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Proton beam radiotherapy for choroidal and ciliary body melanoma in the UK—national audit of referral patterns of 1084 cases

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INTRODUCTION: Proton beam therapy has been utilised for the treatment of uveal melanoma in the UK for over 30 years, undertaken under a single centre. In the UK, all ocular tumours are treated at one of four centres. We aimed to understand the variation in referral patterns to the UK proton service, capturing all uveal melanoma patients treated with this modality.

METHODS: Retrospective analysis of data regarding all patients treated at the Clatterbridge Proton service between January 2004 and December 2014.

RESULTS: A total of 1084 patients with uveal melanoma were treated. The mean age was 57 years (range 9–90 years), basal diameter of 11.5 mm (range 2.0–23.4 mm) and tumour thickness of 3.9 mm (range 0.1–15.4 mm). The majority were TNM stage I (39%) or II (36%). The distance to the optic nerve varied from 0 to 24.5 mm with 148 (14%) of patients having ciliary body involvement. There were variations in the phenotypic characteristic of the tumours treated with protons from different centres, with London referring predominantly small tumours at the posterior pole, Glasgow referring large tumours often at the ciliary body and Liverpool sending a mix of these groups.

DISCUSSION: In the UK, common indications for the use of proton treatment in uveal melanoma include small tumours in the posterior pole poorly accessible for plaque treatment (adjacent to the disc), tumours at the posterior pole affecting the fovea and large anterior tumours traditionally too large for brachytherapy. This is the first UK-wide audit enabling the capture of all patients treated at the single proton centre.

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INTRODUCTION

Proton beam radiotherapy (PBR) is a highly conformal radiotherapy offering considerable advantages over conventional teletherapy with x-rays. In particular, the radiation dose received by adjacent critical or healthy tissue is significantly lower compared to photons [1]. Significant disadvantages are the much higher capital and running costs and the necessity for technically advanced facilities designed to optimise patient treatment. In addition, there is a paucity of clinical outcome data supporting the use of protons over other types of radiotherapy for a number of potential treatment indications [2]. Despite the theoretical advantages of proton beam treatments and its introduction into clinical practice in the 1950s, it is currently used in less than 1% of all tumours undergoing radiotherapy across all disciplines of oncology [1, 3]. However, the percentage is increasing; in the UK, a recent major investment by the government through the Department of Health has led to the construction of two new PBR treatment centres, focussing mainly on head/neck and central

nervous system tumours in paediatric patients, teenagers and young adults [4].

In contrast to other oncology subspecialties, PBR has established itself as one of the core treatments of ocular tumours worldwide. Since the first treatment in the USA in 1975, a number of centres specifically designed for eye tumours have been established; based on previously published series, it can be projected that now more than 43,000 patients have been treated with this method worldwide [5, 6]. Multiple clinical studies have been published, demonstrating excellent results regarding the major parameters in judging successful treatment of uveal melanoma (UM): eye preservation, tumour recurrence and vision [7, 8]. Some recent studies suggested that early treatment of UM may have a beneficial effect on survival [9–11]. PBR could be of particular advantage, as the damaging side effects on vision caused by the destruction of non-malignant tissue surrounding the tumour seem to be less pronounced in small T1 tumours compared to other methods of radiotherapy [12]. This could lower

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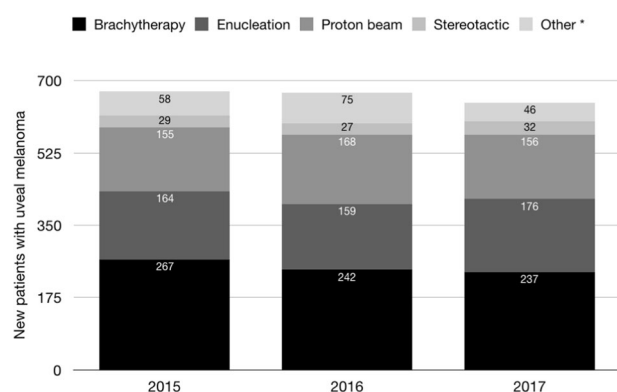


Fig. 1 Primary treatment for new patients with uveal melanoma in the UK from 2015 to 2017. Combined data from the centres in Glasgow, Liverpool, London and Sheffield presented at the Annual Meetings of the Adult Ocular Oncology Services in the UK. *Other includes surgical resection, photodynamic therapy, declined treatment, and management with observation.

the threshold for early treatment of small tumours near the fovea and disc.

In the UK, between 650 and 700 new cases of UM are treated per year (Fig. 1). Four centres within the National Health Service (NHS), in Glasgow, Liverpool, London and Sheffield, have been commissioned as Highly Specialized Services for Adult Ocular Oncology. In the UK, about 70% of patients undergo radiotherapy as the initial treatment method, with the remaining 30% treated surgically with enucleation or surgical resection (Fig. 1). Three types of radiotherapy are currently used in the UK to treat UM: Ruthenium-106 plaque brachytherapy is the most commonly applied method in 40–50% of all new patients. PBR is used to treat between 20 and 40%. Stereotactic radiotherapy is performed in the Sheffield Centre and is used in approximately 4% of all new patients [13–15].

In the UK, the cyclotron service at Clatterbridge was established as the first hospital-based cyclotron unit for patient treatment in 1989 [14]. The use of PBR varies from centre to centre and from country to country, mainly depending on the availability of proton beam facilities and the experience with the method.

This study was conducted as a national audit of referral patterns across the four centres in the UK, for proton treatment over a 10-year period.

MATERIALS AND METHODS

Patients

Inclusion criteria: in this retrospective study, clinical notes from all patients treated at the Clatterbridge proton beam service from January 2004 to December 2014 were reviewed. All patients with choroidal or ciliary body melanoma treated by PBR as their primary treatment were included.

Exclusion criteria: iris and ocular surface melanomas were excluded as the AJCC tumour classification and potential for metastatic disease are significantly different from ciliary body and choroidal lesions. Non-UK resident patients were also excluded as their follow-up would be limited.

All baseline visits consisted of a complete clinical ophthalmological examination, colour tumour photography and ultrasonography. Local patient records as well as Clatterbridge recorded data were utilised in unison and collected by each oncology centre, and subsequently collated. Parameters recorded include age, gender, best-corrected visual acuity, tumour dimensions (largest tumour diameter, height), location of anterior and posterior tumour margin (iris, ciliary body, pre-post equatorial choroid), ciliary body involvement, distance to fovea, disc involvement, extraocular spread, infiltration, retinal detachment, TNM staging and tumour volume.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Institutional Review Board/Ethics committee approval was not required due to the retrospective nature of

Table 1. Baseline patient demographics and tumour characteristics.

Baseline patient demographics and tumour characteristics (n = 1084)	
	Mean, median (range)
Age at diagnosis (years)	57, 59 (9–90)
Males:females	571:495 (1.15:1)
Longitudinal base diameter (mm)	11.47, 11.0 (2.0–23.4)
Tumour thickness (mm)	3.93, 3.0 (0.1–15.4)
TNM staging (n = 936)	
I	420 (38.7%)
IIa	391 (36.0%)
IIb	4 (0.4%)
IIc	4 (0.4%)
IIIa	188 (17.3%)
IIIb	11 (1.0%)
IIIc	1 (0.1%)
IV	65 (6.0%)
Ciliary body involvement	148 (13.7%)
Extraocular extension	20 (1.8%)
Distance to nerve (mm)	4.43, 2.5 (0–24.5)
Distance to fovea (mm)	3.88, 1.5 (0–24.4)
Tumour volume (cc)	0.37, 0.25 (0.01–2.00)
Length of optic nerve treated at 90% (mm)	0.67, 0.0 (0–5.8)
Volume of macula at 90% dose (%)	38.92, 0.0 (0–100)
Ciliary body dose (%)	14.79, 0.0 (0–100)
Corneal dose (%)	10.06, 0.0 (0–100)

this audit. Statistical analysis was undertaken with a single-factor ANOVA to assess the significance of differences in tumour characteristics between centres. *P* values <0.05 were considered significant.

RESULTS

Over the study period, 1084 patients were treated for choroidal or ciliary body melanoma in the UK with PBR as primary treatment at the Clatterbridge Centre for Oncology (now The Clatterbridge Cancer Centre). Patients had a mean age of 57 years with a male:female ratio of 1.15:1 (Table 1). The right eye was affected in 563 patients (51.9%). The baseline visual acuity of the affected eye was $\geq \log\text{Mar}$ 0.0 in 463 (42.7%), 0.1–0.3 in 301 (27.8%), 0.4–0.9 in 219 (20.2%) and ≤ 1.0 in 101 (9.3%).

The anterior tumour margin was located post equatorial in 503 (46.4%), between the equator and pars plicata in 358 (33.0%) and involved the angle/iris in 223 (20.6%). The posterior tumour margin was located at the disc in 384 (35.4%), at the fovea in 362 (33.4%), at 1–2-disc diameters away from the disc or fovea in 224 (20.7%), and more anteriorly in 114 (10.5%).

Tumours treated included very small tumours (LBD smallest 2.0 mm and thickness 0.1 mm) and very large tumours (largest LBD 23.4 mm and thickness 15.4 mm). Nearly 75% (*n* = 811) were T1–IIa tumour category.

As per the COMS definitions, 423 patients (39%) had small tumours (LBD ≤ 16 mm and thickness ≤ 2.5 mm), 455 (42%) had medium tumours (LBD ≤ 16 mm, thickness 2.5–10 mm) and 205 (19%) had large tumours (LBD >16 mm or thickness >10 mm).

The ciliary body was involved in 148 (13.7%) cases and extraocular extension was noted in 20 (1.8%). TNM staging data are shown in Table 1. Patients were followed up for a median of 44 months (range 12–1396 months).

Table 2. Patient characteristics according to referring centre.

	Glasgow	Liverpool	London	Sheffield
Number treated	137	765	72	110
Small	8%	51%	22%	18%
Medium	44%	34%	78%	55%
Large	48%	14%	0%	27%
Mean, median tumour diameter (mm)	15.2, 15.5	10.9, 10.5	10.3, 10.5	13.7, 13.4
Mean, median tumour thickness (mm)	6.4, 6.5	3.5, 2.4	4.0, 2.7	4.4, 4.3
Mean, median tumour volume (cc)	x	0.28, 0.12	x	0.5, 0.33
Ciliary body involvement	37 (27.0%)	110 (14%)	1 (1.5%)	x
Mean, median distance to disc (mm)	5.8, 6.1	5.0, 2.2	0.35, 0.0	3.7, 2.0
Mean, median distance to fovea (mm)	x	4.2, 0.9	2.4, 2.0	4.2, 2.0

Table 3. Complications of radiotherapy and rates of secondary enucleation.

	Tumour recurrence	Complications				Secondary enucleation
		Optic neuropathy	Radiation retinopathy	Rubeotic glaucoma	Toxic tumour syndrome	
Sheffield	x	4 (3.8%)	5 (4.7%)	0	0	5 (4.7%)
London	6 (8.6%)	3 (4.3%)	6 (8.7%)	6 (8.7%)	0	12 (17.4%)
Glasgow	26 (17.4%)	0	6 (4.0%)	20 (13.4%)	0	49 (32.9%)
Liverpool	27 (6.4%)	6 (0.8%)	64 (8.3%)	13 (1.7%)	5 (0.6%)	41 (9.7%)

On further analysis of patient subgroups from each referral centre, the tumour characteristics varied considerably (Table 2). The median diameter and thickness of tumours treated with PBR in Glasgow were larger than that of other centres, with a higher proportion of ciliary body involving lesions (27%). In contrast, the median and mean distance of tumours from the disc and fovea referred from London were similarly low, suggesting a preponderance of posteriorly located small to medium tumours referred for PBR (only 1.5% involving the ciliary body, and none were in the large tumour category). Liverpool figures suggested a mixture of cases, with 14% involving the ciliary body, many tumours close to the disc (median distance to disc 0.9 mm) but a mean distance of 4.2 mm; Liverpool also treated a high proportion of small tumours (51% of their cases).

Statistical analysis with a single-factor ANOVA showed a significant difference between the referred tumour thickness and largest basal diameter between Glasgow and the other three centres ($P < 0.001$) with higher values for each. The differences between the remaining three centres were not statistically significant. The variance in referral parameters was lowest in the London cohort (4.16 thickness, 7.62 diameter) and highest in the Liverpool cohort (18.18 thickness, 42.10 diameter).

The data for distance of tumour to disc and fovea was more incomplete. The differences between all centres were statistically different for distance to the optic disc centre except between Liverpool and Glasgow ($P = 0.22$); however, both Liverpool and Glasgow demonstrated the greatest variance (36.0, 24.2) in comparison to London with the lowest variance of 1.88. On the other hand, the distance to the fovea was not significantly different between the centres.

The common complications following proton therapy are shown in Table 3. Tumour recurrence was uncommon, with successful tumour control in 82–93%. Significant side effects eventually lead to secondary enucleation that ranged from 5 to 33%; the variability is likely due to the differences in the tumour phenotypes treated.

DISCUSSION

Proton beam therapy is an effective treatment for UM; local tumour control rates as well as eye preservation in UM are very high at >90% for the period of the study, comparable to brachytherapy [16–21]. Complications include radiation maculopathy, optic neuropathy and toxic tumour syndrome. These complications are in the majority related to the size of the tumour as well the proximity of the tumour to visually sensitive structures such as the fovea and optic nerve head [19].

The availability of proton treatment varies across Europe and the world. As such, the indications for treatment are dependent on individual surgeon choice, the ability to cover the cost of travel and treatment, and accessibility. Some centres use protons predominantly for lesions considered too large for radio-plaque brachytherapy as it is more readily available in many centres [17]. Concurrently, the treatment of small posteriorly located tumours is more successful with proton treatment [5, 22–25], with a slower and more gradual loss of vision, than with subfoveal or notched plaques, and may offer an alternative indication for proton referral [26].

In the UK, the alternative treatments include ruthenium-106 plaque brachytherapy, stereotactic radiotherapy, surgical resection (enucleation, endo/exo-resection) or photodynamic therapy. The choice of this relatively expensive treatment modality in preference to other interventions is case dependent; these decisions will depend on clinician experience and exposure to these different treatment regimens as well as patient choice of available options. The choice of proton treatment may include those lesions difficult to address with radio-plaque treatment (at the disc, or with diffuse edges for example) or those too large for plaque treatment (generally considered for ruthenium-106 to be 6 mm in thickness). It is clear that the referral criteria for proton beam treatment vary between centres even within the UK, despite the availability to all patients under the NHS. Glasgow refers a significantly higher proportion of large ciliary body tumours, whereas Sheffield and London tend to consider medium sized and

more posteriorly located tumours for proton treatment; this may be influenced by the availability of stereotactic radiotherapy in Sheffield for larger tumour subgroups. Liverpool seems to have a combination of both of these groups, with a high proportion of small tumours which may in part be related to the proximity of the proton beam service to the local team with better access, as well as a preponderance to treat smaller tumours early. The rates of complications and secondary enucleations will reflect this variation in the tumour phenotypes treated at these locations. This is the first UK-wide audit enabling the capture of all patients treated at the single proton centre.

Summary

What is known about this topic

- Proton beam radiotherapy is a successful treatment for uveal melanoma.

What this study adds

- There is great variation in the indications for treating uveal melanoma with protons. This includes small tumours at the posterior pole, and larger anterior tumours beyond the range for standard plaque brachytherapy.
- Although this will be surgeon dependent, it will also depend on patient factors such as accessibility and patient choice. This may impact the rates of post-treatment complications, including the need for secondary enucleation.

DATA AVAILABILITY

Raw data are available on request.

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AUTHOR CONTRIBUTIONS

All authors have contributed to the conceptualisation of this paper, data collection, data analysis and/or write-up of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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