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ARTICLE

Comparison between patient-reported outcomes after enucleation and proton beam radiotherapy for uveal melanomas: a 2-year cohort study

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Abstract

Background Uveal melanomas affect 2–8 per million Europeans each year. Approximately 35%, are treated by enucleation. Proton beam radiotherapy (PBR) can be an eye-conserving alternative to enucleation for patients who wish to retain the eye. Both treatments have adverse effects, and it is difficult for clinicians and patients to make fully informed choices between them because the relative effects of enucleation and PBR on patient-reported outcomes are unknown.

Methods We compared differential effects of enucleation and PBR on patient-reported outcomes on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Ophthalmological module (EORTC QLQ-OPT30) in a consecutive sample of 115 treated patients ~ 6, 12 and 24 months after diagnosis. Pre-treatment demographic variables, unrelated health problems, vision in the fellow eye, tumour characteristics and prognosis for metastatic disease were statistically controlled.

Results Patients treated by enucleation experienced greater functional problems at 6 months, which abated at 12 and 24 months ($P = 0.020$). PBR patients reported greater impairments of central and peripheral vision ($P = 0.009$) and reading difficulties ($P = 0.002$) over 24 months. Treatment modality did not influence difficulty in driving ($P = 0.694$), ocular irritation ($P = 0.281$), headaches ($P = 0.640$), appearance concerns ($P = 0.187$) or worry about recurrence ($P = 0.899$).

Conclusions When making treatment decisions, it is important that patients and clinicians consider long-standing difficulties of visual impairment associated with PBR and temporary 6-month difficulties in activities related to depth perception associated with enucleation.

Introduction

Uveal melanoma (UM) is a rare cancer of the eye that affects 2–8 individuals per million Caucasian people per year in Europe, depending on ocular pigmentation [1]. UM treatments aim to preserve the eye with useful vision. Plaque radiotherapy is a preferred treatment in many centres [2] but not recommended in some centres where tumours are large or close to the optic disc. In these cases, enucleation can be considered [3, 4].

Enucleation is performed in ~ 35% of patients [5]. Adverse outcomes are loss of binocular vision, potential socket-related complications and phantom symptoms such as visual sensations [6]. Proton beam radiotherapy (PBR) is sometimes an alternative to enucleation when patients wish to retain the eye. PBR preserves the eye but carries risks of neovascular glaucoma, radiation retinopathy, papillopathy, retinal detachment, local tumour recurrence [7, 8] and collateral damage to extraocular structures such as eyelids, lacrimal gland and tear ducts [9].

Decisions of whether to preserve the eye or not are not always clinically clear cut. In these cases, careful consideration of the consequences of treatments are necessary for effective treatment decisions [4]. Patients may prefer to retain the eye, although doing so confers clinical disadvantage, or prefer enucleation in the absence of decisive

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clinical need [4, 10]. To make informed decisions, clinicians and patients need to understand potential consequences of enucleation and PBR.

Objective probabilities of adverse side effects, local and distant recurrence and overall survival are known [3, 11, 12] and patients are routinely informed of these [4]. To our knowledge, no study has examined how enucleation and PBR influence patients' experiences of adverse treatment outcomes. Loss of binocular vision after enucleation causes a range of problems associated with distance perception, whereas prostheses can cause irritation, discomfort, pain and appearance dissatisfaction [13, 14]. Adverse patient-reported outcomes of PBR can include progressive visual impairments, linked to known central and peripheral visual loss and the presence of unwanted visual sensations, and cause discomfort owing to tissue damage to extraocular structures [9]. These outcomes are associated with the likelihood of developing long-term clinically relevant anxiety and depression in UM patients [15].

It is unknown whether enucleation and PBR differentially affect worry about cancer recurrence (WREC). In our unit, that treats between 200 to 250 new patients with UM per annum, some patients worry about local recurrence and wish to reduce this worry through enucleation [4]. Studies in other cancers confirm that patients sometimes request radical surgeries to remove organs because they fear local cancer recurrence [16]. WREC is linked to clinically relevant anxiety [15], thus clinicians may regard reducing patients' fears of recurrence as a valid consideration for treatment choice [17]. However, there is as yet no evidence that enucleation reduces fear to a greater extent than PBR in UM patients.

Our aim was to identify any differential effects of treatment modality (enucleation versus PBR) on patient-reported outcomes of ocular irritation, visual impairment, headaches, appearance concerns, functional problems, reading and driving problems, and WREC. We compared treatment modalities ~ 6, 12 and 24 months after diagnosis (Some data used in this report are the same of those used by Damato et al. [18]. The Damato study focusses on a broader question pertaining to trajectories of patient-reported outcomes over time after radiotherapy, whereas this paper addresses a specific clinical question pertaining to adverse effects of enucleation compared to PBR). As treatment decisions are influenced by patient and tumour characteristics, we statistically adjusted age, gender, presence or absence of unrelated health problems, visual acuity in the fellow eye at diagnosis, tumour size, and prognosis for metastatic disease. Poor prognosis for metastatic disease was defined by the presence of monosomy 3 (loss of one copy of chromosome 3) in tumour cells.

Methods

This study was approved as a clinical audit by the Health Research Authority North West—Liverpool Central Ethics Committee (03/06/072/A) and was conducted in accordance with the Declaration of Helsinki.

Design

Prospective design with patient-reported outcome measures taken at 6, 12 and 24 months after diagnosis, in non-randomised consecutive samples of enucleated or PBR patients with clinical and demographic variables statistically controlled. As plaque radiotherapy was not considered to be clinically viable owing to tumour characteristics or position, these patients were excluded so as not to dilute the analysis. Data were taken from a larger project, thus no power analyses were made for this specific investigation [19].

Participants

Informed consent was sought from a consecutive series of adult patients treated at the Liverpool Ocular Oncology Centre (LOOC) for posterior UM (i.e., choroid and ciliary body) between 1st April 2008 and 31st December 2011. We excluded non-enucleation or non PBR treatments and patients with tumours that involved the iris. The final sample consisted of patients who provided data at each of the three follow-ups.

Diagnosis and treatment of UM was based on clinical and tumour characteristics, as described by Damato and Heimann [4]. Where tumours were relatively small or medium sized (thickness <6 mm diameter <18 mm) or not close to the optic disc, plaque radiotherapy was the preferred treatment. Enucleation was considered for larger tumour size and PBR for tumours with optic disc involvement or larger tumours (thickness >6 mm) where patients wished to keep the eye and the tumour diameter was <18 mm. Patient preferences for or against particular procedures were considered in treatment selection.

Data collected

At the time of diagnosis, patients were asked if they were willing to participate in an audit to examine long-term patient-reported outcomes of treatment. All patients who gave written consent were posted the self-report questionnaire with enclosed postage-paid envelopes addressed to the audit team 6, 12 and 24 months following diagnosis.

Sociodemographic and clinical characteristics of the sample were collected from patients' clinical records. These were age, gender, patient-identified unrelated health problems, relationship status, employment status, whether the

Table 1 EORTC QLQ- OPT30 subscales

Scale	Example item	No of items	Cronbach's Alpha		
			6 mths	12 mths	24 mths
Ocular irritation	Were you troubled by any discharge from your treated eye?	6	0.71	0.73	0.77
Vision impairment	Were you troubled by any defects in your side vision?	4	0.69	0.73	0.71
Functional problems	Did you have difficulty seeing steps or pavements?	6	0.92	0.92	0.93
Worry about recurrence (local and metastatic)	Were you worried about the tumour recurring in the treated eye?	3	0.87	0.85	0.85
Appearance concerns	Has your appearance bothered you'?	2	0.38[a]	0.54[a]	0.54[a]
Driving difficulties	Did you have difficulty driving in the dark?	2	0.61[a]	0.60[a]	0.48[a]
Headaches	Did you have headaches?	1		NA	
Reading	Did you have difficulty reading because of your vision?	1		NA	

[a]Correlation coefficients used for two-item scales

right or left eye was affected, vision in the fellow eye at diagnosis as logMAR scores, tumour origin (choroid or ciliary body), tumour size (ultrasound height and largest basal diameter) and treatment modality. Prognostication was based on chromosome 3 status as the primary determinant of life expectancy [12, 20] and was categorised as: monosomy 3, disomy 3 (i.e., normal maternal and paternal copies of chromosome 3) and unknown (comprising patients who did not wish to be tested, tumours were small, and those whose genetic test failed). For patients undergoing PBR, prognostic biopsies were usually performed on the last day of treatment.

Following treatment, symptoms and functional problems were measured using the European Organisation for Research and Treatment for Cancer Ophthalmic Oncology Quality of Life questionnaire module (EORTC QLQ-OPT30) [21] designed specifically for UM patients and validated in UM samples [22]. Subscales specific to enucleation or PBR were not used. Details of the subscale items are shown in Table 1.

Statistical analysis

Sample retention

Multivariate logistic regression was used to test whether baseline age, sex, health problems, chromosome 3 status, logMAR scores for the fellow eye, tumour thickness, and largest basal diameter and 6-month EORTC QLQ-OPT30 scores predicted retention in the sample at 12 and 24 months.

Outcomes for each treatment modality

Data were normally distributed and showed homogeneity of variance. First, mixed-model analyses of variance (MANOVAs) were used to predict EORTC QLQ- OPT30 scores at 6, 12 and 24 months. Enucleation versus PBR treatment was a two-group predictor variable. To prevent confounding by pre-treatment differences between treatment groups, these analyses were repeated with statistical adjustment using age, sex, health problems, chromosome 3 status, logMAR scores for the fellow eye, tumour thickness, and largest basal diameter as covariates. Chromosome 3 status was coded into two binomial variables; the first denoting monosomy 3 or not (including those with disomy 3 and those whose chromosome 3 status was unknown), the second denoting disomy 3 or not (monosomy 3 and unknown).

Results

Sample description and retention analysis

Three hundred and sixty patients were approached to participate. Of these, 194 returned questionnaires at 6 months, 155 at 12 months and 132 at 24 months. One hundred and fifteen returned questionnaires at all three time points and were included (59.3% retention). Sixty-six patients were treated by enucleation and 49 treated by PBR. Demographic and clinical characteristics for each treatment group are presented in Table 2. Monosomy 3 was more prevalent in enucleated patients. The logistic regression predicting 24 month retention from 6-month study variables was not significant ($\chi^2 = 15.23$, Nagelkerke $R^2 = 1.06$, $df = 14$, $p = .294$), showing no bias in retention.

Outcomes by treatment modality

Estimated marginal means and results of unadjusted and adjusted significance tests for outcome variables at 6, 12 and 24 months after diagnosis are shown in Table 3 (We examined whether treatment modality effects were moderated or accentuated by covariates. We did not observe clear

Table 2 Sample characteristics for the full sample and by treatment modality

Variable	Category	Full sample $N = 115$		Enucleation $N = 66$ (57.4%)		Proton beam $N = 49$ (42.6%)	
Median age (range)		62.5 (54.6–71.8)		65.2 (56.2–72.8)		62.5 (51.5–70.5)	
		N	***%***	***N***	***%***	***N***	***%***
Sex	Male	56	48.7	32	48.5	24	49
	Female	59	51.3	34	51.5	25	51
Marital status	Married/living with partner	86	74.8	44	66.7	42	85.7
	Divorced/separated	12	10.4	10	15.2	2	4.1
	Widowed	11	9.6	9	13.6	2	4.1
	Single	4	3.5	2	3	2	4.1
	Not recorded	2	1.7	1	1.5	1	2
Employment status	Employed	36	31.3	18	27.3	18	36.6
	Homemaker	4	3.5	1	1.5	3	6.1
	Retired	56	48.7	34	51.5	22	44.9
	Long-term sick/ medically retired	10	8.7	7	10.6	3	6.1
	Not specified	9	7.8	6	9.1	3	6.1
Health problems	Yes	73	63.5	44	66.7	29	59.2
	No	40	34.8	20	30.3	20	40.8
	Not specified	2	1.7	2	3	0	0
Eye	Right	58	50.4	35	53	23	46.9
	Left	57	49.6	31	47	26	53.1
Tumour origin	Choroid	103	89.6	60	90.9	43	87.8
	Ciliary body	12	10.4	6	9.1	6	12.2
Visual acuity: fellow eye at diagnosis	6/5–6/12	112	97.4	63	95.5	49	100
	6/18–6/60	3	2.6	3	4.5	0	0
Prognostication	Monosomy 3 confirmed	55	47.8	45	68.2	10	20.4
	Monosomy 3 not confirmed	60	52.2	21	31.8	39	79.6
Mean tumour size: mm (SD) range	Ultrasound height	5.59 (3.74) 0.6–14.8		7.25 (3.65) 0.8–14.8		3.38 (2.55) 0.6–10.3	
	Largest basal diameter	13.04 (4.56) 0.99–20.5		15.20 (3.55) 6.5–20.5		10.17 (4.18) 0.99–18.9	

patterns of moderation or accentuation of treatment effects.). Enucleation was associated with greater ocular irritation, appearance concerns, and functional problems, with treatment differences in functional problems significantly reducing over time. Unadjusted means show PBR to be associated with greater reading difficulties scores.

Statistical adjustment changed statistical significance in some analyses. Enucleated patients experienced more functional problems at 6 months, but these reduced linearly over 12 and 24 months ($F = 4.00$, $df = 2$ $p = 0.020$) with Bonferroni post-hoc tests showing a significant reduction between 6- and 24- month observations but not between adjacent observations. PBR patients experienced more visual impairment and had more difficulty in reading over all time points than enucleated patients. No differences between treatment modalities were apparent at any time point for ocular irritation, headaches, appearance concerns, driving difficulties or WREC.

Discussion

To our knowledge, this study is the first to document differential effects of enucleation and PBR on patient-reported outcomes. Enucleation was initially associated with greater functional problems, which lessened after 6 months, whereas patients treated by PBR reported greater visual impairment and reading difficulties than those treated by

Table 3 Adjusted and unadjusted means and SEs for the full sample and by treatment modality

Outcome	Sample mean (SE)		Enucleation		Proton Beam		Significance[$]
	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	
Ocular irritation	$N = 112$	$N = 113$	$N = 64$	$N = 65$	$N = 48$	$N = 48$	
6 months	1.74 (0.057)	1.74 (0.057)	1.79 (0.088)	1.79 (0.075)	1.70 (0.107)	1.69 (0.087)	Time F = 0.3.75*
12 months	1.73 (0.054)	1.72 (0.053)	1.78 (0.083)	1.82 (0.069)	1.68 (0.101)	1.62 (0.081)	Treat F = 1.17
24 months	1.72 (0.054)	1.74 (0.054)	1.87 (0.083)	1.87 (0.070)	1.62 (0.101)	1.60 (0.081)	T × T F = 1.04
Visual impairment	$N = 109$	$N = 110$	$N = 62$	$N = 63$	$N = 47$	$N = 47$	
6 months	1.47 (0.049)	1.46 (0.050)	1.34 (0.076)	1.43 (0.066)	1.60 (0.092)	1.49 (0.076)	Time F = 0.18
12 months	1.52 (0.062)	1.50 (0.063)	1.29 (0.097)	1.42 (0.082)	1.74 (0.116)	1.57 (0.095)	Treat F = 7.21*
24 months	1.49 (0.054)	1.47 (0.056)	1.32 (0.095)	1.42 (0.073)	1.66 (0.103)	1.52 (0.085)	T × T F = 0.80
Reading	$N = 113$	$N = 114$	$N = 64$	$N = 65$	$N = 49$	$N = 49$	
6 months	1.83 (0.079)	1.82 (0.083)	1.48 (0.123)	1.69 (0.109)	2.17 (0.147)	1.94 (0.126)	Time F = 0.40
12 months	1.73 (0.078)	1.74 (0.083)	1.45 (0.121)	1.55 (0.109)	2.00 (0.145)	1.92 (0.125)	Treat F = 10.03*
24 months	1.79 (0.078)	1.79 (0.083)	1.54 (0.121)	1.68 (0.105)	2.03 (0.144)	1.90 (0.121)	T × T F = 0.52
Functional problems	$N = 113$	$N = 114$	$N = 64$	$N = 65$	$N = 49$	$N = 49$	
6 months	1.85 (0.059)	1.84 (0.062)	2.06 (0.092)	2.18 (0.081)	1.63 (0.110)	1.50 (0.093)	Time F = .93
12 months	1.79 (0.059)	1.79 (0.064)	1.90 (0.092)	2.03 (0.084)	1.68 (0.110)	1.54 (0.096)	Treat F = 2.75
24 months	1.81 (0.062)	1.82 (0.065)	1.85 (0.096)	1.97 (0.085)	1.76 (0.114)	1.64 (0.098)	T × T F = 4.0*
Appearance concerns	$N = 112$	$N = 113$	$N = 64$	$N = 65$	$N = 48$	$N = 48$	
6 months	1.38 (0.060)	1.34 (0.060)	1.41 (0.093)	1.50 (0.078)	1.35 (0.060)	1.24 (0.091)	Time F = 0.71
12 months	1.32 (0.052)	1.33 (0.054)	1.46 (0.081)	1.49 (0.071)	1.18 (0.052)	1.17 (0.082)	Treat F = 1.77
24 months	1.32 (0.057)	1.32 (0.057)	1.42 (0.087)	1.44 (0.075)	1.22 (0.057)	1.21 (0.087)	T × T F = 1.42
Headaches	$N = 110$	$N = 111$	$N = 63$	$N = 64$	$N = 47$	$N = 47$	
6 months	1.60 (0.082)	1.60 (0.083)	1.58 (0.127)	1.59 (0.108)	1.62 (0.155)	1.60 (0.126)	Time F = 0.56
12 months	1.61 (0.081)	1.60 (0.082)	1.50 (0.125)	1.52 (0.107)	1.72 (0.151)	1.68 (0.125)	Treat F = 0.22
24 months	1.48 (0.76)	1.47 (9.07)	1.49 (0.117)	1.52 (0.101)	1.48 (0.142)	1.43 (0.118)	T × T F = 0.79
Driving difficulties	$N = 73$	$N = 73$	$N = 41$	$N = 41$	$N = 32$	$N = 32$	
6 months	1.56 (0.063)	1.55 (0.064)	1.56 (0.099)	1.66 (0.085)	1.57 (0.117)	1.44 (0.096)	Time F = 0.27
12 months	1.60 (0.069)	1.60 (0.074)	1.60 (0.108)	1.66 (0.098)	1.61 (0.127)	1.53 (0.110)	Treat F = 0.16
24 months	1.72 (0.067)	1.70 (0.070)	1.64 (0.106)	1.78 (0.093)	1.80 (0.125)	1.63 (0.105)	T × T F = 0.45
Worry about recurrence	$N = 112$	$N = 113$	$N = 64$	$N = 65$	$N = 48$	$N = 48$	
6 months	2.45 (0.085)	2.44 (0.089)	2.40 (0.131	2.53 (0.116)	2.49 (0.159)	2.35 (0.134)	Time F = 0.33
12 months	2.18 (0.076)	2.19 (0.081)	2.20 (0.118)	2.28 (0.106)	2.17 (0.144)	2.10 (0.123)	Treat F = 0.02
24 months	2.10 (0.077)	2.09 (0.081)	2.09 (0.120)	2.15 (0.106)	2.10 (0.145)	2.04 (0.123)	T × T F = 0.19

[$]F-ratio statistics for the adjusted time×treatment analyses. *$p < 0.05$

enucleation. Treatment modality did not influence difficulty in driving, ocular irritation, headaches, appearance concerns or WREC. Our findings will allow clinicians to better understand how patients are likely to be affected by consequences of enucleation relative to PBR, and to inform patients accordingly.

Findings are consistent with known clinical effects of enucleation and PBR. Enucleation eliminates binocular vision, creating difficulties with depth perception [23]. The functional problems scale is weighted toward tasks requiring depth perception, such as judging distances, pouring drinks and using stairs. Thus, it is unsurprising that enucleated patients reported greater functional problems. Relative functional improvement over 24 months suggests that patients either developed compensatory strategies, such as using alternative cues to judge distance, or changed daily routines, such as avoiding distance perception tasks [24, 25]. After PBR, patients experienced visual impairments and reading difficulties over 24 months. This is consistent with reports of lower visual acuity and greater visual interference [3, 8, 9].

Treatment modality had little relative effect on ocular irritation, headaches or driving difficulties. It is not feasible to compare our patients to those who had neither

enucleation nor PBR (owing to large initial differences in patient and tumour characteristics). Thus, we do not know whether equivalence between treatment modalities occurs because neither treatment has adverse effects, or that treatments adversely affect outcomes in different but approximately equivalent ways. Ocular irritation and headaches may also arise from equivalent adverse effects; enucleation can cause socket damage [14] and PBR can cause damage to extraocular structures, such as eyelids, canaliculi and the lacrimal gland [9]. Enucleation may adversely affect driving owing to loss of depth perception, and PBR owing to diminished visual acuity. It is unclear as to whether treatment modalities did not differentially affect driving or whether patients did experience driving difficulties after one or the other treatments and simply stopped driving.

It might be expected that enucleation would increase concerns about appearance, as dissatisfaction with prostheses is relatively common [13]. This indeed was the case before statistical adjustment, but no differences in appearance concerns were observed after adjustment. Thus, treatment differences are probably attributable to pre-treatment differences between treatment groups, and unlikely to be a consequence of enucleation. The equivalence of appearance concerns between enucleation and PBR may reflect either recent advances in the development of implants and prostheses [14, 26] or a generally low concern about appearance in our sample of older patients [25].

Some patients may opt for enucleation to avoid worry about recurrence. Unlike breast cancer, where women achieve reductions of fear and worry after mastectomy [27], enucleation did not differentially reduce worry compared to PBR. Enucleated patients were more likely to have monosomy 3, although evidence suggests that this is not necessarily associated with worry about recurrence [15]. Enucleation can reduce the small probability of local cancer recurrence, but we have no evidence that it reduces patients' subjective worry about recurrence.

This study has several limitations. Owing to initial disparity in patient and tumour characteristics, it was unfeasible to compare our findings with patient groups who had neither enucleation nor PBR. Thus, we cannot comment on how each procedure affects patients in absolute terms. Second, patients could not be randomised to treatment modality. Although we used a series of statistical adjustments, we cannot exclude the possibility of confounding. Nonetheless, findings are not confounded by pre-treatment group differences in demographic variables, unrelated illnesses, tumour size or chromosome 3 status, which were statistically controlled. We used a relatively small sample and had 53.9% initial recruitment and 59.3% retention, although retention analysis showed retention to be unbiased. Last, questionnaires were self-administered without supervision, which might lead to greater error than professionally-administered scales.

Findings of this study can help clinicians and patients to make informed decisions between enucleation and PBR. First, enucleation can lead to greater functional difficulties associated with depth perception tasks, although this difference between the treatments seemed to abate after 12 months. PBR on the other hand is more likely to lead to patient-reported difficulties with visual impairments, experienced as loss of vision or visual problems in the treated eye affecting vision in the fellow eye. This is problematic for reading. Secondly, patients can be informed that enucleation will reduce the possibility of local recurrence in the affected eye, but it is unlikely to help them to reduce worry about recurrence. Finally, choice of treatment modality is unlikely to cause greater difficulties associated with ocular irritation, appearance or driving.

Summary

What was known before

- Some UMs can be treated by enucleation or PBR. To make effective decisions about which treatment to use, clinicians and patients need to understand potential adverse outcomes of each. Adverse clinical effects of each procedure are widely understood, but it is not known how patients experience these effects.

What this study adds

- Enucleation was associated with transient functional problems on tasks requiring binocular vision. PBR was associated with greater impairments of central and peripheral vision, and reading difficulties. No differences in adverse effects were reported for driving, ocular irritation, headaches, appearance concerns or WREC. Findings can help patients and clinicians to make better informed decisions between enucleation and PBR.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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