size – largest basal diameter by B scan ultrasound)/2. Difference in clinical margins between plaque types was compared using 2-tailed independent Student *t* tests. Differences between GEP classes were compared using 2-tailed independent Student *t* tests. Tumor location was identified by the ophthalmologist and could include >1 location. For example, a patient could have a tumor that extended to the equator and also had macula involvement. For this reason, normalized percent was used for tumor location versus clinical margin. The all institution averages in Table 1 are an average of all patients except for the Apex prescribed dose to delivered dose which is an average of the institution averages.

Results

Evaluation of the OOSC Database

Of the cases recorded in the OOSC database, 406 had sufficient information for inclusion (Table 2). Cases were equally distributed between genders (206 male, 200 female) and affected eye (205 right, 200 left). The average patient age at time of plaque insertion was 60 years (range 15–95). Average largest basal diameter was 7.8 mm (range 1–20.5), and average apical height was 4.6 mm (range 0.7–13). Most tumors were located between the macula and the equator with the second most common location between the equator and the ora serrata. Class 1 tumors were more common (278) than Class 2 tumors (119).

To examine the choice of plaque size, clinical margin, location, and tumor diameter were evaluated (Fig. 1, Table 1). Plaque size increased with tumor diameter. Overall, notched plaques were associated with a larger clinical

Table 2. Subject demographics for patients included in the OOSC database

Gender, <i>n</i>	
Male	206
Female	200
Age, years, median (IQR)	
At insertion	60 (15–94)
Affected eye, <i>n</i>	
Right	205
Left	200
Unknown	1
Tumor dimensions, mm, median (IQR)	
Basal diameter	7.8 (1–20.5)
Height	4.6 (0.7–13)
Location, <i>n</i>	
Macula	59
Equator to macula	171
Equator to ora	83
Ciliary	49
Peripapillary	38
Unknown	24
GEP class, <i>n</i>	
1A	190
1B	88
2	119
Unknown	9

OOSC, Ocular Oncology Study Consortium; GEP, gene expression profile.

margin than non-notched plaques, with an average clinical margin of $3.3 \text{ mm} \pm 1.3$ (0–6.4 mm) and $2.7 \text{ mm} \pm 0.9$ (0.3–6.2 mm) respectively ($p < 0.0001$). There were differences among clinical centers in the average clinical margin as well, with 2–3 mm clinical margins at 5 institutions, and 3–4 mm at 4 centers. In 2 cases, the clinical margin was >6 mm. The largest clinical margins were primarily used for peripapillary plaques.

Dosimetry information was available for 8 institutions. Of the institutions that reported dose to the apex (Table 1), 6 delivered average doses greater than or equal to 85 Gy, and 2 delivered average doses <85 Gy. Dose to the optic disc was consistent between all but one institution, which reported a higher average dose. Average dose to the optic disc was 39 Gy (5–156). Similarly, average dose to the macula was 55 Gy (6–263) and fairly consistent, and average lens dose was 23 Gy with all but 2 of the reporting institutions delivering <25 Gy.

2018 Practice Patterns

Discussions among members of the OOSC indicated that practice patterns were evolving at most institutions

over time, and therefore, a survey was developed to investigate current practice patterns. Practice patterns as of 2018 from responding institutions, as well as ABS recommendations, are shown in Table 3. All but one program has switched to image-based planning with Eye Physics Plaque Simulator software. Wide field fundus imaging with or without computed tomography (CT), magnetic resonance imaging, and/or optical coherence tomography is most commonly used in planning.

At most institutions, plaque choice is ophthalmology-driven, with the initial plaque size and type selected by the treating ocular oncologist. Interestingly, one institution does not choose plaque size based on the tumor basal dimension plus margin. Instead, they choose a plaque that delivers 95–100% of the prescription to the tumor + 2 mm base margin. In this case, the physicist/radiation oncologist selects the plaque based on a patient specific eye model created using a CT or magnetic resonance imaging. Most plaques are ordered pre-loaded with uniform seed strengths. One institution regularly prescribes 63 Gy to the prescription point using heterogeneity corrections with Eye Physics plaques. This delivers a physical dose that covers the tumor with at least a 2 mm lateral margin with approximately the same dose as 70 Gy prescribed with a COMS plaque because the radiation is attenuated approximately 10% in COMS plaques by the silastic membrane insert. All other institutions prescribe to 85 Gy as a first choice. Two institutions do not use any correction for an 85 Gy prescription, though they generate a corrected plan for comparison. Dose is prescribed to the tumor apex or beyond the apex for small tumors to improve coverage. Dose rates vary from 50 to 118 cGy/h. Two institutions observe optic disc and macula constraints (maximum dose <45 –50 Gy) when possible, and one institution observes a scleral constraint (maximum dose <400 Gy). Treatment planning at OOSC institutions is most variable with regard to dosimetry. Only 2 institutions follow COMS dosimetry, and all others include some heterogeneity correction. Most institutions correct for a line source and seed collimation.

Discussion

This study found good agreement between practices at different institutions both evaluating a retrospective database for patients treated 2010–2014, as well a follow-up survey-based approach in 2018. Most institutions follow TG-129 recommendations for dose, prescription point, and margin; however, some variation exists, particularly

Fig. 1. Choice of plaque size and clinical margin. **a** Plaque size increases with largest basal diameter. Mean and SD are shown. **b** There is no difference in clinical margin per plaque size. Mean and SD are shown. **c** 2–3 mm is the most common clinical margin, and ≤2 and 3–4 mm are also prevalent. **d** Peripapillary lesions were treated with the largest clinical margins.

in dosimetry. Although Plaque Simulator by Eye Physics is not FDA approved, it is currently the sole planning system for 7 of 9 institutions. No other widely available software based on AAPM TG-43 data corrects for carrier placement, plaque material and geometry, and the loss of surface scatter.

COMS initially recommended a prescription dose of 100 Gy; this was later changed to 85 Gy to reflect improved dose calculations [2, 3, 23]. With correction for anisotropy, line source geometry, plaque and lip collimation, geometric penumbra, gold and air scattering, and silastic insert attenuation, the 85 Gy using a COMS plaque is equivalent to 75 Gy at 5 mm depth on the central plaque axis [5]. These corrections reduce dose to tumor and OARs by 10–50% [5, 6]. Most OOSC institutions account for heterogeneity, but only one uses a corrected dose for Eye Physics plaques that lack the silastic mem-

brane and therefore deliver a higher physical dose to the tumor and normal tissues compared to COMS plaques for the same prescription dose. All others continue to prescribe to 85 Gy, which delivers a higher physical dose to the tumor and normal tissues than needed when heterogeneity corrections are applied. While higher prescription dose may compensate for deficiencies in coverage, this potential advantage needs to be considered in the context of increased radiation dose to normal tissues, which likely increases ocular toxicity.

Similarly, dose rates impact both treatment efficacy as well as toxicity. By TG-43, COMS prescribed 42–105 cGy/h, and ABS recommends no <60 cGy/h [2, 4]. This is based on a 1996 publication analyzing tumor dose and dose rate. Quivey et al. [24] found greater local control for apex dose rates ≥50 cGy/h. This is in agreement with other studies that found control and survival rates compa-

Table 3. 2018 practice patterns as determined by survey responses

ABS, TG 129	Institution								
	A	B	C	D	E	F	G	H	I
Planning program	FDA approved software	Eye physics plaque simulator	Pinnacle and eye physics plaque simulator	Eye physics plaque simulator	Eye physics plaque simulator	Eye physics plaque simulator	Eye physics plaque simulator	Eye physics plaque simulator	Eye physics plaque simulator
Year changed to current method	2016	2013	2015	2016	2015	2013	1995	2013	2017
Imaging	Fundus image, ultrasonographs, and/or CT and MRI	Fundus image and CT	Fundus image ± CT/MRI	Fundus image	CT	Fundus image and OCT	Fundus image and CT	Ultrasound	Fundus image AND ultrasound AND CT
Fundus camera	Not reported	Wide field	Wide field and standard	Standard		Wide field and standard	Wide field and standard		Wide field
Plaque style	Eye physics	Eye physics	COMS style	COMS style	Eye physics	COMS style	Eye physics	COMS style	Eye physics and COMS style
Who chooses plaque size	Not reported	Ophthalmology	Ophthalmology	Ophthalmology	Medical physics	Ophthalmology and radiation Oncology	Medical physics	Ophthalmology	Ophthalmology
Plaque margin, mm	3.27±1.00 (1.15–6.17)	3.62±1.02 (0.75–5.5)	2.42±0.40 (1.75–3.35)	3.40±1.00 (2–6.4)	2.34±1.46 (–2–3.5)	2.24±0.97 (0–7.7)	4.08±1.63 (0.29–5.53)	2.6±0.7 (1–3.6)	2.3±0.3 (1.6–3.3)
Margin no notch, mm	3.13 ±0.91 (1.15–6.17)	3.38±0.90 (0.75–4.5)	2.38±0.37 (1.75–3.2)	3.27±0.86 (2–5.3)	1.69±1.67 (–2–3.5)	2.27±1.01 (1–7.7)	3.52±2.05 (0.29–5.41)	2.6±0.7 (1–3.3)	2.3±0.3 (1.6–3.3)
Margin notch, mm	3.64±1.15 (2–5.75)	4.13±1.05 (2.25–5.5)	2.56±0.54 (2.15–3.35)	4.49±1.50 (2.7–6.4)	2.82±1.15 (2–5)	2.14±0.79 (0–3.5)	4.63±1.00 (3.04–5.53)	2.6±0.7 (1.5–3.6)	2.6±0.1 (2.5–2.8)
Plaque loading	Pre-loaded	Pre-loaded	Pre-loaded	In house	Pre-loaded	Pre-loaded	Pre-loaded	Pre-loaded	Pre-loaded
Isotope	I-125	I-125	I-125	I-125	I-125	I-125	I-125	I-126	I-127
Seed uniformity	Uniform	Uniform	Primarily uniform, 2 activities if needed for sparing or coverage	Primarily uniform, 2 activities if needed for sparing or coverage	Uniform	Uniform	Variable	Uniform	Uniform
Duration, h	96	168	72	100	96	100	168	120–168	89–96
Prescription dose, Gy	63	85	85, 75–80 to spare sclera	85	85	85	85	85	85
Dose rate, cGy/h	66	51	118	85	89	85	51	50	88–100
Prescription point	Tumor apex, add height to achieve coverage as needed	≥5 mm: tumor apex, <5 mm: 5 mm from inner sclera	Tumor apex ±1 mm, short tumors: beyond apex	≥5 mm: tumor apex, <5 mm: 1 mm beyond apex	≥5 mm: tumor apex, <5 mm: tumor apex + margin	Tumor apex, add height to achieve coverage as needed	≥5 mm: tumor apex, <5 mm: tumor apex + margin	≥5 mm: tumor apex, <5 mm: tumor apex + margin	≥3.5 mm: Tumor apex, <3.5 mm: 3.5 mm
Normal tissue constraints	None	None	Optic disc Dmax <45 Gy, macula Dmax <45 Gy	Sclera Dmax <400 Gy	Optic disc Dmax <50 Gy, macula Dmax <50 Gy	None	None	None	None
General corrections	Linear source model, 2-D anisotropy function	Linear source model, 2-D anisotropy function, air scatter correction	Linear source model, 2-D anisotropy function	Linear source model, 2-D anisotropy function, air scatter correction	Linear source model, 2-D anisotropy function	None	Linear source model, 2-D anisotropy function	None	Linear source model, 2-D anisotropy function, air scatter correction
COMS corrections	Homogeneous water AND silastic carrier attenuation, lipped collimation, and shell collimation ^b	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation	Silastic carrier attenuation, lipped collimation, shell collimation
Eye physics corrections	Gold correction, slotted collimation	Gold correction, slotted collimation	Gold correction, slotted collimation	Gold correction, slotted collimation	Slotted collimation	Gold correction, slotted collimation	Gold correction, slotted collimation	Gold correction, slotted collimation	Gold correction, slotted collimation
CT, computed tomography; COMS, Collaborative Ocular Melanoma Study; ^a American Brachytherapy Society (ABS) dose rate recommendation is ≥60 cGy/h; American Association of Physicists in Medicine Task Group-43 (TG-43) recommendation is 42–105 cGy/h. ^b It is recommended by the ABS and AAPM to use homogeneous water for dose calculation but to simultaneously calculate heterogeneity corrected doses for comparison.									

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rable to those in the COMS study for dose rates as low as 58–63.5 cGy/h [10, 11]. However, it is difficult to compare recent studies to earlier work, given differences in plaque type and updated standards. Based upon survey responses, 2 institutions reported an average apex dose rate of <60 cGy/h, both of which correct for heterogeneity. This is in line with recommendations when they are corrected (51–89 cGy/h) [25]. The highest dose rate reported, 118 cGy/h, is slightly above the COMS recommendation of 105 cGy/h. Often in real-world practice, considerations such as availability of operating room time may impact the dose-rate used.

Prescription point is an issue debated in literature. TG-129 recommends prescribing to the apex or 5 mm if the tumor is <5 mm [5]. While all institutions but one prescribe to the apex for tumors ≥ 5 mm, prescription practices for tumors <5 mm vary. Our survey results and the literature demonstrate that the tradeoff of better coverage and adequate dosing versus excessive toxicity is far from settled [7–10, 12, 13]. Prescribing to the apex for tumors <5 mm, particularly large or thin tumors, may result in low basal doses, and there is concern that there is insufficient margin to avoid error for tilted or displaced plaques [7, 8, 13]. Supporting the argument of prescribing to the apex for tumors <5 mm, one retrospective study compared 10-year outcomes for patients prescribed 85 Gy to the apex or 5 mm. No difference in local recurrence, distant metastasis, or disease specific death was found, but rates of radiation retinopathy and cataract were more than doubled for the 5 mm dosing arm [9]. In such cases, 2 OOSC institutions regularly prescribe to 5 mm for tumors <5 mm in height, one prescribes to 3.5 mm for tumors smaller than 3.5 mm, and others prescribe to the apex with a margin. All prescribe beyond the apex if needed to improve coverage.

Radiation planning accounts for inherent and treatment specific uncertainties through the use of margins. For plaque brachytherapy, uncertainties in tumor size/edge location, plaque location, plaque movement during treatment, and dosimetry contribute to the PTV [7]. ABS recommends a clinical margin of 2–3 mm. However, other factors affect plaque size selection. Among surveyed OOSC centers, the treating ocular oncologist most commonly chooses the plaque based on the ABS recommendation and surgical considerations. Minimizing uncertainty with regard to tumor dimensions, dimensions of the eye being treated, and the intraoperative plaque location promises to reduce required clinical margins without compromising treatment effectiveness. This can be achieved by utilizing fundus images and orbital imaging

in treatment planning as well as confirming accurate intraoperative placement of the plaque with methods such as intraoperative ultrasound. Currently, most OOSC institutions use wide field fundus imaging for planning purposes. Some also use CT, which may improve the reliability of calculations, as it has been reported that variations in eye size and anatomy lead to inaccuracies in doses predicted by the stylized-standard model, particularly for optic disc dose calculation when the tumor is close to the optic nerve [18]. With one exception, all institutions use preloaded plaques. Three of 9 institutions use non-uniform seed strength. A high degree of confidence in tumor volume and location are needed in order to take advantage of non-uniform loading.

This study is limited by the content of the OOSC database and the number of centers responding to the follow-up survey. This content is self-reported from the 9 institutions that comprise the OOSC. While these are all tertiary referral centers, they may not reflect practice patterns across the US, and treatment patterns may not reflect current trends as these may evolve over time. We attempted to capture this information through a follow-up survey of OOSC institutions, which collected information from all 9 centers. The database only includes patients that were eligible for and underwent biopsy for GEP testing, which could bias results, as some patients with tumors not amenable to biopsy, such as very small tumors, may have been excluded. Future studies comparing treatment planning practices among a wider range of institutions would be of interest, with inclusion of centers outside the United States being of particular interest, as practice patterns, including choice of radioisotope, are known to vary. All centers included in our study use Iodine-125 exclusively for treatment of uveal melanoma.

Although there were differences in dosimetric practices and prescription dose, there was otherwise good agreement among plaque brachytherapy practices at the participating OOSC institutions. Clinical margins and planning methodology were similar among institutions. With newer technology that allows accurate dose calculations to normal structures and improved tumor dose, refinement of plaque brachytherapy techniques to maximize control while minimizing radiation toxicity will likely be possible. Further studies are required to refine uncertainties in planning and to determine a minimally effective dose and margin for achieving local control. Variability in real-world clinical practice highlights the importance of prospective multi-center collaboration in defining treatment parameters.

Statement of Ethics

This study was institutional review board approved and conducted in compliance with the Declaration of Helsinki.

Disclosure Statement

P.M.: consultant – Castle Biosciences, Optos Inc.; personal fees – Santen, Spark Therapeutics. J. William Harbour: consultant and royalties – Castle Biosciences. Miguel Materin and A.C.S.: consultant – Castle Biosciences. Thomas Aaberg Jr.: consultant – Castle Biosciences, Alcon, Baush, and Lomb, True Vision, Regeneron. Peter Hovland: advisory panel – Castle Biosciences. D.G.K.: scientific advisory board, own equity, and royalties – Lumicell Inc., co-founder and own equity – XRAD therapeutics. Research support: Merck, Eli Lilly, and Bristol-Myers Squibb. Jesse Berry: consultant – Immunocore. A.H.S.: consultant – Castle Biosciences, Immunocore. The other authors have no conflicts of interest to disclose.

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