Primary Photodynamic Therapy with Verteporfin for Pigmented Posterior Pole cT1a Choroidal Melanoma: A 3-Year Retrospective Analysis

[1,2]Ido D Fabian, [1,3]Andrew W Stacey, [1]Lamis Al Harby, [1]Amit K Arora, [1,4]Mandeep S Sagoo, [1,4]Victoria M L Cohen

[1]Ocular Oncology Service, Moorfields Eye Hospital, London, UK; [2]Ocular Oncology Service, Goldschleger Eye Institute, Sheba Medical Center, Tel-Aviv University, Tel Aviv, Israel; [3]Department of Ophthalmology, University of Washington, Seattle, Washington, USA; [4]NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital & University College London Institute of Ophthalmology, London, UK

Corresponding author: Ido Didi Fabian, Moorfields Eye Hospital, 162 City Road, London EC1V 2PD.

E-mail address: didifabian@gmail.com

Phone no: +44 (0)20 72533411

SYNOPSIS

Primary photodynamic therapy for pigmented posterior pole cT1a choroidal melanoma resulted in the present cohort of 26 patients (26 eyes) with 62% success rate after an average of 27 months follow-up.

Abstract

Aims: To investigate the outcomes of primary photodynamic therapy (PDT) for pigmented posterior pole cT1a choroidal melanoma.

Methods: Retrospective interventional consecutive case series of 26 patients (26 eyes) with pigmented posterior pole cT1a choroidal melanoma, who were treated with 3 sessions of PDT and followed-up thereafter.

Results: Included were 11 males and 15 females that presented at a median age of 66 years (mean: 64) with transformed naevi (n=11) or suspicious lesions (n=15) with ≥3 risk factors for growth, with lipofuscin in all. In all cases, diagnosis was clinically based (no tissue biopsy). Tumour control was achieved in 16 (62%) patients in a median follow-up time of 29 months (mean: 27). Ten patients failed treatment by form of radial expansion, diagnosed in a median time of 13 months (mean: 12) from last treatment. By Kaplan-Meier analysis, success rate after 1, 2 and 3 years was 85%, 59% and 51%, respectively. On statistical analysis, number of suspicious features was found to be the only risk factor predicting failure (p=0.046). One patient developed macula-sparing branch retinal artery occlusion after treatment. Following PDT, subretinal fluid resolved in all cases and visual acuity significantly improved in all treatment-success cases (p=0.043). There were no cases of metastatic spread.

Conclusion: Primary PDT resulted in tumour regression of small, pigmented choroidal melanoma in 62% after a mean of 27 months. Treatment was more effective in tumours with 3 or less risk factors for growth, and resulted with fluid elimination and significant improvement in vision in treatment-success cases.

Introduction

Uveal melanoma is the most common primary intraocular malignancy in adults and choroidal melanoma is the most common subtype.[1] The American Joint Committee on Cancer (AJCC) classifies uveal melanomas according to several variables, including tumour size, location, presence or absence of extraocular extension, and serves as a prognostic tool.[2] Those features that comprise the AJCC scheme are also used to guide primary treatment. For choroidal melanoma, eyes classified as cT3-4 commonly undergo primary enucleation, although conservative therapy was attempted,[3–5] with variable results. cT2 and the larger spectrum of cT1 (3.1-6.0mm in thickness) cases are primarily treated in most centres by means of local radiotherapy,[6] whether plaque or proton beam radiotherapy. For the smallest choroidal melanoma category, cT1a with tumours ≤3mm in thickness, and especially the borderline cases (i.e. suspicious naevi),[7] there is however no consensus regarding the preferred management choice. While some advocate early treatment with local radiotherapy, in order to reduce the chances for adverse cytogenetic alterations[8] and lower the risk of metastatic spread,[9] others are reluctant to treat small lesions with only suspicious features but no evidence of tumour growth, and especially when patients are visually asymptomatic, as radiotherapy is associated with vision deterioration in over 50% of cases.[10]

Over the years, before and during the local radiotherapy era, several laser-based modalities were tested for small choroidal melanoma, including photocoagulation, transpupillary thermotherapy and photodynamic therapy (PDT). While the prior two were abandoned as primary treatment due to relatively high recurrence rate,[11,12] PDT was reported to result with high tumour control rate when used in both pigmented and non-pigmented choroidal melanomas.[13,14] In the London Ocular Oncology Service, PDT with verteporfin has been used since 2014 for selected cases of choroidal melanoma. Our group recently published the short-term results of primary PDT used in 15 patients with small (T1a) posterior pole choroidal melanoma, where all tumours were pigmented.[15] In a short follow-up time of 15 months, tumour control was achieved in 80% of cases, no complications were recorded and visual acuity (VA) improved. In the present study, we aimed to investigate the safety and efficacy of PDT with verteporfin for clinically diagnosed pigmented posterior pole T1a choroidal melanoma in a larger cohort, followed-up for a longer course.

Methods

The study was performed in a retrospective manner and approved by the Moorfields Eye Hospital institutional review board in concordance with the declaration of Helsinki. All patients with pigmented posterior pole T1a choroidal melanoma that presented to the London Ocular Oncology Service from April 2014 to December 2015, were treated with PDT with verteporfin, and followed-up thereafter, were included in the study. Of the study cohort, 15 patients (15 eyes) which were reported previously following a median follow-up time of 15 months,[15] were also included and reported herein with extended follow-up.

To be included in the study, tumours had to be pigmented in at least 50% of their surface area, have thickness of less than 3mm and either demonstrate documented recent growth (i.e. malignant transformation or transformed naevus), or to have at least 3 risk factors for growth. The established risk factors for growth are as follows: lesion thickness >2mm, presence of subretinal fluid, presence of lipofuscin, related symptoms or margin to optic disc ≤3mm.[16] For the suspicious naevi subgroup, the presence of lipofuscin was defined as prerequisite sign, to differentiate leaking naevi from early melanoma. Patients were also offered alternative radiotherapy (i.e. plaque brachytherapy or proton beam radiotherapy) or an option of close monitoring with no intervention, according to the clinical scenario, and advantages and disadvantages of each treatment option was discussed. As part of the prior interventional radiotherapy option, all patients were offered to undergo tissue biopsy for definite diagnosis and prognostication.

All patients underwent a full ophthalmic evaluation at each appointment, including slit lamp bimicroscopy, colour fundus photography, autofluorescence imaging, enhanced depth imaging optical coherence tomography of the lesion and fovea and B-scan ultrasonography.

Prior to PDT, written consent was obtained, after patients were informed regarding the possible risks, benefits and potential short-term success rate associated with PDT.[15]

Treatment protocol included an infusion of verteporfin (Visudyne, Novartis, UK), 6mg per m^2 body surface area of over 10 minutes. Five minutes after infusion completion, laser treatment commenced. Parameters were set to a light dose of 50J/cm^2, power density of 600mW/cm^2, double duration treatment time (83 sec x 2) and spot size to

cover the entire lesion. Where the basal diameter of the tumour was greater than the maximal spot size, multiple confluent spots were used. Following treatment, patients were instructed to avoid exposure to direct light for 48 hours. Altogether, patients received 3 PDT sessions, 4-8 weeks apart, and were closely monitored thereafter, once every 3 months. Treatment failure was defined as tumour growth in diameter, height, or both, following PDT. All patients underwent systemic staging at diagnosis, received shared care with a medical oncologist and were enrolled in our metastatic surveillance program with 6 monthly abdominal ultrasound scans.

Patient data retrieved from medical charts included sex, age, race, past ocular and medical history, visual acuity and the presence of symptoms. Tumour characteristics recorded included location, height and maximum diameter on B scan ocular ultrasound, the presence or absence of subretinal fluid, and the degree of pigmentation. Treatment parameters were recorded and the interval between treatments was specified. Tumour response and ocular complications were recorded. Length of follow up, defined from the first PDT treatment to the last follow up visit in clinic, was noted.

Statistical Analysis

Calculations and plotting were done using the R Statistical Environment.[17] Continuous variables were evaluated with Student t tests and categorical variables with Fisher's Exact Test or Wilcoxon Rank-sum Test. Kaplan-Meier Survival Estimate curves were used to predict non-failure rate. P-value<0.05 was considered significant. Risk factors for treatment failure were analyzed by means of univariate analysis and significant factors were included in a multivariate analysis. Snellen visual acuity (VA) was converted to logMAR equivalent. Approximations for VA worse than 20/400 were as follows: counting fingers, 20/2000; hand motions, 20/4000; light perception, 20/8000; and no light perception, 20/16000.[18]

Results

Twenty-six patients (26 eyes), 11 (42%) males and 15 (58%) females that presented at a median age of 66 years (mean; 64, range: 32-89), fulfilled the inclusion criteria for the study and they comprise the study cohort. **Tables 1 and 2** depict the demographic and clinical features of the study patients at presentation. Eleven (42%) of the patients were diagnosed with a transformed naevus due to documented growth (**Figure 1**) after a median follow-up time in our service of 61 months (mean: 67; range: 44-193), prior to transformation. The remaining (58%) patients had a suspicious pigmented choroidal lesion with a median number of 4 risk factors for growth (mean: 4; range: 3-5). Of the tumours, 23 (89%) were ≤2mm in elevation and in 23 (89%) of the eyes subretinal fluid was present.

Table 1. Primary photodynamic therapy with verteporfin for pigmented cT1a choroidal melanoma in 26 patients: Patients demographic and clinical features at presentation.

Variable	Number	Percentage
Age (years) Median (mean, range)	 66 (64, 32-89)	
Gender Male Female	 11 15	 42 58
Laterality Right Left	 14 12	 54 46
LogMAR tumour eye Median (mean, range)	 0.18 (0.16, -0.08-0.48)	
Transformed naevus Suspicious naevus*	11 15	42 58
Number of risk factors for growth	0 – 1 1 – 1 2 – 2 3 – 7 4 – 13 5 - 2	4 4 8 27 50 8
Tumour dimensions (mm) Median (mean, range) Height Base	 1.3 (1.4, 0.9-2.7) 5.1 (5.4, 3.0-8.9)	
Distance of tumour from (mm): Median (mean, range) Optic disc Fovea	 2.0 (2.0, 0.0-9.0) 1.0 (1.6, 0.0-4.5)	
Presence of subretinal fluid: General Foveal	 23 14	 89 54
Tumour pigmentation		

Full	19	73
Partial	7	27
* Patients with at least 3 risk factors for growth (from the following: lesion thickness >2mm, presence of subretinal fluid, presence of lipofuscin, related symptoms or margin to optic disc ≤3mm).[7] Presence of lipofuscin was considered a prerequisite, to differentiate cases of early choroidal melanoma from leaking naevi.		

Table 2. Primary photodynamic therapy with verteporfin for pigmented cT1a choroidal melanoma in 26 patients: Presentation details per patient and follow-up time.

Patient number*	Presentation age (years)	Gender	Laterality	LogMAR tumour eye	Tumour type** (# risk factors)	Tumour height (mm)	Tumour – optic disc (mm)	Tumour – fovea (mm)	Follow-up from 1st PDT (months)
1*	66	F	L	0.24	Suspicious (4)	1.8	2.5	0	36
2	56	F	R	-0.08	Transformed (3)	0.9	0.5	4	38
3*	60	M	L	0	Suspicious (4)	0.9	0.5	0	32
4*	32	F	R	0.18	Suspicious (4)	0.9	0	0	30
5	70	F	L	0.08	Suspicious (3)	1.1	0	3	36
6	80	M	L	0.18	Transformed (1)	1.1	3.5	2.5	29
7	66	F	R	0.3	Transformed (0)	1.5	5	3	31
8	44	F	L	-0.08	Suspicious (4)	1.2	2.5	0.5	38
9*	78	F	R	0.18	Suspicious (5)	2.7	1	4	35
10*	53	M	R	0.18	Transformed (4)	1	0	0	33
11	81	M	R	0	Suspicious (3)	1	0	1.5	39
12	74	F	L	0.2	Suspicious (4)	0.9	1.5	0.5	19
13	41	F	R	0.18	Transformed (3)	1.65	0	3.5	36
14	62	F	R	0.3	Suspicious (4)	1.2	3	1	35
15*	80	M	L	0.48	Suspicious (4)	1.5	0	2	29
16	63	F	L	0	Transformed (2)	1.4	9	4	24
17*	53	M	L	0.176	Suspicious (3)	1.3	4.5	1	26
18	89	M	R	0	Transformed (3)	1	2.5	0.5	17
19*	80	M	R	0	Transformed (4)	2	4.5	1.5	24

20	54	F	R	0.301	Suspicious (4)	1.1	2.5	1	20
21	66	M	R	0.301	Transformed (4)	2.2	2.5	0	22
22*	77	F	R	0.301	Transformed (2)	1.3	3	0.5	9
23	50	M	L	0.176	Suspicious (4)	1.66	0	2	18
24	66	F	R	0	Suspicious (4)	1.6	0	4.5	19
25	76	M	L	0	Transformed (3)	1.8	3	1	20
26*	55	F	L	0.477	Suspicious (5)	2.4	1	0	19

* Failure

** Suspicious naevus: patients with at least 3 risk factors for growth (from the following: lesion thickness >2mm, presence of subretinal fluid, presence of lipofuscin, related symptoms or margin to optic disc ≤3mm).[7] Presence of lipofuscin was considered a prerequisite, to differentiate cases of early choroidal melanoma from leaking naevi. Transformed: naevus with documented tumour growth.

F: female, M: male, L: left eye, R: right eye, PDT: photodynamic therapy

All patients (100%) received 3 sessions of PDT with a median interval between sessions of 56 days (mean: 51; range: 28-79). No procedural complications were recorded during or after PDT, but a single patient that noticed a visual field defect one day after treatment, and was diagnosed with macula sparing branch retinal artery occlusion.

At a median follow-up time of 29 months (mean: 27; range: 9-39) from first PDT session (**Table 2**), tumour control was achieved in 16 (62%) of the cases. By Kaplan-Meier analysis (**Figure 2**), success rate after 1 and 2 years was 85% and 59%, respectively, and after 3 years was 51% (Standard Error: 0.12; 95% Confidence Intervals: 26%-72%).

The remaining 10 (38%) cases showed tumour growth, despite PDT. The median time to detect treatment failure was 13 months (mean: 12; range: 1-26) from last treatment. In all treatment failure cases, tumours showed a radial expansion pattern (**Figure 3**), 2 (20%) of the 10 tumours also demonstrated an increase in elevation.

All uncontrolled tumours (n=10) received second line treatment. Second line therapies included proton beam radiotherapy (n=3), plaque brachytherapy (n=8) and secondary PDT (n=2). Of note, 3 of the 10 uncontrolled tumours (30%) required third line treatment. These tumours received successful third line proton beam radiotherapy following failure of second line plaque brachytherapy, plaque brachytherapy following failure of second line PDT and one eye was enucleated following failure of second line plaque brachytherapy.

The results of the univariate analysis of risk factors for PDT failure are shown in **Table 3**. The presence of subfoveal fluid (p=0.051), related symptoms (p=0.087) and distance to fovea (p=0.053) showed a statistical trend towards significance. However, only total number of suspicious features, analyzing both cases of transformed and suspicious lesions, was found to be a significant risk factor for PDT failure (p=0.046). On calculation, odds ratio for treatment failure following PDT was 2.1 for tumours manifesting 3 or more risk factors for growth and 5.1 for tumours manifesting 4 or more risk factors for growth. Multivariate analysis was not executed, as only a single variable was found to be significant on univariate analysis.

Table 3. Primary photodynamic therapy with verteporfin for pigmented cT1a choroidal melanoma in 26 patients: Univariate analysis for treatment failure (n=10)

Variable	P value
Age at presentation (median (mean; range)) Failures: 62.6years (63.4; 31.8-80.3)	0.81

Non-Failures: 65.5years (64.9; 40.8-89.0)	
Gender Failures: 5/10 Male Non-Failures: 6/16 Male	0.69
Etiology (Suspicious vs. transformed naevus) Failures: 7/10 suspicious Non-Failures: 8/16 suspicious	0.43
Laterality Failures: 5/10 Right Non-Failures: 9/16 Right	0.99
LogMAR acuity at presentation (median (mean; range)) Failures: 0.2 (0.2; 0.0-0.5) Non-Failures: 0.1 (0.1; -0.1-0.3)	0.11
Presence of any SRF Failures: 10/10 Yes Non-Failures: 13/16 Yes	0.051
Ocular Symptoms Failures: 9/10 Yes Non-Failures: 8/16 Yes	0.087
Presence of Lipofuscin Failures: 9/10 Yes Non-Failures: 14/16 Yes	0.99
Distance to Optic Nerve head (median (mean; range)) Failures: 1.0mm (1.7; 0.0-4.5) Non-Failures: 2.5mm (2.2; 0.0-9.0)	0.53
Distance to Optic Nerve head (Categorical Variable) Failures: 8/10 Closer than 3mm Non-Failures: 13/16 Closer than 3mm	0.99
Distance to Fovea (median (mean; range)) Failures: 0.3mm (0.9; 0.0-4.0) Non-Failures: 2.0mm (2.1; 0.0-4.5)	0.053
Tumour Height at presentation (median (mean; range)) Failures: 1.4mm (1.6; 0.9-2.7) Non-Failures: 1.2mm (1.3; 0.9-2.2)	0.28
Largest Basal Diameter at presentation (median (mean; range)) Failures: 5.4mm (5.7; 3.0-8.9) Non-Failures: 5.1mm (5.3; 3.5-6.9)	0.54
Full or mixed pigmentation Failures: 7/10 Full Non-Failures: 12/16 Full	0.99
Total number of risk factors*(median (mean; range)) Failures: 4.0 (3.9; 2.0-5.0) Non-Failures: 3.0 (3.1; 0.0-4.0)	0.046
* Lesion thickness >2mm, presence of subretinal fluid, presence of lipofuscin, related symptoms or margin to optic disc ≤3mm.	

In all (100%) cases, including those that had treatment failure, subretinal fluid was totally eliminated following PDT. Median final logMAR of the treatment success group was 0.00 (mean: 0.04; range: -0.08-0.18). At presentation, median logMAR for

this subgroup was 0.13 (mean: 0.12; range: -0.08-0.30), significantly worse than after PDT (p=0.043).

None of the patients developed distant metastasis during follow-up and all were alive at last visit, but a single patient who died from a stroke, 8 months following PDT.

Discussion

In this study, Primary PDT with verteporfin for small pigmented posterior pole cT1a choroidal melanoma resulted in tumour control in only 62% of cases at 2.5 years. In comparison, 86% tumour control rate was reported following iodine plaque radiotherapy for juxtapapillary choroidal melanoma,[19] and 88% and 94% following ruthenium plaque radiotherapy and proton beam radiotherapy for choroidal melanoma, respectively.[20,21] In the present study, increased number of risk factors for growth[7] was found to be the only significant factor to predict failure, with odds ratio of 5.1 for tumours with 4 or more risk factors. We conclude that PDT for small pigmented choroidal melanoma may be more effective in tumours with fewer risk factors for growth, particularly in patients that are unfit for surgery. Given these results it is more appropriate to offer the most suspicious tumours, with 4 or more risk factors, local radiotherapy treatments in the form of plaque brachytherapy, proton beam radiotherapy or stereotactic radiosurgery, despite their risk of loss of vision.

In the absence of a biopsy-proven diagnosis, one may argue that PDT failed in the genuine melanoma cases with more suspicious features (risk factors for growth), and was successful in the naevi cases with less suspicious features. However, it should be noted that of the 16 tumours successfully controlled with PDT, 8 (50%) demonstrated relatively rapid tumour growth before treatment. In the absence of biopsy, the majority of Ocular Oncologists would use growth in a short period of time to confirm a diagnosis of choroidal malignant melanoma. In the remaining 8 cases, 6 (75%) had 4 risk factors for growth, reflecting cases that are selected for treatment in specialist centres. Fine needle aspiration biopsy (FNAB) is usually performed for prognostication of uveal melanoma at the time of treatment.[22,23] Very few Ocular Oncologists currently biopsy tumours to make a diagnosis, as clinical examination combined with ultrasound are sufficient in the majority of cases.[24,25] In addition, the potential risk of visual complications following FNAB are greater for tumours located at the posterior pole.

In our previous report on short-term outcomes of PDT for small posterior pole choroidal melanoma,[15] all 3 failed cases occurred in a relatively narrow time frame (3-6 months) after treatment and were thereafter immediately and successfully treated with secondary local radiotherapy. In the present study, of the 10 failed cases, 3 (30%) had to undergo an additional treatment after secondary line, one of which was enucleation. The median interval between completion of treatment and local relapse was 13 months in the present study, indicating that close follow up for more than one year following treatment is required.

Similar to our initial results,[15] here too, in a larger cohort, the failure pattern was of radial tumour growth in all cases, although in 2, an increase in elevation was also noted. Interestingly, PDT with verteporfin has been found to be effective in small amelanotic melanomas.[26] However, it has been speculated that PDT is ineffective for pigmented choroidal melanoma because pigment might block penetration of the laser,[27,28, 29] likely resulting with radial growth of the deeper undamaged malignant cells. From a mechanistic perspective, PDT with verteporfin is believed to cause damage to cellular components by the formation of free oxygen radicals,[30] hence dependent on laser-tissue penetration. However, verteporfin may also have a role, independent of its activation by PDT, as an anticancer compound associated with the Hippo pathway.[31] In this study, the independent and possibly additive actions of PDT and verteporfin were nevertheless found to be insufficient in controlling the tumours in 10 of the cases.

PDT was found to be useful in eliminating overlying subretinal fluid in all cases, resulting with improved VA in the non-failed cases. These results are in agreement with a previous report, which showed its beneficial outcome in resolving subretinal fluid in choroidal naevi cases.[32]

PDT is considered generally a safe treatment modality, although some ocular complications were reported in association with its use, including transient visual disturbances, choroidal atrophy, vitreous hemorrhage, exudative retinal detachment,[30] and also a case of branch retinal artery occlusion.[33] Although rare, patients should be informed of the possibility of sight-threatening complications which has immediate negative visual consequences. In contrast, the alternative treatments with standard radiotherapy for uveal melanoma carry a much greater incidence of visual loss for posterior pole choroidal melanoma albeit many years later. Serious, non-ocular, adverse events were also reported following PDT, likely in relation to exposure to verteporfin, including anaphylactoid reaction, syncope, and also a case of cerebrovascular accident.[34–36] However, all were reported to occur during or immediately after verteporfin infusion, unlike the patient from the present series that died of stroke 8 months following treatment.

This study was partly based on a retrospective chart review, hence had inherent limitations in respect to data collection. However, nearly 60% of the patients included in the present cohort were previously reported in a prospective study,[15] allowing collection of full and detailed clinical variables. Similarly, full clinical details

were also available for the remaining patients that were not included in the initial report. In terms of cohort size, this study is based on a relatively small sample; however, it is currently the largest found in the literature on PDT for choroidal melanoma in general and specifically pigmented melanomas.

In summary, while management algorithms are relatively straightforward for large and medium-sized choroidal melanomas in terms of both when and how to treat, for small choroidal lesions suspected to be early melanomas this is not the case. For the latter, current management options include careful observation versus local radiotherapy, which is associated with vision loss in many of the cases.[37] PDT with verteporfin for posterior pole pigmented cT1a choroidal melanomas may have a potential role in this scenario. It resulted with significant reduction in fluid, but only 62% success rate after less than 3 years, which is a concern, especially as longer follow-up is desired. If PDT with verteporfin is used as a primary treatment for choroidal melanoma, close follow up is recommended.

ACKOWLEDGMENT

The authors indicate no funding support and no competing interest.

Competing interests: None declared.

Ethics approval: Institutional Review Board of the Barts Health NHS Trust institutional review board (number 6622).

Contributors: IDF had substantial contribution to the design of the work, collection and analysis of the data, drafting the work, final approval of the version published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, AWS had substantial contribution to the design of the work, collection and analysis of the data, drafting the work, final approval of the version published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, LAH had substantial contribution to the acquisition, collection and analysis of the work, drafting the work, final approval of the version published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, AKA had substantial contribution to the conception of the work, collection and analysis of the data, drafting the work, final approval of the version published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, MSS had substantial contribution to the conception of the work, collection and analysis of the data, drafting the work, final approval of the version published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and VMLC had substantial contribution to the design of the work and analysis of the data, significantly drafting the work, final approval of the version published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1 Egan KM, Seddon JM, Glynn RJ, *et al.* Epidemiologic aspects of uveal melanoma. *Surv Ophthalmol* 1988;**32**:239–51.

2 Kivela T, Sampson ER, Grossniklauss HE, Jager MJ, Singh AD, Caminal JM, Pavlick AC, Kujala E, Coupland SE FP. *Uveal Melanoma. In: Amin MB, Edge SB, Greene FL, et al., eds. AJCC Cancer Staging Manual. 8th ed.* 2017.

3 Mosci C, Lanza FB, Barla A, *et al.* Comparison of clinical outcomes for patients with large choroidal melanoma after primary treatment with enucleation or proton beam radiotherapy. *Ophthalmologica* 2012;**227**:190–6.

4 Weber B, Paton K, Ma R, *et al.* Outcomes of Proton Beam Radiotherapy for Large Non-Peripapillary Choroidal and Ciliary Body Melanoma at TRIUMF and the BC Cancer Agency. *Ocul Oncol Pathol* 2015;**2**:29–35.

5 Bensoussan E, Thariat J, Maschi C, *et al.* Outcomes after Proton Beam Therapy for Large Choroidal Melanomas in 492 Patients. *Am J Ophthalmol* 2016;**165**:78–87.

6 Shields JA, Shields CL. Management of posterior uveal melanoma: Past, present, and Future: The 2014 Charles L. schepens lecture. Ophthalmology. 2015;**122**:414–28.

7 Shields CL, Furuta M, Berman EL, *et al.* Choroidal nevus transformation into melanoma: analysis of 2514 consecutive cases. *Arch Ophthalmol (Chicago, Ill 1960)* 2009;**127**:981–7.

8 Shields CL, Say EAT, Hasanreisoglu M, *et al.* Cytogenetic Abnormalities in Uveal Melanoma Based on Tumor Features and Size in 1059 Patients: The 2016 W. Richard Green Lecture. *Ophthalmology* 2017;**124**:609–18.

9 Shields CL, Furuta M, Thangappan A, *et al.* Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol* 2009;**127**:989–98.

10 Sagoo MS, Shields CL, Emrich J, *et al.* Plaque radiotherapy for juxtapapillary choroidal melanoma: treatment complications and visual outcomes in 650 consecutive cases. *JAMA Ophthalmol* 2014;**132**:697–702.

11 Shields JA, Glazer LC, Mieler WF, *et al.* Comparison of xenon arc and argon laser photocoagulation in the treatment of choroidal melanomas. *Am J Ophthalmol* 1990;**109**:647–55.

12 Singh AD, Kivelä T, Seregard S, *et al.* Primary transpupillary thermotherapy of 'small' choroidal melanoma: is it safe? *Br J Ophthalmol* 2008;**92**:727–8.

13 Rundle P. Treatment of posterior uveal melanoma with multi-dose photodynamic therapy. *Br J Ophthalmol* 2014;**98**:494–7.

14 Jmor F, Hussain RN, Damato BE, *et al*. Photodynamic therapy as initial treatment for small choroidal melanomas. *Photodiagnosis Photodyn Ther* 2017;20:175-81.

15. Fabian ID, Stacey AW, Papastefanou V, *et al.* Primary photodynamic therapy with verteporfin for small pigmented posterior pole choroidal melanoma. *Eye* 2017;**31**:519–28.

16 Shields CL, Cater J, Shields JA, *et al.* Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol* 2000;**118**:360–4.

17 R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

18 Anonymous. The ischemic optic neuropathy decompression trial (IONDT): design and methods. *Control Clin Trials* 1998;**19**:276–96.

19 Sagoo MS, Shields CL, Mashayekhi A, *et al.* Plaque radiotherapy for juxtapapillary choroidal melanoma: Tumor control in 650 consecutive cases. *Ophthalmology* 2011;**118**:402–7.

20 Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. *Ophthalmology* 1999;**106**:1579–87.

21 Damato B, Kacperek A, Chopra M, *et al.* Proton beam radiotherapy of choroidal melanoma: The Liverpool-Clatterbridge experience. *Int J Radiat Oncol Biol Phys* 2005;**62**:1405–11.

22 Singh AD, Medina CA, Singh N, *et al.* Fine-needle aspiration biopsy of uveal melanoma: outcomes and complications. *Br J Ophthalmol* 2016;**100**:456–462.

23 Sellam A, Desjardins L, Barnhill R, *et al.* Fine Needle Aspiration Biopsy in Uveal Melanoma: Technique, Complications, and Outcomes. *Am J Ophthalmol* 2016;**162**:28–34.

24 Nathan P, Cohen V, Coupland S, *et al.* Uveal Melanoma UK National Guidelines. *Eur J Cancer* 2015;**51**:2404–12.

25 Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. *Arch Ophthalmol (Chicago, Ill 1960)* 1990;**108**:1268–73.

26 Campbell WG, Pejnovic TM. TREATMENT OF AMELANOTIC CHOROIDAL MELANOMA WITH PHOTODYNAMIC THERAPY. *Retina* 2012;**32**:1356–62.

27 Favilla I, Barry WR, Gosbell A, *et al.* Phototherapy of posterior uveal melanomas. *Br J Ophthalmol* 1991;**75**:718–21.

28 Kaviani A, Ataie-Fashtami L, Fateh M, *et al.* Photodynamic therapy of head and neck basal cell carcinoma according to different clinicopathologic features. *Lasers Surg Med* 2005;**36**:377–82.

29. Favilla I, Favilla ML, Gosbell AD, *et al*. Photodymanic theapy: a 5-year study of its effectiveness in the treatment of posterior uveal melanoma, and evaluation of haematoporphyrin uptake and phototoxicity of melanoma cellsin tissue culture. *Melanoma Res* 1995;5:355-64.

30 Cerman E, Çekiç O. Clinical use of photodynamic therapy in ocular tumors. Surv. Ophthalmol. 2015;**60**:557–74.

31 Harvey KF, Zhang X, Thomas DM. The Hippo pathway and human cancer. Nat. Rev. Cancer. 2013;**13**:246–57.

32 Pointdujour-Lim R, Mashayekhi A, Shields JA, *et al.* Photodynamic therapy for choroidal nevus with subfoveal fluid. *Retina* 2017;**37**:718–23.

33 Xiao Y, Guo X, Ouyang P. Branch retinal artery occlusion associated with photodynamic therapy in a circumscribed choroidal haemangioma. *Photodiagnosis Photodyn Ther* 2013;**10**:644–6.

34 Doshi AB, Moshfeghi DM, Jack RL. Anaphylactoid reaction after verteporfin therapy. *Am J Ophthalmol* 2005;**140**:936–7.

35 Quintyn J-C, Massy-Guillement N, Brasseur G. [Cerebrovascular accident following photodynamic therapy]. *J Fr Ophtalmol* 2007;**30**:e5.

36 Cahill MT, Smith BT, Fekrat S. Adverse reaction characterized by chest pain, shortness of breath, and syncope associated with verteporfin (Visudyne). *Am J Ophthalmol* 2002;**134**:281–2.

37 Melia BM, Abramson DH, Albert DM, *et al.* Collaborative Ocular Melanoma Study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma: I. Visual acuity after 3 years, COMS Report No. 16. *Ophthalmology* 2001;**108**:348–66.

Figure Legend

Figure 1

A fundus image of a suspicious choroidal naevus with overlying orange pigment as the sole risk factor for growth (A). After 10 years of follow-up the tumour has increased in its dimensions (B) and overlying fluid was noticed (C), as evidence for malignant transformation.

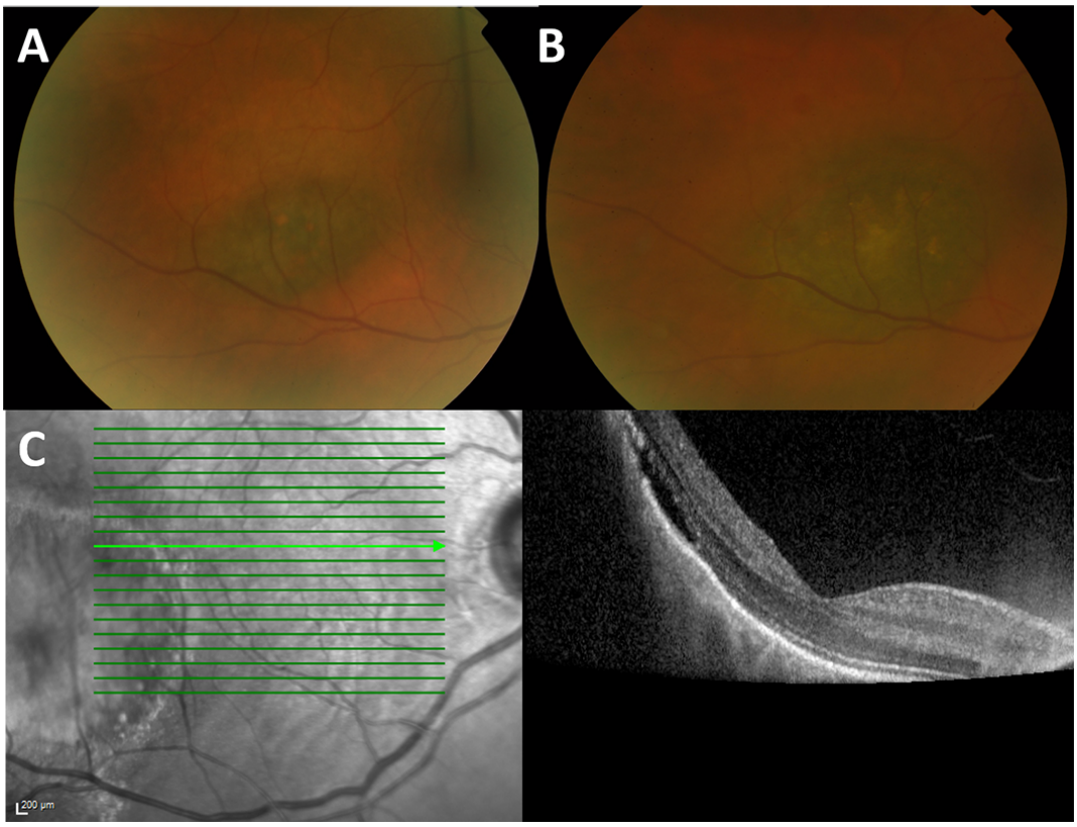

Figure 2

Kaplan-Meier estimate for success. success rate after 1 and 2 years was 85% and 59%, respectively, and after 3 years was 51% (Standard Error: 0.12; 95% Confidence Intervals: 26%-72%).

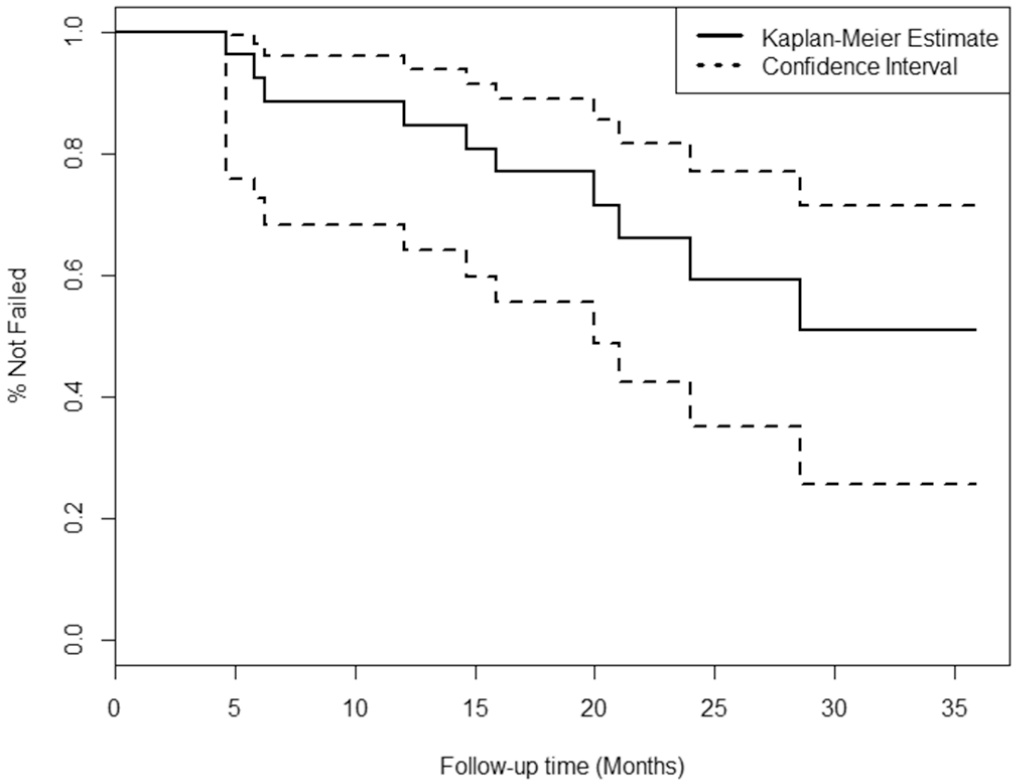

Figure 3

A fundus image of a small T1a choroidal melanoma (A) with overlying subretinal fluid (B), also over the fovea (C). Eighteen months following primary PDT, the tumour have transformed into a scar (D, arrow), but a small area of radial expansion (arrowhead). There was no evidence of overlying subretinal fluid (E and F). The patient was treated with secondary PDT and followed-up for additional 6 months with good tumour control.