Primary Photodynamic Therapy with Verteporfin for Small Pigmented Posterior Pole Choroidal Melanoma

Running title: PDT for pigmented choroidal melanoma

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Abstract

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

Methods: Prospective interventional consecutive case series of 15 patients with small pigmented posterior pole choroidal melanoma, who were treated with 3 sessions of PDT and followed-up thereafter. Risk factors for failure were assessed and outcome measures at presentation were compared to those at last follow-up visit.

Results: Tumour control was achieved in 12 (80%) patients in a median follow-up time of 15 months (mean 14, range 8-18). Three patients failed treatment, diagnosed in a median time of 5 months (mean 4, range 3-6) after first PDT. In all failed cases, lesions were 100% pigmented; de-novo melanoma rather than transformed naevi, and showed a radial growth pattern rather than increased thickness. All failed cases were subsequently successfully treated with radiotherapy. In this cohort, SRF was significantly reduced (p<0.001), vision did not deteriorate (p=0.11) and even improved in patients with subfoveal SRF at presentation (p=0.018), tumour height significantly decreased (p=0.037) and no complications were recorded.

Conclusion: Primary PDT was found to be a safe and efficient treatment modality for small pigmented posterior pole choroidal melanoma, achieving short term tumour control in 80% of patients. PDT offers patients the opportunity to preserve vision by avoiding the retinopathy associated with conventional radiation treatments for choroidal melanoma. However, the long-term local control of these tumours remains uncertain.

Introduction

The most commonly used treatment modality for choroidal melanoma is radiotherapy.[1] This treatment, while achieving good local control, results with complications compromising vision in more than 50% of cases.[2] Loss of vision is often accepted by patients who have already experienced visual loss from medium and large sized tumours, especially as larger tumours are associated with a poorer survival.[3] However, the risk benefit ratio is perceived less for small posterior pole melanoma where vision may be normal and survival figures are better.

Timing of treatment for an evolving melanoma is a matter of debate. While some studies looked into the risk factors for tumour growth,[4] a synonym to active melanoma, there is no consensus as to how many or what combination of risk factors should be present to decide treatment is appropriate. In light of the abovementioned, many clinicians are reluctant to treat small suspicious choroidal lesions and wait until there is documented tumour growth, especially if the patient has no visual symptoms.

In search of an ideal treatment for a small posterior pole choroidal melanoma, such a modality would result in both high rate tumour control and cause little or no collateral damage, maintaining visual function. Such a treatment would be most useful for patients diagnosed in an early stage of their disease and who still have intact vision, and especially for those diagnosed with a tumour in an only seeing eye.

Photodynamic therapy (PDT) with verteporfin, potentially, is one such treatment. Originally used for choroidal neovascularization in age-related macular degeneration,[5] in ocular oncology it is an efficient modality for selected cases of

benign vascular tumours and choroidal metastasis.[6] The main mechanism of action of PDT with verteporfin is believed to be the formation of free oxygen radicals, which in turn cause damage to cellular components.[6] Since the treatment is localized and does not comprise of delivering of thermal energy, minimum collateral damage is caused.

As primary treatment for choroidal melanoma, PDT was successfully used in experimental animal studies,[7] including when verteporfin was used as a photosensitizer.[8,9] Clinically, PDT with verteporfin was tested only in a handful of studies and case reports,[6,10–14] with positive response in most. Interestingly, while in some reports PDT was effectively used for both amelanotic and pigmented tumours,[12] others raised doubt as to its efficacy in treating pigmented ones.[6,14] As most choroidal melanomas are pigmented, it is important to investigate its role in treating these tumours. We aimed in this study to prospectively investigate the outcomes of primary PDT with verteporfin for small pigmented posterior pole choroidal melanomas.

Subjects and Methods

The study was performed in a prospective manner and approved by the Moorfields Eye Hospital institutional review board in concordance with the declaration of Helsinki. Since 01 April 2014, all patients in the London Ocular Oncology Service with small posterior pole choroidal tumours were offered treatment with PDT. To be included, tumours had to either demonstrate documented growth, or to have at least 3 risk factors for growth.[4] Of the risk factors, the presence of lipofuscin was a prerequisite, to differentiate cases of choroidal melanoma from leaking choroidal naevi. Patients were also offered the option of observation or conventional treatment with plaque radiotherapy or proton beam radiotherapy, according to each clinical scenario. The potential benefits and disadvantages of each management option were discussed and informed consent was obtained.

Included for analysis were tumours treated with 3 PDT sessions and followed-up for at least 6 months from first session. In addition, analysis was restricted to tumours that were 100% pigmented or partly pigmented, defined as pigmentation involving at least 50% of the tumour's surface area.

At presentation and on ensuing follow-up clinical appointments, patients underwent a full ophthalmic evaluation, including slit lamp examination, color fundus imaging, autofluorescence, optical coherence tomography of the lesion and macula and B-scan ultrasonography.

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. After completion of treatment, patients were instructed to avoid exposure to direct light for 48 hours. Patients received 3 PDT sessions, 4-8 weeks apart, and were closely monitored thereafter, once every 3 months. At completion of the study all clinical, imaging and technical data were retrieved from medical records and analyzed.

Data and Statistical Analysis

For treatment success cases, variables from presentation and last follow-up visit were used for analysis, whereas for failed treatment cases those at presentation and at time of failure were used. Treatment success was defined as achieving tumour control after PDT and throughout follow-up.

All calculations and plotting were completed using the R Statistical Environment. Continuous variables were evaluated with Student t tests and categorical variables with Fisher's Exact Test. P-value<0.05 was considered significant. Snellen acuity was converted to logMAR equivalent.

Results

Fifteen patients were found to fulfill the inclusion criteria for the study. There were 5 males and 10 females at a median age of 66 years (mean 64, range 32-81). **Table 1** depicts the demographic and clinical features of the study patients at presentation and the PDT parameters used. Four (27%) tumours showed documented growth at a median time of 7 years (mean 8, range 2-16) after first presentation. Seven (47%) tumours were located within one disc diameter (DD) from the fovea and 10 (67%) within one DD from the optic disc (**Figure 1)**. Tumour control was achieved in 12 (80%) cases (**Figure 2**), and for these, median follow-up time from first PDT session to last visit was 15 months (mean 14, range 8-18).

Treatment failure

PDT failed in 3 cases (**Figure 3**), detected at a median time of 5.0 months (mean 4.3, range 2.5-5.5) from first PDT session and 2.0 months (mean 1.8, range 0.5-3.0) after last PDT session. In all 3 cases the tumours were 100% pigmented and de-novo. Treatment failure was characterized by tumour enlargement in base diameter rather than in thickness. The median base diameter in these 3 cases was 4.9mm pre-PDT (mean 5.3, range 3-8) and 6.8mm post-PDT (mean 6.8, range 3.9-9.7).

One of the failed treatment cases (number 9 in **Figure 1**) was of a relatively thicker tumour with apical height of 2.7mm. This patient was originally offered plaque radiotherapy, however declined treatment owing to concern regarding possible visual loss.

In all 3 failure cases the amount of SRF was reduced after PDT, in one it was totally eliminated. In two cases logMAR remained the same after treatment and in one it improved. On statistical analysis, none of the demographic or clinical variables were found to be significant risk factors for failure. This was also the case when a subgroup analysis was performed, after excluding the pre-treatment documented growth cases. The 3 PDT-failed cases required further treatment, which included ruthenium plaque radiotherapy (n=2) and proton beam radiotherapy (n=1), they continue to be under surveillance in our clinic and show good tumour response to the radiotherapy.

The impact of PDT on subretinal fluid, vision and tumour dimensions and treatment complications

Figure 4 shows the change in SRF over the lesion and fovea, logMAR and tumour height between presentation and last follow-up visit for the whole cohort. SRF was detected in 13 cases at presentation, but was only seen in 4 cases at the last follow-up visit. Of these 4 cases, the amount of SRF was reduced in 3 after treatment. In total, SRF over the lesion was reduced by a median of -179µm (mean -162, range 0-395; $p<0.001$). Seven patients had subfoveal SRF at presentation but none of them had subfoveal SRF at last follow-up visit ($p=0.03$).

Median final logMAR visual acuity was 0 (mean 0.07, range -0.08-0.48). It remained the same or improved in 12 out of 15 of the cases, a change that was not found statistically significant ($p=0.11$). A significant improvement in median vision logMAR

was however found on subanalysis of patients with subfoveal SRF at presentation: -0.08 (mean (-0.12), range 0.00 – (-0.24); p=0.018).

In terms of tumour dimensions, for the entire cohort, final median tumour thickness (median 1.0mm, mean 1.1mm, range 0.4-2.6mm) was found to be significantly reduced compared to presentation (p=0.037). Final tumour base diameter (median 4.7mm, mean 4.8mm, range 2.5-9.7mm) showed no significant change as compared to presentation (p=0.72).

No local complications were recorded after PDT and throughout follow-up, no systemic side effects were reported, and none of the patients developed metastatic disease.

Discussion

Our early experience of treating small pigmented posterior choroidal melanoma is encouraging, especially as we report on tumour control rate of 80%. Furthermore, using this modality, treatment also resulted with significant reduction in SRF, no worsening of vision, significant anatomical change, namely reduced tumour height, and no treatment complications.

Treatment failure

Treatment failure was documented in 20% of cases. These rates are higher compared to juxtapapillary choroidal melanoma treated with plaque radiotherapy, in which failure rates were 3% at one year and 7% at 2 years.[15] Nevertheless, close follow-up of the failed cases enabled early detection of the active tumours, and successful treatment with radiotherapy. All PDT-failed cases remained in the "small tumour" category and their definitive treatment was delayed only by several months, not posing them at significant additional local or systemic risk.

All failed cases were 100% pigmented and de-novo tumours. It is noteworthy that in all failure was diagnosed in a narrow time frame after last PDT session, and most interestingly, all showed horizontal growth failure pattern rather than increase in tumour height. These findings however were not statistically significant and their impact as potential risk factors for treatment failure, for the prior, or treatment failure characteristics, for the latter, is yet to be determined.

The impact of PDT on subretinal fluid, vision and tumour dimensions and complications

For the entire cohort, SRF was significantly reduced as a result of PDT, a beneficial impact of treatment. The mechanism of action of this effect is not fully understood and might be related to choriocapillary occlusion.[8,16] It remains to be proved whether PDT has a direct effect on the choroidal tumour, or an effect purely on its vascular supply, as SRF was reduced in cases in which tumours remained active. Interestingly, PDT also resulted with fluid elimination in cases of leaking choroidal naevi, as reported by Pointdujour-Lim et al.[17] It is important to emphasize that lack of tumour growth after treatment, not resolution of SRF, implies successful tumour control. Hence long term follow up of all cases is required to fully determine the success of primary PDT for small choroidal melanoma. However, our early results coupled with close observation and treatment with radiotherapy is a useful strategy for the treatment of these lesions.

Visual acuity was found not to worsen during the study period. At final follow-up visit, 14 (93%) patients had vision of 20/30 or better, 10 of which had vision of 20/20 or better. Importantly, patients with SRF at the fovea showed a significant improvement in visual acuity, underscoring the cause for reduced vision on the first place.

Two thirds of tumours in this cohort were juxtapapillary. Several studies investigated the visual outcomes after radiotherapy for juxtapapillary or juxtafoveal choroidal melanoma.[2,18–20] Recently, Patel et al. reported on their experience with proton beam radiotherapy as treatment for juxtafoveal choroidal melanoma.[18] At

presentation, approximately 50% of patients had vision of 20/50 or worse, worsening due to radiotherapy complications to over 80% of patients with vision in that range, half of which had vision of counting fingers or worse at last follow-up visit. Of the patients with tumour elevation of 5 mm or less at presentation, after one year, 70% retained 20/40 vision, dropping to approximately 50% after 2 years. Similar findings were reported also in additional studies.[19,20] Visual outcomes of juxtapapillary choroidal melanoma cases treated with plaque radiotherapy were reported by Sagoo et al,[2] who found that 7% of patients had final visual acuity of 20/200 or worse after one year and nearly 20% at 2 years. Though the initial Snellen acuity in that series was not reported, 53% of their cohort presented with reduced visual acuity.[15] In that study most clinical factors predictive of poor final vision were related to tumour and plaque sizes, radiation dose and tissue damaged by radiation.[2] When comparing the abovementioned studies with the present one, in terms of visual function, juxtapapillary tumours are better diagnosed early and treated with PDT, rather than at a later stage and treated with radiation. It should be stressed that these clinical management suggestions are valid for juxtapapillary or perifoveal tumours where the risk of permanent vision loss after radiotherapy is high. Choroidal melanoma located away of the fovea and optic disc should still be managed with plaque brachytherapy as this treatment may have little or no negative impact on vision.

Tumour dimensions are important factors to take into account prior to using PDT for pigmented choroidal melanoma. In our hands, and in others, tumours <2mm in apical height benefit the most from this treatment modality. Canal-Fontcuberta et al. treated 3 cases of pigmented choroidal melanoma >2mm in height with PDT, one of

which was 8.7mm in elevation, and found that treatment failed in all.[14] In contrast, Rundle used PDT on 9 patients with pigmented choroidal melanoma measuring <2mm in average and found treatment to be successful in 8 out of 9 cases. Treatment failed in only one case where the melanoma was 3mm in height.[12] Interestingly, Kim et al. used PDT as treatment for pigmented choroidal melanomas ≥3mm in apical height in an *in-vivo* animal model and showed complete tumour arrest in all treated animals.[8] This however was not shown in humans.

In terms of tumour response to treatment, interestingly, PDT resulted with a significant reduction in tumour height, and not only had an impact on indirect measures, i.e. SRF and vision. This, of all variables, emphasizes its beneficial effect on these tumours. The observed reduction in tumour height might be related to damaged tumour cells or local necrosis as a result of occlusion of tumour vascular supply.[8,16]

Few complications of PDT are reported in the literature and these include transient visual disturbances, vascular occlusion, choroidal atrophy, intravitreal hemorrhage and exudative retinal detachment.[6] None of these complications however occurred in the present study.

The limitations of this study include its small cohort size and relatively short follow-up time. Nevertheless, it provides significant information on the outcomes of PDT for this subset of patients. While all patients in this study received treatment, some might hold the view that patients in such an early stage of their disease are better observed, and only treated when there is documented growth. This issue is under constant debate and there is no agreement on this management dilemma.[21]

Nevertheless, it is our assumption that those who advocate observation first, prefer this option as the only modality currently available for these tumours is radiotherapy which causes iatrogenic damage. In terms of justification to treat, we selectively chose only patients with 3 or more risk factors for growth, of these, 73% had 4 or 5 risk factors, and all showed lipofuscin.[4,22]

In summary, in this cohort, primary PDT with verteporfin was found to be an efficient treatment modality for small, pigmented posterior pole choroidal melanoma with a success rate of 80%. Close follow-up, once every 3 months following PDT, enabled early detection of growing tumours in 3 patients, all successfully treated with radiotherapy. PDT resulted with significant reduction in SRF, no worsening of visual acuity and no complications. Longer follow-up studies with larger cohorts are required to see if these beneficial results are maintained.

Conflict of Interest

The authors report on no conflict of interest.

Acknowledgments

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Figure Legend

Figure 1

Schematic diagram of tumour locations (x marks approximate tumour center, + the fovea). Table includes patient's corresponding tumour height and base diameter.

* Patients who failed PDT.

** Choroidal melanoma with documented growth.

Figure 2

Pigmented choroidal lesion (A; patient number 8 in **Figure 1**), 2.5mm from the optic disc, with scattered lipofuscin orange pigment, corresponding to areas of hyper-autofluorescence (B). Optical coherence tomography demonstrated SRF over the lesion, but not over the fovea (D). Sixteen months after first PDT session, the lesion is stable in size (E) and SRF eliminated (F).

Figure 3

Pigmented choroidal melanoma (A; patient number 3 in **Figure 1**), 0.5mm from the optic disc, with scattered orange pigment and overlying SRF (B). The patient was treated with 3 PDT sessions; however showed tumour radial enlargement (C), detected 5 months after first and 3 months after last PDT session. Note that despite treatment failure SRF over the lesion was eliminated. The patient was thereafter successfully treated with a notched plaque.

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Figure 4 369

Graphs to changes in clinical measures from presentation to last follow-up visit, 370
including SRF over the lesion (n=13, p<0.001; A), SRF over the fovea (n=7, p=0.03; B), 371
logMAR (n=15, p=0.11; C) and tumour thickness (n=15, p=0.037; D). 372

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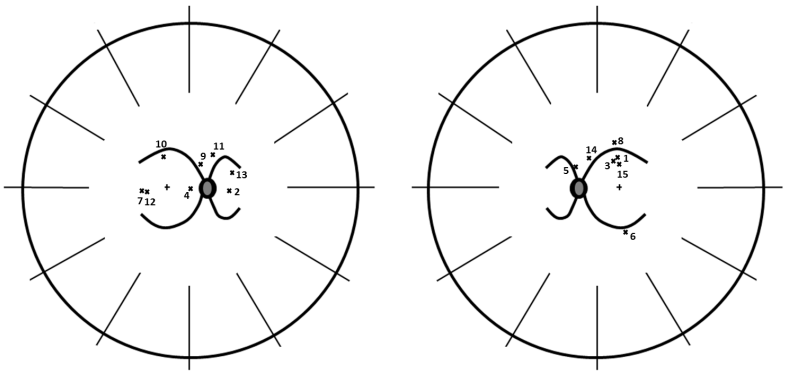
Figure 1



Patient	Tumour height (mm)	Tumour base diameter (mm)
1	1.8	6
2**	0.9	5
3*	0.9	4.9
4*	0.9	3
5	1.1	4
6**	1.1	4.7
7	1.5	5.1
8**	1.2	5
9*	2.7	8
10	1	4
11**	1	4
12	0.9	3.5
13	1.65	6.3
14	1.2	4.5
15	1.5	5

Figure 2

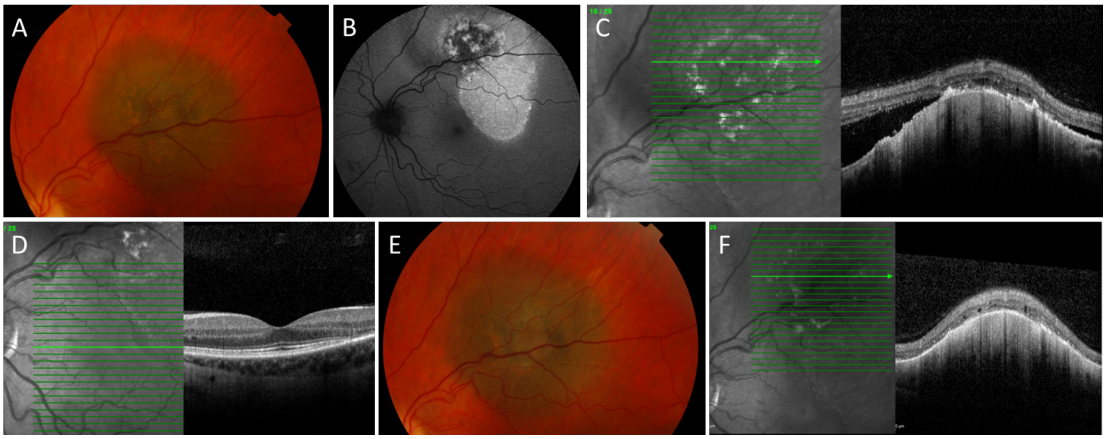


Figure 3

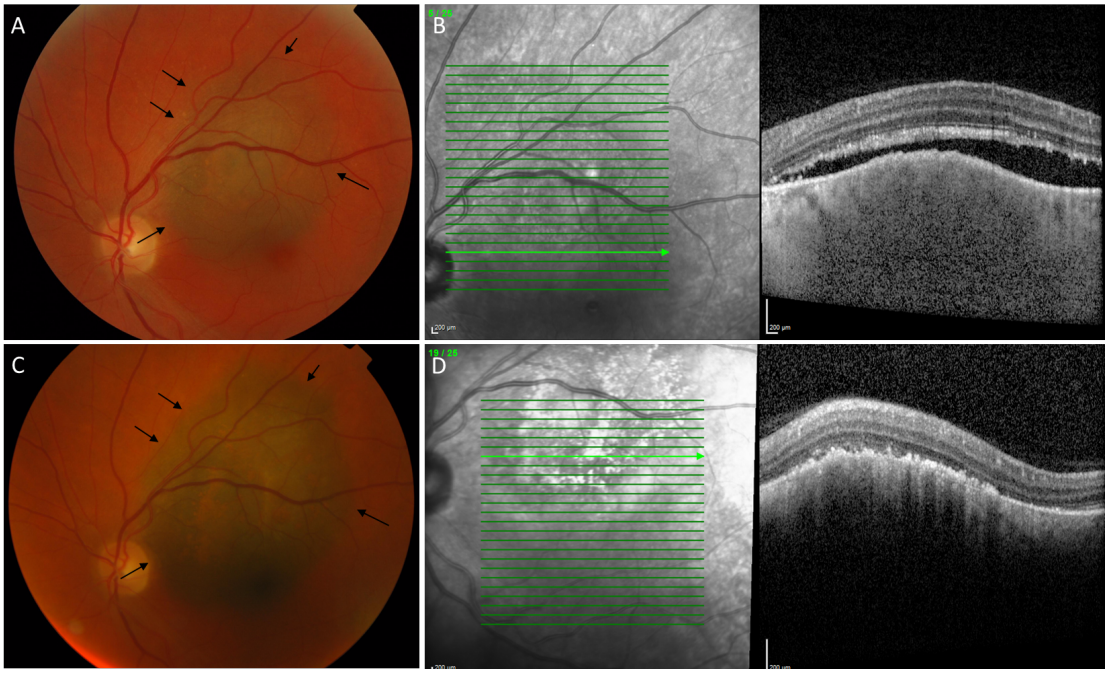


Figure 4

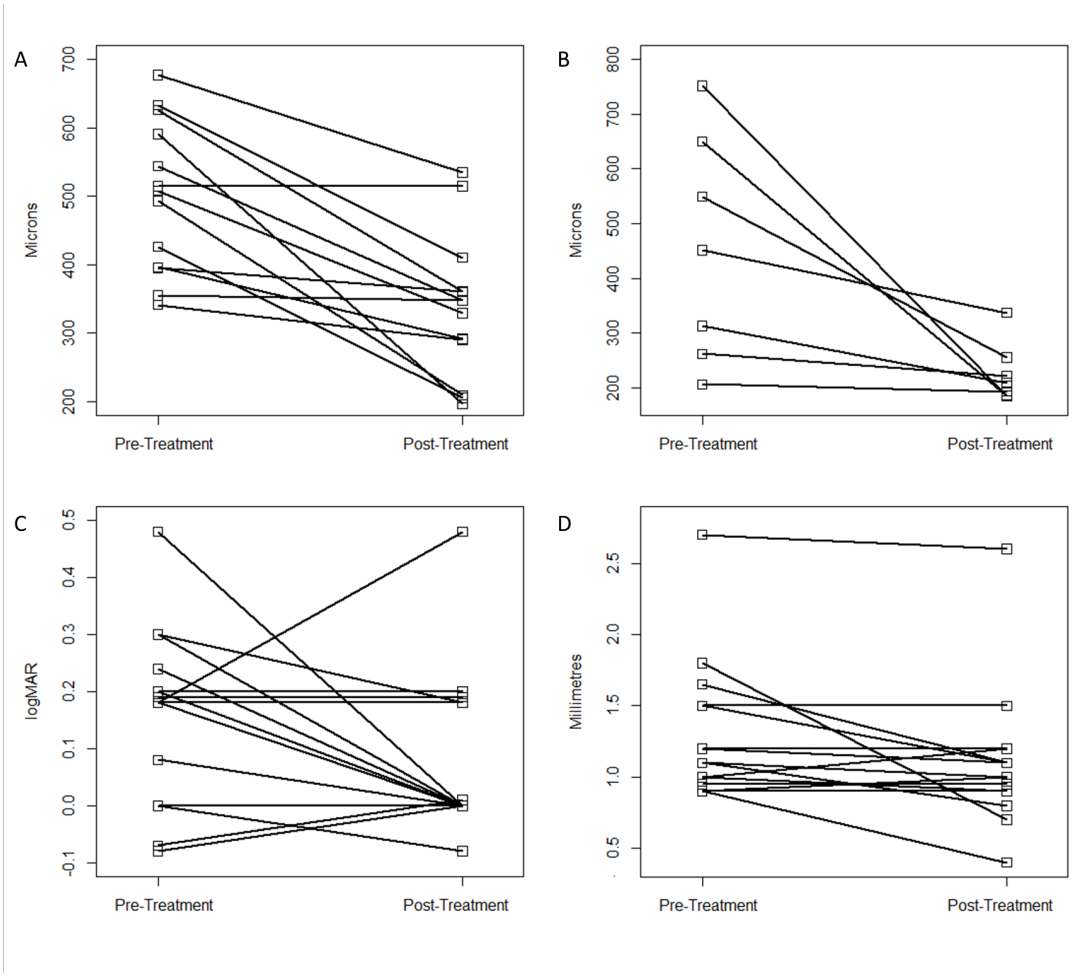


Table 1. Primary photodynamic therapy with verteporfin for small pigmented choroidal melanoma in 15 patients: Patient's demographic and clinical features at presentation and treatment data.

Features	Number	Percentage
Age (years) Median (mean, range)	66 (64, 32-81)	
Gender Male Female	5 10	33 67
Laterality Right Left	8 7	53 47
LogMAR visual acuity in tumour eye Median (mean, range)	0.18 (0.16, -0.08-0.48)	
LogMAR visual acuity in fellow eye Median (mean, range)	0.00 (0.15, -0.10-1.30)	
Documented growth	4	27

Number of risk factors for growth* (n=11)	3 risk factors – 3 4 risk factors – 7 5 risk factors - 1	27 64 9
Symptoms Photopsia Blurred vision None	 2 8 5	 13.3 53.3 33.3
Tumour dimensions (mm) Median (mean, range)	Height: 1.1 (1.3, 0.9-2.7) Base: 5.0 (4.9, 3.0-8.0)	
Distance of tumour from (mm): Median (mean, range)	Optic disc: 0.5 (1.3, 0-5) Fovea: 1.5 (1.7, 0-4)	
Presence of subretinal fluid: Above lesion Subfovea	 13 7	 87 47
Tumour pigmentation 100% >50%	 12 3	 80 20
PDT spot size (µm, summary of 3 sessions) Median (mean, range)	5600 (5139, 3800-5600)	
* Lesion thickness >2mm, presence of subretinal fluid, presence of lipofuscin, related symptoms or margin to optic disc ≤3mm.[4]		

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