Long term outcomes of small pigmented choroidal melanoma treated with primary photodynamic therapy

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PRECIS: Treatment of small, pigmented, posterior choroidal melanomas using PDT with verteporfin preserves visual acuity; however, 5-year treatment success is only 38.4%. Recurrence most commonly occurred along the tumor edges, often with minimal increase in thickness.

ABSTRACT:

Purpose: To report the long-term outcomes of patients with small, pigmented posteriorly located choroidal melanoma undergoing primary treatment using photodynamic therapy (PDT) with verteporfin at the London Ocular Oncology Service.

Design: Retrospective interventional consecutive case series

Subjects: All patients undergoing primary treatment using PDT with verteporfin from April 2014 and December 2015 and followed until December 2019.

Methods: This is a long-term follow up study of the same cohort of patients previously reported by our group in 2017 and 2018.

Main Outcome Measure: Local tumor control, visual outcomes and metastasis-free survival.

Results: Twenty-six patients were included with a mean (± SD) age and tumour thickness of 62 ± 14 years and 1.3 ± 0.5 mm, respectively. Tumours were posteriorly located (mean distance to optic nerve and fovea = 2.0 ± 2.2 and 1.6 ± 1.5 mm, respectively) and the majority were fully pigmented (73%). Overall, patients were followed for a median [IQR, range] of 49.5 [15.3, 7.0 – 66.0] months from first PDT to last follow up. Over the course of this study, 14/26 (54%) have developed a local recurrence at a median of 20.0 months [20.5, 4.7 – 60.9 months]. The most common pattern of recurrence was an isolated increase in basal dimensions (9/14; 64%). Median [IQR] final LogMAR visual acuity of the whole cohort was 0.2 [0.5]. The only statistically significant difference in baseline and outcome characteristics between treatment failures and non-failures was distance to fovea (median [IQR]: 0.5 [1.3] versus 2.5 [2.8]; P = 0.002) and final LogMAR visual acuity (median [IQR]: 0.50 [0.80] versus 0.00 [0.14]; P-value = 0.002), respectively.

Conclusions: While treatment of small pigmented posterior choroidal melanoma with PDT effectively preserves visual acuity, five-year treatment-success calculated by Kaplan-Meier analysis was only 38.4%. Recurrences after PDT tend to occur along the tumor edges, often with minimal increase in thickness. Given the substantial risk of treatment failure, primary PDT with vertepofrin is recommended in exceptional cases of choroidal melanoma, where other treatments with greater tumor control are not a feasible option.

INTRODUCTION:

Photodynamic therapy (PDT) is used to treat a number of conditions in ocular oncology, including circumscribed choroidal[1] and retinal capillary hemangiomas,[2,3] choroidal metastasis,[4] and vasoproliferative,[5] conjunctival[6] and eyelid tumors.[7] While choroidal melanoma is most commonly treated with radiotherapy,[8] several groups have investigated the potential role of PDT[9,10] given its minimally invasive nature and potential to preserve visual function, particularly in patients with small, posteriorly located choroidal melanomas.

Three primary mechanisms of action appear to be responsible for the anti-tumoral effects induced by PDT. On a cellular level, PDT generates cytotoxic intermediates causing direct tumor cell photodamage and resulting in tumor cell apoptosis. Immunologically, PDT activates NK-κB and other transcription factors which modulate and induce the local non-specific immune response. Finally, PDT causes destruction of the peritumoral vasculature, resulting in subsequent tumor cell necrosis.[7,11-13]

Tse et al reported encouraging results following the use of PDT with hematoporphyrin in 7 cases of uveal melanoma in 1984.[14] Subsequently, several animal studies have evaluated the effect of PDT on both pigmented[15-18] and amelanotic[19,20] choroidal melanomas, with tumor regression seen in the majority of cases. Histologic examination of these tumors showed prominent vascular damage,[15] tumor necrosis,[15,16,20] and infiltration of mononuclear cells.[17]

Later study in humans suggested a correlation between the degree of tumor pigmentation and the amount of regression following PDT with haematoporphyrin, with lighter tumors responding better than heavily pigmented ones.[21,22] Further to this, in 2005, Wachtlin et al treated 4 eyes with uveal melanoma destined for enucleation with PDT with verteporfin 2-3 days prior to surgery. Upon histopathological examination, they noted destructive effects within the two minimally pigmented tumors while the two heavily pigmented lesions had no appreciable necrosis.[23]

To date the options for treating posteriorly located choroidal melanoma while preserving vision are limited. Although greater pigmentation has previously been suggested as a risk factor for failure, the majority of choroidal melanomas fall into this category. We aimed to determine the role for PDT with verteporfin in this specific subset of patients in an effort to help answer one of the most common questions faced by ocular oncologists: is there a way to safely treat small, pigmented posteriorly located choroidal melanoma while preserving visual function? We have recently reported our 1- and 3-year results finding a tumor control rate of 80%[24] and 62%,[25] respectively. Herein, we provide the longer-term outcomes of primary PDT with verteporfin for small, pigmented, posterior uveal melanoma, from the same cohort. This study is a follow up study on the original series first published in 2017[24] and later, the 3-year outcomes published in 2018.[25]

METHODS:

This retrospective study was approved by the Moorfields Eye Hospital clinical audit department (number 456), was conducted in accordance with the declaration of Helsinki and informed consent was obtained from all patients at the time of treatment. As this was a follow up study, the same inclusion criteria and treatment parameters were used as has been outlined in the previously described study methodology.[24,25] Patients presenting to the London Ocular Oncology Service between April 2014 and December 2015 with AJCC 8th edition T1a pigmented choroidal melanoma located in the posterior pole undergoing primary treatment with PDT with verteporfin were included if they had pigmentation of ≥ 50% of their surface area, thickness <3mm and either (a) documentation of recent growth or (b) ≥ 3 risk factors for future growth. Risk factors included: Thickness >2mm, presence of sub-retinal fluid, visual symptoms, presence of orange pigment and margin to the optic disc ≤3 mm.[26]

Patient data, including sex, age, past ocular and medical history, visual acuity and tumor characteristics were collected from medical charts. Tumor response, complications and length of follow up, defined from the first PDT treatment to the last follow-up visit in clinic, was noted. Treatment failure was defined as growth in basal dimensions, thickness or both following PDT. All patients underwent systemic staging and were referred to a medical oncologist at the time of diagnosis. Subsequent metastatic surveillance was by way of abdominal ultrasounds every 6 months.

Treatment protocol:

Patients were treated following the protocol that has been previously described elsewhere[24,25] (3 sessions of PDT 4-8 weeks apart with verteporfin [6mg/m^2 body surface area] light dose of 50J/cm^2, power density of 600mW/cm^2 and double duration [83s x 2] with a spot size titrated to cover the entire lesion). Concentric double duration spots were placed to ensure that the entire lesion and its margins were covered beyond the edge of the visible tumour. A light dose of 50J/cm2 rather than 100J/cm2 as chosen, as the latter has been shown to induce closure of deeper choroidal vessels[27] and therefore, may be associated with a greater risk of visual morbidity. Double duration was selected in an effort to overcome the potential cytoprotective effects imparted by melanosomes, and three sessions were performed to increase the likelihood of inducing necrosis throughout the entire thickness of the lesion.

Statistical analysis:

Data are presented as mean ± standard deviation (SD) when normally distributed or as median [interquartile range (IQR) and range], if not. Conventional descriptive statistics were used and all variables were assessed for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. When continuous variables were normally distributed, the students t-test was employed and the variance between groups was again checked using Levene's test for quality of variances. For non-normally distributed variables, the Mann-Whitney U test was used. Differences in categorical variables were analysed using Fisher's exact test with the Freeman-Halton extension and Pearson Chi-Square. Kaplan-Meier survival estimate curves were used to predict treatment failure rate. A P-value of <0.05 was considered statistically significant. All data were analyzed using a commercially available software package (SPSS 2019®; IBM Corporation, Armonk, NY, USA).

RESULTS:

Twenty-six patients were included with a mean age of 62 ± 14 years. Fifteen (58%) were female and the right and left eyes were affected with equal frequency. The median [IQR, range] tumor height was 1.3 [0.7, 0.9 – 2.7] and the mean (± SD) largest basal dimension was 5.4 ± 1.4 mm. As included cases were, by definition, posteriorly located, the median distance to the optic disc (2.0 mm [3.0 mm; 0.0 – 9.0 mm]) and fovea (1.0 mm [2.5 mm; 0.0 – 4.5 mm]) were relatively small. Almost two-thirds of patients were symptomatic (17/26; 65%). The majority of tumors were fully pigmented (19/26; 73%), and had sub-retinal fluid (23/26; 88%) and/or orange pigment (23/26; 88%). (Table 1)

Pre and post treatment characteristics between failures and non-failures were compared. The two groups were similar with respect to age (p=0.417), gender (p=0.130), laterality (p=0.695), initial LogMAR visual acuity (p=0.734) and tumour height (p=0.661) and largest basal dimension (p=0.221). Cases with treatment failure had a shorter distance to the fovea (median [IQR, range]: 0.5 mm [1.3, 0.0 – 4.0 mm]) versus non-failures (2.5 mm [2.8, 0.5 – 4.5 mm]; p=0.002). As may be expected, cases that were successfully treated with PDT had better final LogMAR visual acuity compared to cases that failed to maintain local tumour control following PDT (median [IQR, range]: 0.00 [0.14, 0.00 – 0.30] versus 0.50 [0.80, 0.00 – 2.00]; p=0.002). (Table 2)

Overall, patients were followed for a median [IQR, range] of 49.5 [15.3, 7.0 – 66.0] months from first PDT to last follow up. Throughout this time period, 14/26 (54%) of patients developed a local recurrence necessitating additional treatment. The most common pattern of recurrence was an isolated increase in basal dimensions (9/14; 64%); however, 5 patients (5/14; 36%) also had a concurrent increase in thickness. Five-year treatment-success calculated by Kaplan-Meier analysis was 38.4% (Figure 1). The median time to failure was 20.0 months [20.5, 4.7 – 60.9 months].

Two patients (patient 1 and 14) underwent a second treatment of PDT. Patient 14 developed an edge recurrence 21-months following the second PDT and received an additional course of PDT (total of 9 session). He has remained stable with a maximum tumor thickness of 0.7mm at last follow up, 4.1 years after initial PDT. Patient 1 also had an edge recurrence necessitating plaque brachytherapy 6-months following the second course of PDT. This patient went on to developed a third recurrence 33 months following plaque brachytherapy and has recently undergone proton beam radiotherapy, 64 months following initial PDT.

A total of 8 patients underwent plaque brachytherapy as secondary treatment, however three of these patients (37%) developed subsequent recurrences at 9-, 17- and 32- months following plaque. One of these patients was enucleated (patient 8) and two (patients 3 and 9) underwent proton beam radiotherapy. (Table 3). Histopathological analysis of the globe undergoing enucleation did not reveal any evidence of extraocular extension; however, there was also no evidence of tumour necrosis. Ten patients who are actively under ongoing close observation at our unit and have remained stable with no episodes of recurrence over a median follow up of 50.5 months (15.5, 14.0 – 66.0 months) (Table 4, Figure 2)

One patient (patient 5) died from metastatic prostate cancer 27 months after PDT and one patient (patient 19) died 7 months following PDT from unknown causes. Patient 8 was discharged for ongoing local follow up after undergoing enucleation 21 months following initial PDT. One patient (patient 11) was lost to follow up 14 months after PDT. To the best of our knowledge, none of the patients in this study has developed metastatic disease to date.

DISCUSSION:

While the decision to proceed with radiotherapy for medium size uveal melanoma tends to be a rather straightforward one, the timing of treatment for small, posteriorly located lesions is less widely agreed upon given that roughly half of these patients will have visual acuity <20/200 5 years following iodine plaque brachytherapy.[28] Although visual morbidity associated with ruthenium plaque brachytherapy may be less, if the posterior margin of the tumour is <3 mm to the fovea, only 25% of patients maintain 20/40 vision or better 3 years after treatment.[29] In an effort to decrease the visual morbidity associated with treatment, several groups have investigated PDT for use in such cases.

A number of case reports[30,31] and case series[9,10,21,22,24,25,32-34] have reported the effect of PDT on choroidal melanoma. (Table 5) In 2017, Fabian et al reported promising initial results in a prospective study of 15 patients with small, pigmented posterior pole choroidal melanoma. Following three sessions of PDT, tumor control was achieved in 80% of cases at a median follow up of 15 months.[24] In a subsequent study however, the rate of local tumor control decreased to 62% at 29 months.[25] In this report, we have found a local control rate of only 29% at 5 years.

This relatively low success rate is a stark contrast to the effectiveness of PDT with verteporfin for the treatment of other choroidal tumours, such as circumscribed choroidal hemangiomas (CCH).[1,35,36] There are several potential explanations for these fundamentally different success rates. Photodynamic therapy has been shown to cause selective occlusion of the choriocapillaris due to the increased expression of low-density lipoprotein receptors in the endothelium.[37] Hence, the primary mechanism of action of verteporfin PDT in cases of CCH appears to be thrombosis of angiomatous vessels,[38] a theory supported by post-treatment fluorescein and indocyanine green angiography showing occlusive effects within the choroid.[39] This contrasts to the proposed mechanisms of action in cases of choroidal melanoma, where PDT with verteporfin is thought to induce cellular damage via cytotoxic intermediates and activation of transcription factors.[7,11-13] Moreover, although definitive evidence is lacking, some have hypothesized that verteporfin itself may play a direct role as an anticancer agent via its interaction with the Hippo pathway.[40]

The effect of PDT in pigmented versus amelanotic uveal melanoma:

Although the majority of animal studies examined the effect of PDT on cases of pigmented uveal melanoma[15-18] several early human studies suggested an inverse correlation between the efficacy of PDT and the degree of tumor pigmentation.[21-23] On a cellular level, this

finding may be due to the cytoprotection provided by melanosomes in the RPE and uveal tract,[41,42] with heavily pigmented tumors being more resilient in the face of oxidative stress.

In a series of 12 patients with amelanotic (83%) or lightly pigmented (17%) melanoma, Turkoglu et al found that primary PDT resulted in complete tumor regression in 67% at 5 years.[10] O'Day et al recently published a series of 41 patients with amelanotic choroidal melanoma treated with up to 6 sessions of PDT at 3 month intervals. The majority (88%) showed regression after initial PDT, however 51% required additional treatment over a mean follow up of 3.5 years. Similar to our current study, their time to recurrence was highly variable, ranging from 6 months to 5.5 years[9] (versus 4.7 months to 5.1 years in our study). (Table 5) However in contrast to the large series of amelanotic melanoma treated with PDT reported from Melbourne, Australia[9], our publication included mainly pigmented tumours which may account for the 10% difference in local tumour control rates in the same time period. Interestingly, we found a higher rate of failure for lesions located close to the fovea ($p = 0.002$). One potential explanation for this finding is the anatomic changes that occur within the macula. The taller and narrower RPE cells in this area are more densely packed with melanin granules, theoretically imparting an enhanced level of cytoprotection, thus limiting the destructive effects of PDT.

Histopathological findings following PDT:

With respect to the histopathological effects inducted by PDT, Schlotzer-Schrehardt et al suggested that PDT has a dose related effect on choroidal and retinal structures, with 50J/cm^2 resulting in selective occlusion of the choriocapillaris versus 100J/cm^2 which also caused closure of deeper choroidal vessels and focal RPE alterations.[27] Canal-Fontcuberta et al also noted closure of the superficial vasculature following a single session of PDT; however, 2 of the 5 eyes in this series showed viable melanoma cells with optic nerve and scleral invasion on histopathological examination.[43] Of note, the one patient who underwent enucleation in our cohort did not have evidence of extrascleral extension on histopathology; however, there was no tumor necrosis noted.

The majority of the recurrences (9/14; 64%) in the present study occurred in the form of isolated radial expansion, with little concurrent increase in apical thickness noted on ultrasound in most cases. This may be due to the overlying superficial fibrosis induced by PDT, potentially leaving residual tumor cells at the base of the lesion free to grow posteriorly and laterally along the path of least resistance.[43]

A similar phenomenon has been suggested to occur following TTT, with most recurrences presenting as lateral extensions with minimal increases in thickness.[44] In a series of 357 consecutive patients receiving primary TTT for choroidal melanoma, 10 patients (2.8%) eventually required enucleation. Compared to cases of choroidal melanoma undergoing primary enucleation, those that are enucleated following failed primarily treatment with TTT have a much higher incidence of extra-scleral extension (8%[45] versus 40 – 71%,[44,46] respectively). It remains unclear whether or not this risk holds true for patients undergoing primary treatment with PDT given the small cumulative number of cases requiring enucleation reported in the literature.

It is likely that the small tumours included in this study were melanomas rather than nevi, as documentation of growth was seen in 42% and there was the presence of ≥3 risk factors for future growth in all cases, especially lipofuscin. Most ocular oncologists would consider these to be reasonable indicators for offering treatment for choroidal melanoma. Therefore, this cohort is representative of the real-world population with small, posteriorly located choroidal melanocytic tumours who would be offered treatment as choroidal melanoma. Although correlation of PDT response with cytopathologic or cytogenetic results would be of interest, the small size and posterior location of these tumors makes this difficult to achieve. Although in the majority of instances intraocular biopsy can be carried out uneventfully,[47] there is a small risk of visual complications, an unwanted sequela when the motivation for these patients was to preserve their vision.

Use of PDT as adjuvant and neo-adjuvant treatment in uveal melanoma:

Photodynamic therapy has also been reported as an adjuvant and neo-adjuvant treatment in combination with plaque brachytherapy. Tuncer et al reported a case of a 6.5mm amelanotic choroidal melanoma that responded poorly to plaque brachytherapy but showed dramatic regression following three sessions of PDT.[48] Barbazetto et al similarly found PDT useful as a salvage treatment in four patients with recurrences following plaque brachytherapy and TTT.[49] In a case series of 26 patients, Blasi et al suggested that pre-radiotherapy PDT can reduced tumor thickness in the majority of cases (73.4%) allowing for a smaller radiation dose and subsequently less effect on visual function without compromising disease control.[50]

Effect of PDT on future radiotherapy and risk of systemic metastasis:

Although some authors have advocated the use of PDT in a neo-adjuvant fashion proceeding plaque brachytherapy, finding no difference in recurrence rates at 2 years,[50] we found a relatively high rate of failure following secondary plaque (3/8; 37%). O'Day et al reported similar findings with 2 of 9 (22%) patients undergoing secondary plaque later developing recurrent disease requiring enucleation. They hypothesized that the tumoral ischemia induced by PDT could theoretically reduce radiotoxicity, accounting for a higher than typical rate of local recurrence following plaque brachytherapy.[9] Although our ability to discern whether or not there is a statistically significant increase in the risk of failure following secondary plaque radiotherapy, this potential consequence should be carefully weighed prior to proceeding with primary PDT, particularly for pigmented lesions.

Plaque and proton beam radiotherapy have excellent local tumor control rates, with 89.7-96.8% of patients exhibiting tumor control at 5 years.[51,52] Although short term local tumor control following primary treatment with PDT is encouraging (80% at 1 year)[24] this appears to decrease over time to only 38% by five years. While exceptions to the rule may arise in certain clinical scenarios, PDT with verteporfin is not recommended for primary treatment of choroidal melanoma in the majority of instances. Local tumor control is an important outcome metric, as some have found tumor recurrence to be independently associated with an increased risk of metastasis and tumor-related death.[52] Although no patient in our study, and only one patient in the published literature,[9] developed metastatic disease following primary treatment with PDT, it is likely that our follow up time is not yet long enough to adequately evaluate this outcome, particularly given the small size of tumors included.

The notion of a local laser treatment to activate an appropriately sensitised substrate for small melanomas to preserve vision is an attractive one. This principle is being applied to the Aura biosciences compound (AU-011), which is injected into the vitreous cavity and then activated by laser.[53] It is hoped that such an approach will be superior to verteporfin PDT, in the setting of treating small melanomas while at the same time trying to preserve vision.

In summary, due to the substantial risk of recurrence, primary treatment with verteporfin PDT for small pigmented choroidal melanoma is not recommended in the majority of cases. As rare exceptions to this recommendation will arise in the real-world setting, in the instance that treatment with PDT is performed, close long-term follow up is of paramount importance given the highly variable time to recurrence. As most recurrences after PDT tend to occur along the tumor edges, often with minimal increase in thickness, close monitoring with serial fundus photography and enhanced depth imaging OCT is of paramount importance in detecting recurrence early. (Figure 3) The relatively high rate of recurrence following plaque brachytherapy in both our study and the series published by O'Day et al requires further investigation, and should be taken into account when counseling a patient for primary treatment with verteporfin PDT. However, this treatment strategy allows for maintenance of excellent vision, supporting a possible role for use of verteporfin PDT, particularly in monocular patients or those with other co-morbidities.

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TABLE and FIGURE LEGENDS:

Table 1. Demographic and baseline clinical features of 23 patients with cT1a choroidal melanoma undergoing primary treatment with photodynamic therapy

Table 2. Comparison of pre- and post-treatment characteristics between failure and non-failures.

Table 3. Long term outcomes of 23 patients with small choroidal melanomas undergoing primary treatment with photodynamic therapy.

Table 4. Outcome characteristics of the 7 patients with ongoing follow up and no recurrence following PDT

Table 5. Summary of selected case series evaluating the use of PDT with verteporfin for treatment of choroidal melanoma

Figure 1. Kaplan-Meier estimate for treatment-success following PDT with verteporfin.

Figure 2. A 75-year-old man (patient 22) presented with (A) a lightly pigmented choroidal melanoma with (B) shallow sub-retinal fluid noted on OCT. Forty two months later he remains stable with (C) chorioretinal scaring and atrophy overlying the lesion and (D) no evidence of residual choroidal thickening on OCT.

Figure 3. A 56-year-old male (patient 14) presented with a small choroidal melanoma in May 2015. (A and B) Colour fundus photographs show a pigmented choroidal lesion with lipofuscin, highlighted on autofluorescence. (C) OCT through the lesion confirms the presence of subretinal fluid. (D) Six months following primary treatment with three sessions of PDT, atrophy and chorioretinal scarring are aparent and (E and F) enhanced depth imaging OCT through the central (white star/arrow) and superior margin (black star/arrow) of the lesion confirm regression. (G) While the basal dimensions noted on fundus photographs 14 months later appear relatively unchanged, (H and I) a subtle thickening of the central portion of the lesion (white star/arrow) and a more marked thickening of the superior border (black star/arrow) noted on EDI-OCT allowed for an early detection of recurrence.

549 Table 1. Demographic and baseline clinical features of 26 patients with cT1a choroidal
550 melanoma undergoing primary treatment with photodynamic therapy
551

Age (years)	
(Mean ± SD, Median [IQR, range])	62 ± 14
Gender (%)	
Female	15 (58)
Male	11 (42)
Laterality (%)	
Right	13 (50)
Left	13 (50)
Initial LogMAR affected eye	
(Median [IQR, range])	0.18 [0.3, -0.08 – 0.50]
Tumor dimensions (mm)	
Height (Median [IQR, range])	1.3 [0.7; 0.9 – 2.7]
Largest basal dimension (Mean ± SD, range)	5.4 ± 1.4, 3.0 – 8.9
Distance of tumor from (mm)	
Optic Disc (Median [IQR, range])	2.0 [3.0; 0.0 – 9.0]
Fovea (Median [IQR, range])	1.0 [2.5; 0.0 – 4.5]
Presence of subretinal fluid	
General (%)	23 (88)
Foveal (%)	14 (54)
Symptomatic (%)	17 (65)
Orange pigment	23 (88)
Pigmentation	
Complete	19 (73)
Partial	7 (27)
Amelanotic	0 (0)
Diagnosis	
Diagnosed as melanoma on first visit	15 (58)
Transformed choroidal nevus	11 (42)
Time to transformation (months)	
(Mean ± SD, Median [IQR, range])	67 ± 55, 60 [69, 3 – 190]

552 SD = standard deviation
553 IQR = interquartile range
554
555

Table 2. Comparison of pre- and post-treatment characteristics between failure and non-failures.

	Failure (n=14)	Non-failure (n=12)	P-value
Age	64 ±16	59 ± 11	0.417*
Gender			0.130†
Male	8 (57)	3 (25)	
Female	6 (43)	9 (75)	
Laterality			0.695†
Right	8 (57)	5 (42)	
Left	6 (43)	7 (58)	
Initial LogMAR visual acuity (Median [IQR, range])	0.18 [0.30, -0.08 – 0.50]	0.18 [0.28, -0.08 – 0.30]	0.734‡
Tumor dimensions (mm)			
Height (Median [IQR, range])	1.3 [1.0, 0.9 – 2.7]	1.3 [0.5, 0.9 – 1.8]	0.661‡
Largest basal dimension (Mean ± SD)	5.8 ± 1.7	5.0 ± 0.9	0.221*
Distance of tumor from (mm)			
Optic Disc (Median [IQR, range])	1.8 [2.6, 0.0 – 4.5]	2.0 [3.4, 0.0 – 9.0]	0.694‡
Fovea (Median [IQR, range])	0.5 [1.3, 0 .0– 4.0]	2.5 [2.8, 0.5 – 4.5]	0.002‡
Sub-retinal fluid at initial exam			
General	14 (100)	9 (75)	0.085†
Sub-foveal	9 (64)	5 (42)	0.431†
Symptomatic (%)	10 (71)	7 (58)	0.683†
Orange pigment	13 (93)	10 (83)	0.580†
Pigmentation			0.838§
Complete	10 (71)	9 (75)	
Partial	4 (29)	3 (25)	
Amelanotic	0 (0)	0 (0)	
Final LogMAR visual acuity (Median [IQR, range])	0.50 [0.80, 0.00 – 2.00]	0.00 [0.14, 0.00 – 0.30]	**0.002‡**
Total follow up (months) (Median [IQR, range])	49.5 [13.8, 7.0 – 63.0]	50.5 [15.5, 14.0 – 66.0]	0.918‡

* students t-test
† Fishers exact test
‡ Mann-Whitney U test
§ Chi-square test

Table 3. Long term outcomes of 26 patients with small choroidal melanomas undergoing primary treatment with photodynamic therapy.

Primary treatment with PDT	
Success (%)	12 (46)
Failure (%)	14 (54)
Time to failure from primary treatment with PDT (months)	
Median [IQR, range]	20.0 [20.5, 4.7 – 60.9]
Secondary treatment	
PDT	2
Success (%)	0 (0)
Failure (%)	2 (100)
Time to failure	6- and 21-months
Ruthenium plaque brachytherapy	8
Success (%)	5 (63)
Failure (%)	3 (37)
Time to failure	9-, 17- and 32- months
Proton beam radiotherapy	4
Success (%)	4 (100)
Failure (%)	0 (0)
Tertiary treatment	
PDT	1 *
Success (%)	1 (100)
Failure (%)	0 (0%)
Ruthenium plaque brachytherapy	1
Success (%)	0 (0)
Failure (%)	1 (100)**
Time to failure	33-months
Proton beam radiotherapy	2
Success (%)	2 (100)
Failure (%)	0 (0)
Enucleation	1

* This patient underwent a total of 3 sessions of PDT and has remained stable 4.1 years following initial PDT

** this patient underwent proton beam radiotherapy as a quaternary treatment 64 months following initial PDT

571 Table 4. Outcome characteristics of the 10 patients with ongoing follow up and no recurrence
572 following PDT
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Study Number	Age	Diagnosis	Pigmentation	Thickness pre-treatment (mm)	Thickness at last follow up (mm)	SRF involving the fovea and/or lesion at last follow up	Systemic status	LogMAR at last follow up	Total follow up (months)
2	51	Transformed nevus	Complete	0.9	0.5	No	Alive, no metastasis	0	66
6	56	Transformed nevus	Partial	1.5	1.1	Yes	Alive, no metastasis	0	58
13	58	Transformed nevus	Complete	1.4	1.5	No	Alive, no metastasis	0	54
17	54	Melanoma	Complete	1.1	1.2	No	Alive, no metastasis	0	44
20	50	Melanoma	Complete	1.7	0.4	No	Alive, no metastasis	0	47
21	65	Melanoma	Partial	1.6	0.8	No	Alive, no metastasis	0.2	45
22	75	Transformed nevus	Complete	1.8	0.8	No	Alive, no metastasis	0	42
24	69	Melanoma	Partial	1.1	0.7	No	Alive, no metastasis	0.2	64
25	38	Transformed nevus	Complete	1.7	0.8	No	Alive, no metastasis	0.0	54
26	55	Melanoma	Partial	1.2	0.8	No	Alive, no metastasis	0.0	58

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577 Figure 1
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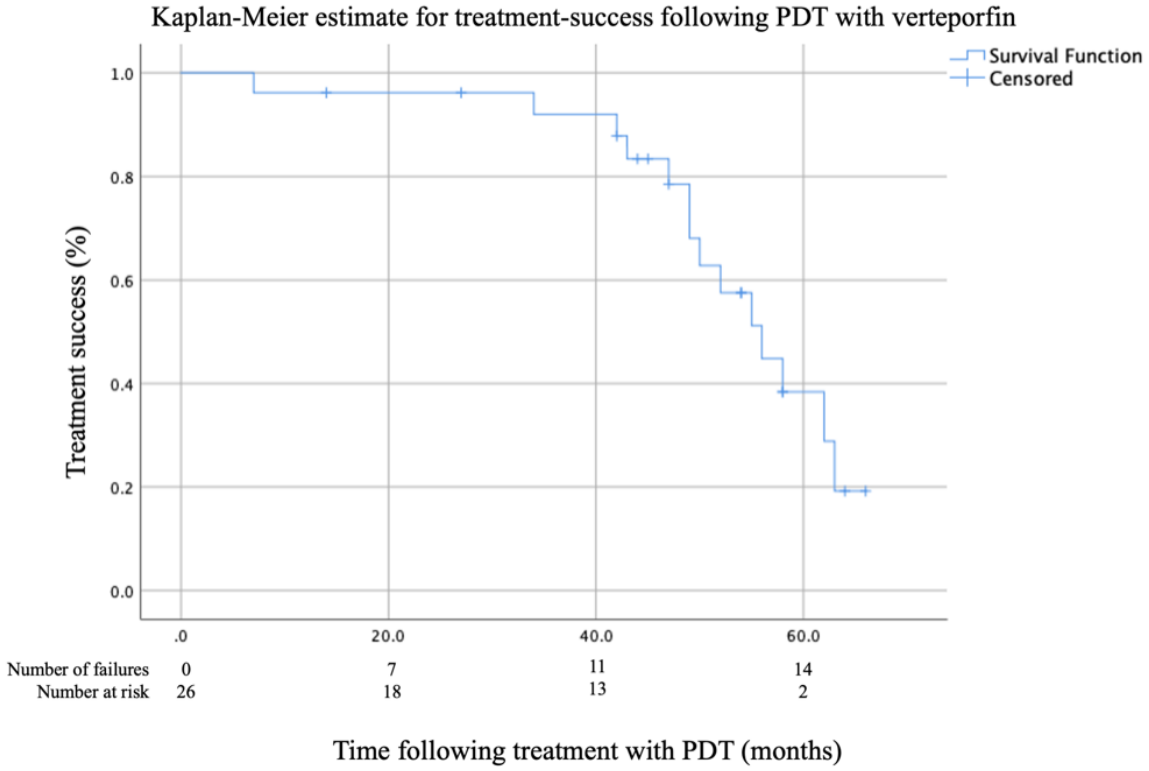

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581 Figure 2
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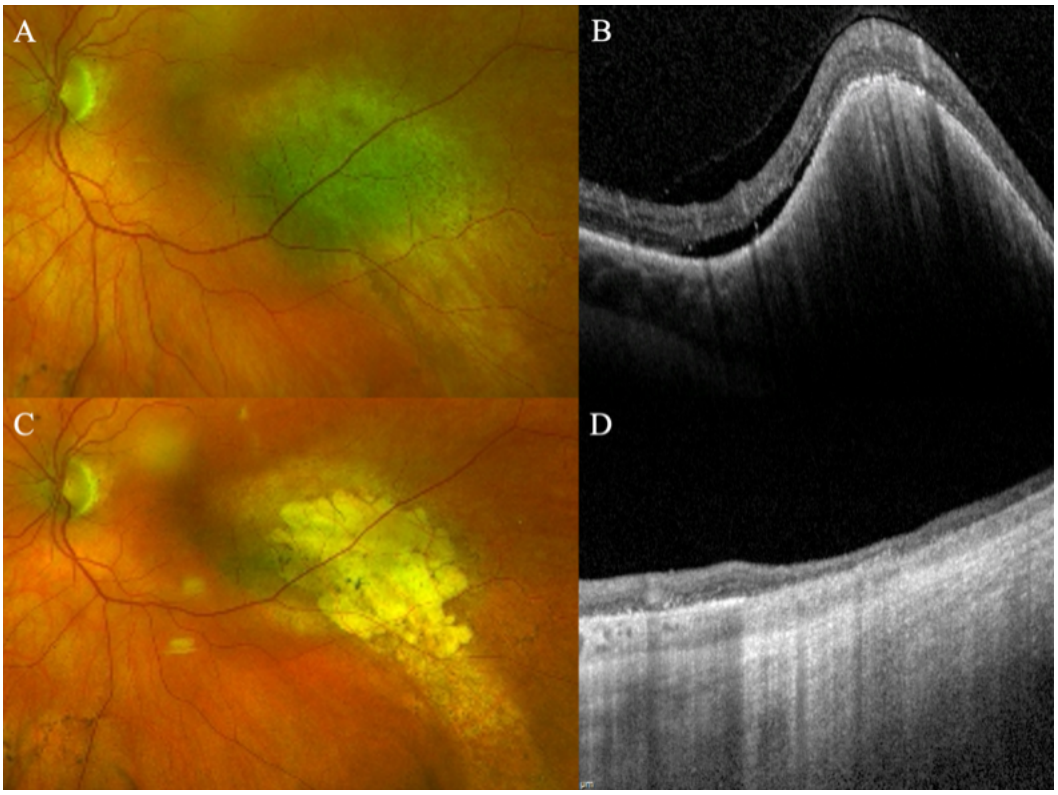

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587 Figure 3
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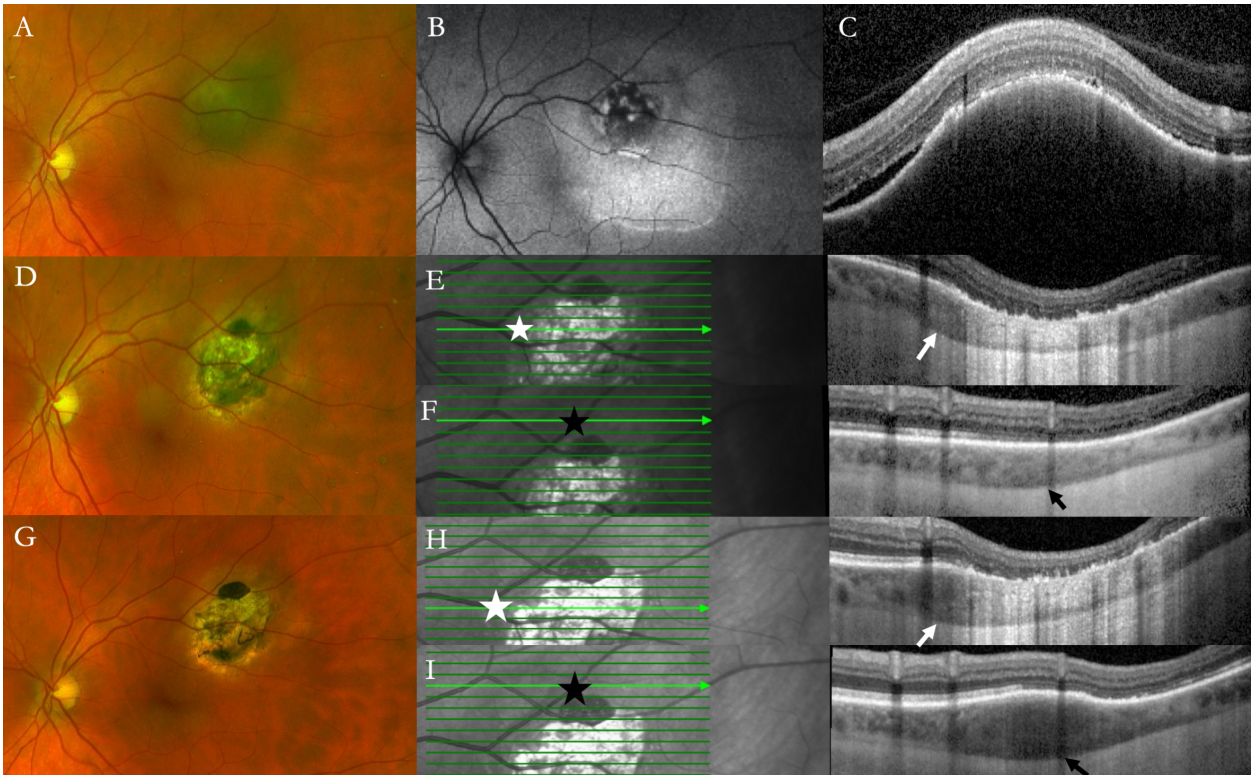

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