

Regression patterns of choroidal melanoma: After palladium-103 (¹⁰³Pd) plaque brachytherapy

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Abstract

Purpose: To describe the patterns of regression of choroidal melanoma after treatment with plaque brachytherapy.

Methods: Retrospective interventional case series including 170 consecutive patients treated with ¹⁰³Pd eye plaque radiation for choroidal melanoma. Outcome measures were changes in tumor thickness, surface characteristics, tumor vascularity, ultrasonography, fluorescein angiography, optical coherence tomography, and histopathology.

Results: The mean initial tumor thickness was 3.9 mm (median 2.8 mm; range 2–11.3 mm) that decreased to 1.7 mm (median 1.2 mm; range 0–7.1 mm) after plaque brachytherapy. On imaging, tumors were pigmented in 51% ($n=86/170$), amelanotic in 10% ($n=17/170$), and variably pigmented in 39% ($n=67/170$). Tumor pigmentation increased in 64% ($n=106/166$), decreased in 18% ($n=30/166$), and was unchanged in 18% ($n=30/166$). Of the 120 that demonstrated intrinsic vascularity, 10% ($n=12/120$) had decreased tumor-related vascularity and 90% ($n=108/120$) showed complete resolution. Subretinal fluid was present in 34% ($n=58/170$) of eyes at presentation. Of them, 15% ($n=9/58$) had persistent SRF at last follow-up. On ultrasound imaging, 88% ($n=149/170$) tumors presented with low to moderate internal reflectivity of which 61% ($n=91/149$) showed increased reflectivity on regression. We noted a crescendo–decrescendo fluctuation in the presence of orange pigment lipofuscin along with complete resolution of drusenoid retinal pigment epithelial detachments. In the entire series of 170 patients, there was 0.5% (1) failure of local control, 2% (4) secondary enucleations, and 6% (10) patients developing metastasis.

Conclusion: Findings related to choroidal melanoma regression after ¹⁰³Pd plaque brachytherapy included decreased intrinsic tumor vascularity, decreased tumor-related subretinal fluid, increased pigmentation, specific changes in orange pigment lipofuscin and resolution of drusenoid retinal pigment epithelial detachments, as well as decreased tumor thickness with an increase in internal reflectivity on ultrasound.

Keywords

Choroidal melanoma, regression, pigment, exudative, ultrasound

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Introduction

Radiation has increasingly replaced enucleation as an eye and vision-sparing alternative treatment for uveal melanoma. Five-year mean local control rates of up to 97% have been reported.¹ Though tumor size is the most well validated predictor of metastatic disease, the importance of initial local control cannot be understated.^{2,3} In 2016, a multicenter, international data-sharing study involving 3217 patients reported significantly increased risk (6.3 hazard ratio) of metastasis if their initial uveal melanoma treatment fails.^{3,4}

Death typically follows metastasis, because there exists no curative treatment for metastatic uveal

melanoma. In that local tumor recurrence has been proven to be associated with a significantly higher risk of systemic metastasis,⁴ definitive local control (to prevent recurrence-related added metastatic risk) is currently the best way to “treat” metastatic uveal melanoma.^{3,4}

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That said, the best way to make plaque radiation therapy effective is to follow consensus guidelines for medical physics measurements and clinical application.^{5,6} Both the American Association of Physicists in Medicine (AAPM) and the American Brachytherapy Society (ABS) have sponsored multicenter, international efforts to define quality assurance, medical physics practices, and consensus guidelines. The ABS standards were created by 47 eye cancer specialists from 10 countries.⁶

In 1990, P.T.F. initiated the first preclinical and clinical studies using ¹⁰³Pd ophthalmic plaques for treatment of choroidal melanomas.^{7,8} Since that time, multiple comparative dosimetry studies (including those of the AAPM TG-129) have demonstrated that in comparison to iodine-125 (¹²⁵I), ¹⁰³Pd photons are more rapidly absorbed within uveal melanomas, while less radiation reaches most normal ocular structures.^{5,9,10} These attributes, coupled with careful ¹⁰³Pd plaque-size selection (2- to 3-mm safety margins) and precise episcleral placement, has yielded some of the highest reported rates of local control associated with low rates of metastatic melanoma.^{11,12}

Once irradiated, eye cancer specialists are tasked with monitoring the tumor for regression and recurrence. Prior descriptions of uveal melanoma regression have largely concentrated on tumor-size (typically height) following brachytherapy with cobalt (⁶⁰Co), iodine (¹²⁵I) and ruthenium (¹⁰⁶Ru) plaques, charged particles, and gamma knife.¹³⁻²⁴ However, in 1982, Wilkes and Gragoudas²⁵ examined choroidal melanoma regression after proton beam irradiation, where they considered tumor thickness, pigmentation, vascularity, and subretinal fluid (SRF). Most recently, our group described regression patterns of iris melanoma following ¹⁰³Pd plaque.²⁶ Therein, we noted that tumor vascularity, pigmentation, and thickness were the most important parameters when looking for regression.

In this era of a shifting paradigm toward eye and vision-sparing radiation, it is important to know which tumor characteristics are associated with local control. Herein, we describe the clinical features of regressing choroidal melanomas seen after ¹⁰³Pd plaque brachytherapy.

Methods

This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. We obtained approval from The New York Eye Cancer Center Internal Review Board to perform a retrospective chart review of 170 consecutive patients who met our inclusion criteria and had undergone ophthalmic plaque brachytherapy for choroidal melanoma between 2001 and 2012.

To provide a long-term perspective, no patients treated after 2012 were included in this study. Specific inclusion criteria were patients with at least 1-year follow-up, tumors

not involving ciliary body, tumors in which location allowed observation, eyes in which media permitted adequate fundus photography, optical coherence tomography (OCT), fundus auto fluorescence (FAF), ultrasonography, and fluorescein angiography (FA).

Ophthalmic examinations were inclusive of but not limited to history, Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, pupillary reactions, ocular motility, intraocular pressure, anterior segment, and fundus examination. Features recorded at presentation included tumor pigmentation (melanotic, amelanotic, or variable), tumor epicenter quadrant, and tumor location (posterior, equatorial, or anterior).

Fundus photography was used to determine the presence of orange pigment lipofuscin (OP) and drusenoid retinal pigment epithelial detachments. FA was used to evaluate tumor intrinsic vascularity as well as SRF. OCT was most sensitive for the presence of SRF as was FAF for OP. Ultrasonography was primarily used to determine tumor configuration (dome or mushroom-shaped), internal tumor reflectivity (low, moderate, or high), tumor basal dimensions, and tumor thickness.

Initial American Joint Committee on Cancer (AJCC) staging involved whole-body positron emission tomography-computed tomography (PET-CT).²⁷ Post-treatment surveillance involved abdominal radiographic imaging every 6 months for the first 5 years and then every year thereafter. Based on the American College of Radiology Appropriateness Criteria for hepatic metastasis, the order of sensitivity was contrast-enhanced magnetic resonance imaging, computed tomography, and lastly ultrasound imaging.²⁸

For this study, local recurrence was defined as ≥ 0.5 mm of apical tumor growth (by ultrasonography) or ≥ 1 mm of vascularized marginal growth (by comparative fundus photography and FA). Hemorrhagic or exudative tumor enlargement was observed for regression prior to being considered growth.

Palladium-103 plaque radiation therapy

Comparative preoperative dosimetry (¹²⁵I vs ¹⁰³Pd seeds in gold ophthalmic plaques) were performed for each patient in this series. Plaque parameters included plaque size, type of plaque, apical tumor dose, and hours of irradiation. Critical ocular structures were defined as the tumor, sub-jacent sclera, lens, fovea, and central optic disc. Calculations of dose to opposite eye wall most closely represented organ dose. This analysis resulted in the use of ¹⁰³Pd in every case.^{5,10}

In this series, plaque treatments were consistent with the 2014 multicenter international ABS consensus guidelines for plaque brachytherapy of uveal melanoma. Therefore, surgery comprised tumor localization and plaque insertion, including scleral trans-illumination and

Table 1. Dosimetry and plaque treatment parameters.

Variable	Value	
Plaque size (mm), no. (%)	10	4 (2)
	12	17 (10)
	14	57 (34)
	16	48 (28)
	18	25 (15)
	20	12 (7)
¹⁰³ Pd seeds, no.	22	7 (4)
	Median	13
	Mean	15
Radiation dose to tumor apex (Gy)	Range	5–30
	Median	80
	Mean	79.5
Dose to lens (Gy)	Range	5.9–99.8
	Median	6.5
	Mean	11.2
Dose to fovea (Gy)	Range	0.9–100.3
	Median	33.8
	Mean	53.9
Dose to optic nerve (Gy)	Range	2.6–291.9
	Median	32.4
	Mean	47.2
Duration of treatment (hours)	Range	3.6–257.3
	Median	166
	Mean	164.1
	Range	118–172

¹Gray (Gy) = 100 cGy.

intraoperative ultrasound to define tumor margins.²⁹ Each plaque was constructed and placed to cover the entire tumor plus a 2- to 3-mm tumor-free safety margin.^{5,6,30} All patients received continuous radiation for 5–7 days.⁶

The mean tumor apex palladium-103 radiation dose was a mean 79.5 Gray (Gy) (median 80 Gy; range 5.9–99.8 Gy). The mean plaque size was 15 mm (median 16 mm; range 10–22 mm; Table 1).

Follow-up

As possible, posttreatment fundus photography, ultrasonography, OCT, and FAF were obtained every 3–4 months after brachytherapy. FA was typically performed every 6 months to monitor changes in tumor vascularity, radiation retinopathy, and optic neuropathy. Ultrasound-imaging was used to measure the tumor and monitor for extra scleral extension. At each visit, these test results were compared with the patient's prior test examinations.

Results

The mean age of the patients was 61.3 years (median 63 years; range 22–86 years). The mean follow-up duration was 71 months (median 69.5 months; range 12–201 months).

Table 2. Patient demographic data and pretreatment tumor classifications.

Features	Categories	No.	%
Race	White	161	95
	Hispanic	5	3
	Asian	3	2
Gender	Male	91	54
	Female	79	46
Eye	Right	75	44
	Left	95	56
Associated comorbidities	Hypertension	64	38
	Diabetes	19	11
	Other cancers	24	14
Tumor epicenter quadrant	Superotemporal	57	34
	Inferotemporal	52	30.5
	Superonasal	24	14
	Inferonasal	32	19
	Foveal	4	2
Tumor location	Disc	1	0.5
	Posterior	129	76
	Equatorial	24	14
AJCC staging ^a	Anterior	17	10
	T1	86	51
	T2	59	35
	T3	21	12
	T4	4	2

^aAccording to American Joint Committee on Cancer (AJCC) cancer staging manual, eighth edition.³¹

The mean initial largest basal tumor dimension was 11 mm (median 10.2 mm; range 4–19.4 mm). According to the 8th edition of the American Joint Committee on Cancer staging system for uveal melanoma, there were 86-T1, 59-T2, 21-T3, and 4-T4 sized tumors (Table 2).³¹

Data were available from all 170 patients at 1 year, 136 patients at 3 years, 101 patients at 5 years, and 22 patients at 10 years of follow-up. Data were analyzed for regression patterns with respect to changes in tumor thickness, pigmentation, and vascularity changes in ultrasonography and OCT features at 1-, 3-, 5-, and 10-year follow-up (Table 3).

Comparison of regression characteristics before and after treatment

Change in tumor size on ultrasound. The mean initial tumor thickness was 3.9 mm (median 2.8 mm; range 2–11.3 mm) which reduced to 1.7 mm (median 1.2 mm; range 0–7.1 mm) at last follow-up. Radiation induced a mean 44% reduction in thickness in this series. All tumors showed reduction in tumor thickness except the one with recurrence.

Ultrasonographic internal reflectivity prior to radiation revealed that 13% ($n=22/170$) tumors with low, 75% ($n=127/170$) moderate, and 12% ($n=21/170$) were highly reflective. Of the tumors with low to moderate internal

Table 3. Regression pattern analysis at 1, 3, 5, and 10 years.

Feature	Before surgery (n = 170)	1 year (n = 170)	3 years (n = 136)	5 years (n = 101)	10 years (n = 22)	Last follow-up (mean 6 years; n = 166)
Mean tumor thickness (mm)	3.9	2.4	1.5	1.4	0.7	1.7
Pigmentation, no. (%)	170 (100)	n = 170	n = 136	n = 101	n = 22	n = 166
Increased		123 (73)	84 (62)	62 (61)	11 (50)	106 (64)
Decreased		16 (9)	28 (20)	20 (20)	6 (27)	30 (18)
Persistent		31 (18)	24 (18)	19 (19)	5 (23)	30 (18)
Orange pigment, no. (%)	136 (80)	n = 170	n = 136	n = 101	n = 22	n = 166
Present		144 (85)	39 (29)	14 (14)	2 (9)	37 (22)
Absent		26 (15)	97 (71)	87 (86)	20 (91)	129 (78)
Subretinal fluid, no. (%)	58 (34)	n = 170	n = 136	n = 101	n = 22	n = 166
Absent		116 (68)	112 (82)	83 (82)	21 (95)	117 (70)
Persistent		54 (32)	24 (18)	18 (18)	1 (5)	49 (30)
Intrinsic vascularity, no. (%)	120 (70)	n = 120	n = 86	n = 34	n = 10	n = 120
Resolved		20 (17)	29 (34)	25 (74)	10 (100)	108 (90)
Persistent		100 (83)	57 (66)	9 (26)	0 (0)	12 (10)
Internal reflectivity, no. (%)	170 (100)	n = 170	n = 136	n = 101	n = 22	n = 166
Low		21 (12)	7 (5)	0 (0)	0 (0)	6 (4)
Moderate		63 (37)	39 (29)	30 (30)	0 (0)	48 (29)
High		86 (51)	90 (66)	71 (70)	22 (100)	112 (67)

reflectivity, 61% ($n=91/149$) demonstrated an increase in internal reflectivity (Table 4). Tumors that started with high internal reflectivity remained highly reflective.

Ultrasonographic shape prior to radiation revealed 87% ($n=148/170$) to be dome-shaped and 13% ($n=22/170$) to form a mushroom shape. Of the dome-shaped tumors, 58% ($n=86/148$) remained dome-shaped and 41% ($n=61/148$) became flat. Of the mushroom shaped tumors, 86% ($n=19/22$) maintained their mushroom shape with reduced thickness. No patient had evidence of extra scleral extension.

Change in tumor color. Fundus photography revealed that 51% ($n=86/170$) of tumors were pigmented, 39% ($n=67/170$) were variably pigmented, and 10% ($n=17/170$) were amelanotic. At the last follow-up, tumor pigmentation was found to be increased in 64% ($n=106/166$), decreased in 18% ($n=30/166$), and unchanged in 18% ($n=30/166$; Figure 1).

At last follow-up, subgroup analysis of the 129 tumors located posterior to the equator, 61% ($n=79/129$) became more pigmented, 22% ($n=29/129$) variably pigmented, and 13% ($n=17/129$) became atrophic scars. Of tumors centered at the equator, 91% ($n=22/24$) became more pigmented. Of interest, 76% ($n=13/18$) of the anteriorly located tumors became atrophic scars.

Change in OP. Clinically: at presentation, 50% ($n=85/170$) tumors had granular and 30% ($n=51/170$) had gross OP. After 1 year of treatment, OP was present in 85% ($n=144/170$). After 3 years of treatment, OP diminished to 29% ($n=39/136$) and almost disappeared to 9% ($n=2/22$) after 10 years. It is important to note that 14% ($n=12/85$)

had persistent granular and 49% ($n=25/51$) had persistent gross OP at the last follow-up (Figure 1).

Imaging observations: on fundus autofluorescence, 25% ($n=42/170$) tumors had granular and 12% ($n=20/170$) had gross orange pigmentation. At the last follow-up, 19% ($n=8/42$) had persistent granular and 85% ($n=17/20$) had persistent gross OP. It is important to note that the patient who developed recurrence showed increase in orange pigmentation on autofluorescence at the site of recurrence.

Changes in OCT. Subretinal fluid (SRF) was present in 34% ($n=58/170$) eyes, out of which, 45% ($n=26/58$) had apical, 31% ($n=18/58$) had dependent, and 24% ($n=14/58$) had subfoveal fluid. After 18 months of treatment, resolution of SRF began and only 15% ($n=9/58$) patients had persistent SRF due to tumor at last follow-up. The dependent SRF resolved in all patients and 24% ($n=40/166$) patients developing radiation maculopathy/retinopathy ended up with persistent intraretinal fluid in the macular retina.

Drusenoid retinal pigment epithelial detachments (DRPED) were present on 18% ($n=30/170$) of tumors prior to radiation. All ($n=30/30$) of these tumors showed resolution of DRPED at last follow-up (Figure 1).

Changes on FA. On FA, dot micro-aneurysms were noted in 59% ($n=100/170$) and intrinsic tumor vessels in 12% ($n=20/170$) tumors prior to radiation. At last follow-up, 88% ($n=88/100$) of micro-aneurysms had resolved. Similarly, 100% ($n=20/20$) of intrinsic tumor blood vessels had resolved.

Table 4. Comparison of regression characteristics before and after treatment.

	Features	Characteristics	Before Rx (n = 170)		After Rx (n = 166)	
			No.	%	No.	%
Clinically	Pigmentation	Pigmented	86	51	106	64
		Amelanotic	17	10	30	18
		Variable	67	39	30	18
	Orange pigment	Granular	85	50	12	7
		Gross	51	30	25	15
		Absent	34	20	129	78
FAF	Orange pigment	Granular	42	25	8	5
		Gross	20	12	17	10
		Absent	29	17	47	28
		N/A	79	46	94	57
OCT	Drusenoid retinal pigment epithelial detachments	Present	30	18	0	0
		Absent	140	82	166	100
	Subretinal fluid	Apical	26	16	9	6
		Dependent	18	10	0	0
		Foveal	14	8	40	24
		Absent	112	66	117	70
FFA	Intrinsic vascularity	Microaneurysms	100	59	12	7
		Vessels	20	12	0	0
		Absent	50	29	154	93
USG	Tumor configuration	Dome	148	87	86	52
		Mushroom-shaped	22	13	19	11
		Flat	0	0	61	37
	Internal reflectivity	Low	22	13	6	4
		Moderate	127	75	48	29
		High	21	12	112	67

FAF: fundus auto fluorescence; OCT: optical coherence tomography; FFA: fundus fluorescein angiography; USG: ultrasonography.

Visual acuity. Pretreatment visual acuities were a median of 20/25 (mean, 20/32; range, 20/16 to counting fingers). They decreased to a median of 20/32 (mean, 20/63; range, 20/16 to no light perception) at a mean 71 months follow-up (Table 5).

Subgroup analysis revealed that out of 80% ($n = 136/170$) who had a baseline acuity of 20/16–20/40, 66% ($n = 89/136$) retained 20/16–20/40 at last follow-up. Reductions in visual acuity in 18 patients was attributed to radiation induced retinopathy and maculopathy.

Subgroup analysis of the 14% ($n = 24/170$) who had a baseline acuity of 20/50–20/200 showed that 25% ($n = 6/24$) improved to 20/16–20/40, and 42% ($n = 10/24$) retained 20/50–20/200 at last follow-up.

Subgroup analysis of the 6% ($n = 10/170$) who had a baseline acuity of <20/200, 10% ($n = 1/10$) improved to 20/50–20/200, and 90% ($n = 9/10$) continued with <20/200 at last follow-up. This finding was mainly attributed to tumor location beneath the fovea or involving the optic disc.

Cataract and radiation vasculopathy. Of the patients who were phakic at the time of treatment 10% ($n = 15/151$)

developed radiation-induced cataract. These cataracts were considered as acceptable and safely treatable consequences related to plaque brachytherapy.

Radiation retinopathy alone was the most common cause of treatment-related vision loss present in 48% ($n = 82/170$) patients. All patients were examined for the presence of radiation maculopathy and radiation optic neuropathy (RON) and were staged according to the Ophthalmic Radiation Oculopathy for Vision Prognosis Classification.³² No radiation oculopathy (Stage 0) was noted in 41% ($n = 69/170$) eyes at last follow-up. Stages 1–3 retinopathy was noted in 44% ($n = 75/170$). Stage 4 retinopathy primarily characterized by vitreous hemorrhage and RON was noted in 15% ($n = 26/170$). Initiated at the first clinical sign of neuropathy or maculopathy, 96 patients have been treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy to suppress radiation-induced retinopathy or/and optic neuropathy.^{33–35}

Unusual regression patterns. Seven irradiated melanomas were found to evolve into peculiar donut configuration (atrophy surrounded by pigmentation surrounded by atrophy) at last follow-up. All these tumors shared the

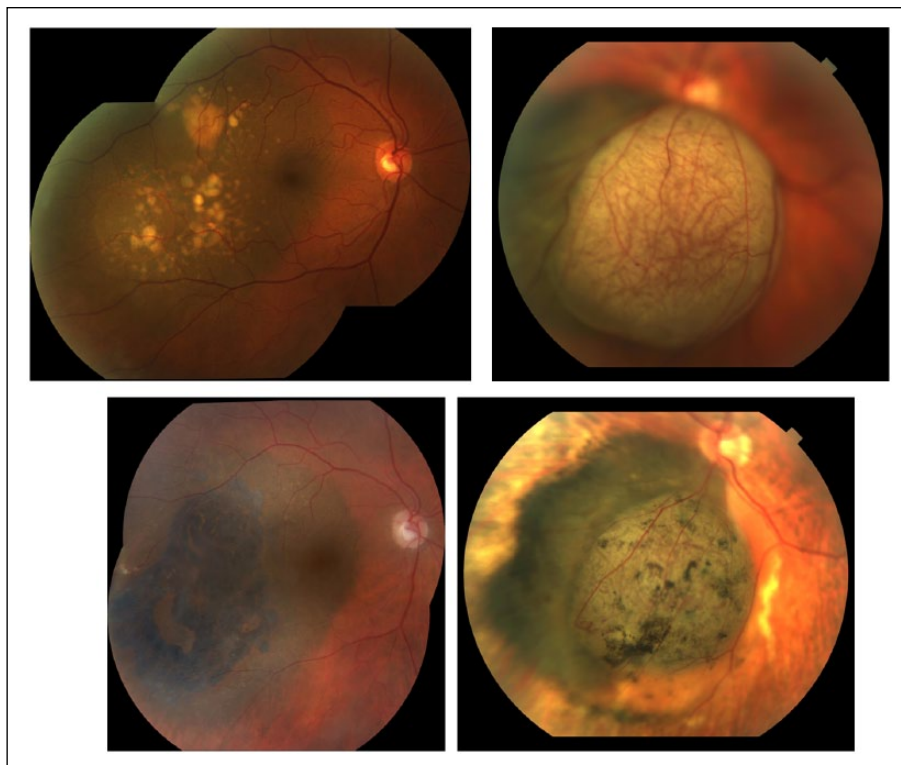


Figure 1. Fundus photographs of a T2-sized choroidal melanoma (top left) before surgery and (bottom left) 8 years after brachytherapy. Note the change in pigmentation to bluish black, resolution of DRPEDs, and increase in orange pigment lipofuscin. Fundus photographs of a mushroom-shaped choroidal melanoma (top right) before surgery and (bottom right) 3 years after brachytherapy. Note the resolution of intrinsic tumor vascularity.

common features of posterior location and an overlying fibrotic component prior to radiation therapy.

Also, melanomas with a mushroom-shape regressed such that the main body of the tumor shrunk, the mushroom configuration persisted, though to a darker color.

Histopathology. On histopathological evaluation of the four enucleated eyes, 75% ($n=3/4$) had 1–2 mitotic figures/40 high-power fields showing that cells can enter mitosis even after irradiation. As radiation induces programmed DNA-damage-mediated cell death, the cytotoxic effect becomes histopathologically apparent only when cells enter mitosis over subsequent years.³⁶ In addition, no radiation-treated choroidal melanoma was reported to have vascular loops. Thus, these four cases offer histopathologic corroboration of our angiographic observations that resolution of vascularity was a consistent finding associated with tumor regression.

Tumor resolution and metastasis. In this series, local tumor control (no recurrence) was achieved in 99.5% ($n=169/170$) patients. Eye retention was seen in 98% ($n=166/170$) patients. Four (2%) patients ($n=4/170$) required secondary enucleation for neovascular glaucoma. Ten (6%) patients ($n=10/170$) developed metastasis.

Discussion

In this study, side-by-side comparison of fundus photographs, OCT, FA, and ultrasonography from each follow-up visit was useful for detecting changes in pigmentation, SRF, vascularity, tumor size, and reflectivity after treatment.

Ultrasonography

Radiation induced a mean 44% reduction in tumor thickness in this series. We observed that the signs of tumor regression are decreased tumor thickness along with increased internal reflectivity.

Tumor color

At last follow-up, tumor pigmentation was found to be increased in 64% ($n=106/166$) eyes. The tumors that were pigmented at presentation typically developed a dark bluish hue. Tumors located in the posterior and equatorial fundus typically regressed with increased pigmentation, whereas the tumors located in the anterior position more commonly regressed to chorioretinal atrophy. This may be due a vaso-occlusive radiation effect on the thinner peripheral choroid.

Table 5. Complications and visual, ocular, and systemic outcomes at last follow-up.

	Variable	No. (n = 170)	%	
Complications	Dry eye	0	0	
	Scleromalacia	0	0	
	Cataract ^a	15	9	
	Glaucoma (including NVG)	10	6	
	Radiation retinopathy	82	48	
	Radiation maculopathy	26	15	
	Radiation optic neuropathy	24	14	
Outcomes	Vision outcomes ^b	Good (20/16–20/40)	95	56
		Intermediate (20/50–20/200)	39	23
		Poor (<20/200)	36	21
	Ocular outcomes	Tumor recurrence	1	0.5
		Enucleation	4	2
		Eye salvage	166	98
	Systemic outcomes	Distant metastases	10	6
No distant metastases		160	94	

NVG: neovascular glaucoma.

^aNew onset and worsening of preexisting disease.

^bFinal best-corrected visual acuity.

Orange Pigment

OP has been found after damage to various other human tissues like heart, liver, colon, and testis and is considered to be a nonspecific sign of cell death.³⁷ In this study, we have noticed that OP gradually increased over the first 3 years after radiation. The clumps of gross OP consolidated and became more prominent, as if the OP revealed itself or more likely increased after treatment. Tumors that started with granular OP evolved to reveal gross OP. Then, 3 years after treatment, OP declined and almost disappeared after 5–10 years of treatment. This latter finding, and as we observed on our solitary recurrence, suggests that the presence of new OP should be considered along with other signs of recurrence.

Radiation vasculopathy

Leakage from the tumor decreased within first 3 years as the tumor regressed. However, radiation-related exudative retinal changes started to appear between 18 and 24 months after treatment.³⁵ The most common cause of SRF at the last follow-up was radiation-related retinal vascular changes (including intraretinal fluid). intraretinal fluid. Radiation maculopathy was largely suppressed with intravitreal anti-VEGF therapy.^{33–35}

Tumor vascularity

Tumor vascularity reduced and typically disappeared over time. This is an “in-vivo” demonstration of radiation’s vaso-occlusive effect on uveal melanoma and choroidal vasculature.³⁸ Partial reduction or complete elimination of

intrinsic tumor vascularity was found to be the most consistent finding related to tumor regression. This finding suggests that the presence of new tumor vascularity suggests tumor recurrence.

In the literature review, descriptions of regression of choroidal melanoma after treatment have largely been limited to ultrasonographic tumor thickness reduction.^{13–24} Rashid et al.³⁹ reported 43% decrease in thickness and 42% decrease in cross-sectional area of tumor after ¹⁰⁶Ru and ¹²⁵I plaque brachytherapy. A recent study by Rashid et al.⁴⁰ also reported that initial tumor thickness was the predominant clinical predictor of regression rate of choroidal melanomas after ¹⁰⁶Ru and ¹²⁵I brachytherapy. Abramson et al.¹⁵ also reported that the amount of reduction in tumor thickness after ⁶⁰Co and ¹²⁵I therapy was the same, irrespective of location of tumor. Salvi et al.⁴¹ noted that the regression of tumor height at 3, 6, and 12 months with ¹²⁵I did not statistically correlate with tumor location. In our study, all lesions, irrespective of location and shape, show similar amounts of reduction in tumor thickness. Using proton therapy, Wilkes and Gragoudas²⁵ noted resolution of the secondary serous retinal detachments in 100% (our study 85%) and destruction of the tumor’s vasculature with elimination of leakage on FA in 66% (our study 90%). In addition, the 1982 Wilkes study could not report on newly available OCT and FAF findings and nor did they analyze radiation-related changes or vision outcomes.

With respect to local control: in a review of 100 patients treated with ⁶⁰Co plaque, Cruess et al.¹³ reported that there was no difference in the rate and extent of tumor regression between the patients who developed metastasis and the ones who did not. Kaiserman et al.⁴² found that the initial tumor thickness regression rate was significantly higher in patients

who developed metastasis (6% per month) compared to patients who did not (4% per month), with ^{106}Ru plaque. Glynn et al.⁴³ following proton beam radiotherapy, found that tumors regressing rapidly were significantly more likely to develop metastasis within 2 years of treatment, while tumors with slow regression developed metastasis after 2 years of treatment. In our study, we found no difference in the rate of tumor regression between patients who developed metastasis and those who remained well systemically.

In terms of visual acuity: Marconi et al.⁴⁴ noted that after ^{106}Ru plaque brachytherapy, 56% of patients had visual acuity of 20/25 initially, out of which more than half stayed with 20/40. Patel et al.⁴⁵ compared ^{103}Pd with ^{125}I and found that >20/40 visual acuity was noted in 65% with ^{103}Pd versus 30% with ^{125}I . Papakostas et al.⁴⁶ noted visual acuity of $\geq 20/200$ in 8.7% patients and counting fingers in 22% patients after proton beam radiotherapy. In our study, we noted excellent median visual acuity of 20/32 with ^{103}Pd plaque brachytherapy.

In that, choroidal melanomas have been reported to appear in various configurations: dome, mushroom-shaped, and irregular. They can be melanotic, amelanotic, or demonstrate variable pigmentation. They may be associated with orange pigment, vascularity, or SRF. Clearly, a single parameter of change (as measured thickness) does not comprehensively define regression of choroidal melanomas.

Advantages of our study

This study benefits from its long duration of follow-up, the use of a single treatment modality, and that all surgeries were performed by one, experienced surgeon (P.T.F.) who has chaired or participated in recent ABS and AAPM guideline initiatives.^{5,6,30} With such high (99.5%) local control (at a mean duration of 71 months after ^{103}Pd plaque brachytherapy), our outcomes should be considered reliable characteristics of choroidal melanoma regression.

Limitations of this study

This study was retrospective. Although reasonably sized compared to published reports in the literature, a large multicenter cooperative “big data” registry study would improve validation and allow for observations after alternative methods of radiation therapy.

In conclusion

Findings related to choroidal melanoma regression (after ^{103}Pd plaque brachytherapy) include increased tumor pigmentation of posterior tumors, an evolution from increased to decreased OP and complete resolution of DRPED. FA and histopathology revealed resolution of intrinsic tumor vascularity, while OCT showed decreased tumor-related, exudative SRF. Finally, ultrasound imaging revealed

decreased tumor thickness with a trend toward synchronous increased internal reflectivity. We hope this study serves to aid to the clinical judgment of those who treat and follow patients with choroidal melanoma.

Declaration of conflicting interests

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