

## *Outcomes after enucleation or proton beam radiotherapy*

What was known before:

Some uveal melanomas can be treated by enucleation or proton beam radiotherapy (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 worries about cancer recurrence. Findings can help patients and clinicians to make better informed decisions between enucleation and PBR

**Comparison between patient-reported outcomes after enucleation and proton beam radiotherapy for uveal melanomas: A two-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 approximately 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 ( $P=.020$ ). PBR patients reported greater impairments of central and peripheral vision ( $P=.009$ ) and reading difficulties ( $P=.002$ ) over 24 months. Treatment modality did not influence difficulty in driving ( $P=.694$ ), ocular irritation ( $P=.281$ ), headaches ( $P=.640$ ), appearance concerns ( $P=.187$ ) or worry about recurrence ( $P=.899$ ).

*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.

1 **Introduction**

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

7 Enucleation is performed in approximately 35% of patients.<sup>5</sup> Adverse outcomes are  
8 loss of binocular vision, potential socket-related complications and phantom symptoms such  
9 as visual sensations.<sup>6</sup> PBR is sometimes an alternative to enucleation when patients wish to  
10 retain the eye. PBR preserves the eye but carries risks of neovascular glaucoma, radiation  
11 retinopathy, papillopathy, retinal detachment, local tumour recurrence<sup>7,8</sup> and collateral  
12 damage to extraocular structures such as eye lids, lacrimal gland and tear ducts.<sup>9</sup>

13 Decisions of whether to preserve the eye or not are not always clinically clear cut. In  
14 these cases, careful consideration of the consequences of treatments are necessary for  
15 effective treatment decisions.<sup>4</sup> Patients may prefer to retain the eye, although doing so  
16 confers clinical disadvantage, or prefer enucleation in the absence of decisive clinical  
17 need.<sup>4,10</sup> To make informed decisions, clinicians and patients need to understand potential  
18 consequences of enucleation and PBR.

19 Objective probabilities of adverse side effects, local and distant recurrence and overall  
20 survival are known<sup>3,11,12</sup> and patients are routinely informed of these.<sup>4</sup> To our knowledge, no  
21 study has examined how enucleation and PBR influence patients' experiences of adverse  
22 treatment outcomes. Loss of binocular vision after enucleation causes a range of problems  
23 associated with distance perception, whilst prostheses can cause irritation, discomfort, pain

24 and appearance dissatisfaction.<sup>13,14</sup> Adverse patient-reported outcomes of PBR can include  
25 progressive visual impairments, linked to known central and peripheral visual loss and the  
26 presence of unwanted visual sensations, and cause discomfort due to tissue damage to  
27 extraocular structures.<sup>9</sup> These outcomes are associated with the likelihood of developing long  
28 term clinically-relevant anxiety and depression in UM patients.<sup>15</sup>

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

37         Our aim was to identify any differential effects of treatment modality (enucleation  
38 versus PBR) on patient-reported outcomes of ocular irritation, visual impairment, headaches,  
39 appearance concerns, functional problems, reading and driving problems, and WREC. We  
40 compared treatment modalities approximately 6, 12 and 24 months after diagnosis.<sup>a</sup> As  
41 treatment decisions are influenced by patient and tumour characteristics, we statistically  
42 adjusted age, gender, presence or absence of unrelated health problems, visual acuity in the  
43 fellow eye at diagnosis, tumour size, and prognosis for metastatic disease. Poor prognosis for  
44 metastatic disease was defined by the presence of monosomy 3 (loss of one copy of  
45 chromosome 3) in tumour cells.

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<sup>a</sup> Some data used in this report are the same of those used by Damato et al<sup>27</sup>. 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 for large tumours.

47

## **Methods**

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

### **Design**

52 Prospective design with patient-reported outcome measures taken at 6, 12 and 24 months  
53 after diagnosis, in non-randomised consecutive samples of enucleated or PBR patients with  
54 clinical and demographic variables statistically controlled. As plaque radiotherapy was not  
55 considered to be clinically viable due to tumour characteristics or position, these patients  
56 were excluded so as not to dilute the analysis. Data were taken from a larger project, thus no  
57 power analyses were made for this specific investigation.<sup>18</sup>

### **Participants**

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

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

### **Data collected**

71

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

76 Sociodemographic and clinical characteristics of the sample were collected from  
77 patients' clinical records. These were age, gender, patient-identified unrelated health  
78 problems, relationship status, employment status, whether the right or left eye was affected,  
79 vision in the fellow eye at diagnosis as logMAR scores, tumour origin (choroid or ciliary  
80 body), tumour size (ultrasound height and largest basal diameter) and treatment modality.  
81 Prognostication was based on chromosome 3 status as the primary determinant of life  
82 expectancy<sup>12, 19</sup> and was categorized as: monosomy 3, disomy 3 (i.e., normal maternal and  
83 paternal copies of chromosome 3) and unknown (comprising patients who did not wish to be  
84 tested, tumours were small, and those whose genetic test failed). For patients undergoing  
85 PBR, prognostic biopsies were usually performed on the last day of treatment.

86 Following treatment, symptoms and functional problems were measured using the  
87 European Organisation for Research and Treatment for Cancer Ophthalmic Oncology Quality  
88 of Life questionnaire module (EORTC QLQ- OPT30)<sup>20</sup> designed specifically for UM  
89 patients and validated in UM samples.<sup>21</sup> Subscales specific to enucleation or PBR were not  
90 used. Details of the subscale items are shown in table 1.

### 91 **Statistical analysis**

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

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

## 106 **Results**

### 107 Sample Description and Retention Analysis

108 360 patients were approached to participate. Of these, 194 returned questionnaires at 6  
109 months, 155 at 12 months and 132 at 24 months. 115 returned questionnaires at all three  
110 time-points and were included (59.3% retention). Sixty six patients were treated by  
111 enucleation and 49 treated by PBR. Demographic and clinical characteristics for each  
112 treatment group are presented in Table 2. Monosomy 3 was more prevalent in enucleated  
113 patients. The logistic regression predicting 24 month retention from 6-month study variables  
114 was not significant ( $\chi^2=15.23$ , Nagelkerke R<sup>2</sup>=1.06,  $df=14$ ,  $p=.294$ ), showing no bias in  
115 retention.

116

### 117 **Outcomes by Treatment Modality**



118 Estimated marginal means and results of unadjusted and adjusted significance tests for  
119 outcome variables at 6, 12 and 24 months after diagnosis are shown in Table 3.<sup>b</sup> Enucleation  
120 was associated with greater ocular irritation, appearance concerns, and functional problems,  
121 with treatment differences in functional problems significantly reducing over time.  
122 Unadjusted means show PBR to be associated with greater reading difficulties scores.

123 Statistical Adjustment changed statistical significance in some analyses. Enucleated  
124 patients experienced more functional problems at 6 months, but these reduced linearly over  
125 12 and 24 months ( $F=4.00$ ,  $df=2$   $p=.020$ ) with Bonferroni post-hoc tests showing a significant  
126 reduction between 6 and 24 month observations but not between adjacent observations. PBR  
127 patients experienced more visual impairment and had more difficulty in reading over all time  
128 points than enucleated patients. No differences between treatment modalities were apparent at  
129 any time point for ocular irritation, headaches, appearance concerns, driving difficulties, or  
130 WREC.

### 131 **Discussion**

132 To our knowledge, this study is the first to document differential effects of enucleation and  
133 PBR on patient-reported outcomes. Enucleation was initially associated with greater  
134 functional problems which lessened after six months, whilst patients treated by PBR reported  
135 greater visual impairment and reading difficulties than those treated by enucleation.  
136 Treatment modality did not influence difficulty in driving, ocular irritation, headaches,  
137 appearance concerns, or WREC. Our findings will allow clinicians to better understand how  
138 patients are likely to be affected by consequences of enucleation relative to PBR, and to  
139 inform patients accordingly.

140 Findings are consistent with known clinical effects of enucleation and PBR.  
141 Enucleation eliminates binocular vision, creating difficulties with depth perception.<sup>22</sup> The

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<sup>b</sup> We examined whether treatment modality effects were moderated or accentuated by covariates. We did not observe clear patterns of moderation or accentuation of treatment effects.

142 functional problems scale is weighted toward tasks requiring depth perception, such as  
143 judging distances, pouring drinks and using stairs. Thus, it is unsurprising that enucleated  
144 patients reported greater functional problems. Relative functional improvement over 24  
145 months suggests that patients either developed compensatory strategies, such as using  
146 alternative cues to judge distance, or changed daily routines, such as avoiding distance  
147 perception tasks.<sup>23,24</sup> After PBR, patients experienced visual impairments and reading  
148 difficulties over 24 months. This is consistent with reports of lower visual acuity and greater  
149 visual interference.<sup>3,8,9</sup>

150 Treatment modality had little relative effect on ocular irritation, headaches or driving  
151 difficulties. It is not feasible to compare our patients to those who had neither enucleation nor  
152 PBR (due to large initial differences in patient and tumour characteristics). Thus, we do not  
153 know whether equivalence between treatment modalities occurs because neither treatment  
154 has adverse effects, or that treatments adversely affect outcomes in different but  
155 approximately equivalent ways. Ocular irritation and headaches may also arise from  
156 equivalent adverse effects; enucleation can cause socket damage<sup>14</sup> and PBR can cause  
157 damage to extraocular structures, such as eyelids, canaliculi and the lacrimal gland<sup>9</sup>.  
158 Enucleation may adversely affect driving due to loss of depth perception, and PBR due to  
159 diminished visual acuity. It is unclear as to whether treatment modalities did not differentially  
160 affect driving or whether patients did experience driving difficulties after one or the other  
161 treatments and simply stopped driving.

162 It might be expected that enucleation would increase concerns about appearance, as  
163 dissatisfaction with prostheses is relatively common.<sup>13</sup> This indeed was the case before  
164 statistical adjustment, but no differences in appearance concerns were observed after  
165 adjustment. Thus, treatment differences are probably attributable to pre-treatment differences  
166 between treatment groups, and unlikely to be a consequence of enucleation. The equivalence

167 of appearance concerns between enucleation and PBR may reflect either recent advances in  
168 the development of implants and prostheses<sup>14,25</sup> or a generally low concern about appearance  
169 in our sample of older patients.<sup>24</sup>

170         Some patients may opt for enucleation to avoid worry about recurrence. Unlike breast  
171 cancer, where women achieve reductions of fear and worry after mastectomy,<sup>26</sup> enucleation  
172 did not differentially reduce worry compared to PBR. Enucleated patients were more likely to  
173 have monosomy 3, although evidence suggests that this is not necessarily associated with  
174 worry about recurrence.<sup>15</sup> Enucleation can reduce the small probability of local cancer  
175 recurrence, but we have no evidence that it reduces patients' subjective worry about  
176 recurrence.

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

188         Findings of this study can help clinicians and patients to make informed decisions  
189 between enucleation and PBR. Firstly, enucleation can lead to greater functional difficulties  
190 associated with depth perception tasks, although this difference between the treatments  
191 seemed to abate after 12 months. PBR on the other hand is more likely to lead to patient

192 reported difficulties with visual impairments, experienced as loss of vision or visual problems  
193 in the treated eye affecting vision in the fellow eye. This is problematic for reading.  
194 Secondly, patients can be informed that enucleation will reduce the possibility of local  
195 recurrence in the affected eye, but it is unlikely to help them to reduce worry about  
196 recurrence. Finally, choice of treatment modality is unlikely to cause greater difficulties  
197 associated with ocular irritation, appearance or driving.

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