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PURPOSE

To test the hypothesis that patients treated with radiotherapy for choroidal melanoma enjoy better quality of life (QoL) than patients who have undergone enucleation.

METHODS

In this non-randomized study, patients with choroidal melanoma treated at the Royal Liverpool University Hospital, UK, were invited to complete QoL questionnaires approximately six months post-operatively and then on each anniversary of their primary treatment. These instruments consisted of the European Organization for Research and Treatment of Cancer (EORTC)-QLQ_OPT30 questionnaire, Hospital Anxiety & Depression Scale (HADS), and the Functional Assessment of Cancer Treatment (FACT-G) questionnaire. Patient-reported outcomes were correlated with: demographics; ocular treatment, social factors; presenting tumor and ocular status; self-reported general health; marital status and employment status.

RESULTS

The 1596 patients were treated with radiotherapy (72.3%) or enucleation (27.7%). Enucleation was associated with male gender ($\chi 2$, P=.004), older age (t-test, P<.001), larger tumor diameter (t-test, P<.001), monosomy 3 ($\chi 2$, P<.001), depression (Linear regression, 95% Confidence Interval [CI], .17 to 1.01) and reduced physical and functional wellbeing (Linear regression, 95% CI, -1.14 to -.12 & -1.96 to -.47 respectively. Poor QoL was attributed to the ocular disease by 21% and 20% of enucleated and irradiated patients respectively ($\chi 2$, P=.938).

CONCLUSIONS

Patient-reported outcomes and QoL were worse in patients who had undergone primary enucleation for choroidal melanoma. These outcomes may have been caused by factors predisposing to enucleation rather than enucleation itself, because enucleated patients tended to be older, with more advanced disease at presentation, and a worse prognosis for survival.

Patient-Reported Outcomes and Quality of Life after Treatment of Choroidal Melanoma: a Comparison of Enucleation vs Radiotherapy in 1596 patients.

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INTRODUCTION

For many years, the standard treatment for uveal melanoma was enucleation, performed in the hope of preventing metastatic disease and also to prevent the eye from becoming severely inflamed and painful. This treatment has largely been replaced by various forms of radiotherapy, phototherapy and surgical resection, which are also aimed at conserving the eye and useful vision.[1,2] The expectation is that if these objectives are achieved, then quality of life (QoL) will be better than if the eye is removed.

Ocular conservation, however, has several downsides. First, many patients experience unavoidable iatrogenic morbidity, often resulting in irreversible visual loss. Some patients develop complications, such as local tumor recurrence, retinal detachment and neovascular glaucoma, which may require removal of the eye. Second, this approach requires more clinic visits for treatment and subsequent surveillance. For these reasons, around 20-40% of patients undergo primary enucleation. [3] The decision as to whether or not to attempt ocular conservation is based on the clinical outcomes that are anticipated by the ophthalmologist as well as the QoL that the patient expects to retain.[4]

Even after successful excision or irradiation of the ocular tumor, almost 50% of patients develop metastatic disease, usually months or years after apparent cure.[5] Such disease occurs almost exclusively in patients whose tumor shows chromosome 3 loss, a class-2 gene expression profile, or both of these.[6,7] Increasingly, patients are undergoing genetic tumor typing for prognostication. Their wellbeing is profoundly affected by predicted life expectancy and by any uncertainty when genetic tumor typing fails.[8-11]

As with other forms of cancer, the impact of uveal melanoma on QoL is likely to be influenced not only by the disease itself, but also by several demographic, clinical, and psychosocial characteristics.[12-14] These include factors such as the condition of the fellow eye, as well as patient age, gender, general health, employment status, marital status, social support, and life stressors (e.g., financial difficulties or recent life events such as bereavement or family illness). Such factors should if possible be taken into account when measuring QoL after treatment for uveal melanoma.

Several groups have investigated QoL after treatment for choroidal melanoma.[10,15-20] These tend to indicate minimal differences between radiotherapy and enucleation, other than visual difficulties. However, most prior studies have been limited by small sample size and low statistical power. There is a need for a better understanding of the impact of ocular treatment on QoL, to improve treatment selection, patient counseling and personalized care, as well as to target psychological support at those experiencing, or likely to experience, reduced wellbeing.

Therefore, the aim of this study was to test the hypothesis that patients treated with radiotherapy for uveal melanoma report better QoL than patients treated with primary enucleation. Secondary goals were to determine the prevalence of adverse patient-reported outcomes and the factors influencing these outcomes.

PATIENTS

The study sample comprised a consecutive series of adult patients with choroidal melanoma, who resided in England or Wales and who were treated at the Liverpool Ocular Oncology Centre (LOOC) between January 1993 and December 2013.

METHODS

IRB APPROVAL

This study was approved as an audit in 2003 by the Liverpool Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Patient consent for treatment was obtained as soon as treatment modality was selected. Patient consent to participate in this study was obtained by means of a consent form that was mailed to them together with an information packet before their initial appointment at our hospital. In the case of patients who were treated before the start of our study and who were referred back to our center, we mailed a consent form to them together with our report on their visit; if they consented to participate in this study, they were then mailed a questionnaire on every anniversary of their primary ocular therapy at our hospital. The data collection was incorporated into our routine clinical practice and not undertaken as a formal clinical trial.

DIAGNOSIS

Melanomas were diagnosed according to generally accepted clinical features (e.g., tumor size, retinal detachment, lipofuscin).[21] If clinical findings were inconclusive, the diagnosis was established by documenting tumor growth or by biopsy.[22]

COUNSELING

On diagnosis of uveal melanoma at our center, we explained to patients the anatomy of the eye, the nature of their condition, the therapeutic options, and the likely ocular outcomes after each possible form of treatment. Treatment was based on

principles of shared decision-making.[4] Briefly, patients were encouraged to select treatment themselves after being informed of all the therapeutic options as well as the risks and likely outcomes of each kind of treatment. At the initial consultation, patients were then informed about their survival probability, after determining how much they wished to know. From 1999 onwards, patients undergoing local resection or enucleation were also offered genetic tumor typing using harvested tissue from the excised tumor. From 2007 onwards, patients undergoing radiotherapy were offered tumor biopsy for prognostication unless the tumor thickness was less than 2-3 mm.[22] The 10-year survival probability was estimated by multivariable analysis that included TNM stage, presence or absence of chromosome 3 loss and histological predictors of metastasis (e.g., epithelioid melanoma cytomorphology, mitotic count, closed loops); this was done using an online tool we developed, which also took account of age and gender (www.ocularmelanomaonline.org).[23] Throughout the study period, all patients were given a 90-page guidebook about ocular oncology and our service as well as an audio-recording of their initial discussion with the ocular oncologist, and printed information sheets relevant to their particular treatment.[24] Immediately after their consultation with the ocular oncologist, they received emotional support from a specialist ocular oncology nurse, who also checked that they understood all they were told, if necessary giving them further explanation about their condition and proposed treatment. All patients were offered support from a health psychologist, who worked exclusively with ocular oncology patients at our hospital. They were also able to self-refer themselves to our health psychologist at any time if they felt in need of specialist emotional support.

TREATMENT

If possible, patients underwent treatment the day after their initial consultation at our hospital, unless they requested a delay. Treatment selection took into account their preferences and was based on tumor size, location and extent.[4] Our first choice of treatment was ruthenium plaque radiotherapy if the tumor thickness did not exceed 5 mm and if we were confident that the plaque could be accurately positioned over the tumor without collateral damage to the optic nerve or fovea.[25,26] If the tumor had an irregular shape and extended far posteriorly, then proton beam radiotherapy was preferred.[27] If radiotherapy was expected to cause optic neuropathy, and if the tumor did not involve the macula, then endoresection was performed, unless the basal tumor diameter exceeded 10 mm.[28] If large tumor size indicated a high risk of exudative retinal detachment and neovascular glaucoma (i.e., termed 'toxic tumor syndrome' by the first author) after proton beam radiotherapy, then the patient was treated by trans-scleral local resection or, if this was not possible, by enucleation.[3,29,30]

SCREENING FOR METASTATIC DISEASE

Pre-operative liver imaging was performed only if we considered the chances of detecting metastases to be greater than 5% (i.e., if the basal diameter of the uveal tumor was 17 mm or more or if the patient reported suspicious systemic symptoms). On receipt of the results of genetic tumor analysis, patients whose tumor showed chromosome 3 loss and who were therefore considered to have a high risk of metastasis were referred to a medical oncologist for surveillance, which consisted of 6-monthly ultrasonography or, more recently, abdominal magnetic resonance imaging.[31] Patients deemed to have a low risk of metastasis (i.e., disomy 3 melanoma) did not undergo surveillance for systemic disease unless we felt that this would alleviate their anxiety, in which case they attended a surveillance clinic led by specialist ocular oncology nurses under the supervision of ocular oncologists at our hospital.[32]

FOLLOW-UP

Ophthalmic surveillance was individualized according to type of ocular treatment, risk of local tumor recurrence, ocular morbidity, and distance between the patient's home and our hospital. After enucleation, patients were generally followed up at their local hospital unless they lived close to our center. Patients treated with radiotherapy were usually reviewed at their hospital after one month, then at our center five months later, when a decision was made as to whether further ocular examinations were to be performed at our center or at the patient's local ophthalmic center or alternating between the two centers. If they were apprehensive about attending their local hospital, patients with a stable ocular condition and a low risk of tumor recurrence were seen at our nurse-led surveillance clinic.[32] We reviewed patients promptly if the local ophthalmologist became concerned about local tumor control or if our assistance was required because of ocular morbidity such as macular edema, retinal detachment, cataract or glaucoma or because the patient requested a second opinion from us.

At every follow-up visit, each patient was asked a set of questions addressing ocular and systemic symptoms, visual difficulties, and psychological problems, including fears about tumor recurrence, loss of the eye and death. This was done using a printed list of items, which was used to document the patient's responses. These answers were then reviewed and discussed with the patient and any accompanying persons.

PATIENT-REPORTED OUTCOME MEASUREMENT

All patients who consented to participate in the QoL study were mailed a questionnaire (Appendix A) six months following treatment, then annually on every anniversary of their treatment unless they notified us that they no longer wished to complete questionnaires. Questionnaires were self-administered without supervision. Before mailing each questionnaire, care was taken to ensure that the patient was still alive, by reviewing our ocular oncology database. When patients submitted several questionnaires, the first completed questionnaire was used for all analyses.

Marital status was categorized as: (1) married/living with partner; (2) divorced/separated; (3) widowed; and (4) single. Employment was categorized as: (1) employed; (2) retired; (3) invalid; and (4) 'other' (e.g., student).

Ocular comfort, worries and visual difficulties were measured using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-OPT30 instrument.[33] This comprises 27 questions measuring the extent of a symptom or worry during the previous week, with four additional questions for patients whose eye was conserved and four questions for patients whose eye was removed (Appendix A). Each item was scored as 'not at all', 'a little', 'quite a bit' and 'very much'.

The first author included additional questions asking the patient to rate their QoL and overall general health by scoring these between 1 (very poor) and 7 (excellent). These were categorized as poor if the score was less than 4. Patients were also asked to rate the extent to which their QoL and general health were affected by their ocular condition, with possible ratings ranging from 0 (not at all) to 7 (completely); scores greater than 4 were interpreted as indicating that their ocular disease strongly influenced their self-reported QoL and general health.

Anxiety and depression were measured using the Hospital Anxiety & Depression Scale (HADS), which poses 7 questions assessing anxiety symptoms and 7 questions assessing depressive symptoms. Each item is rated on a scale of 0 to 3.[34] Scores from 0 to 7 are considered to indicate "normal" levels of anxiety or depressive symptoms; scores from 8 to 10 are classified as "borderline/moderate;" and scores from 11 to 21 are categorized as "abnormal/severe."

Physical, functional, emotional and social wellbeing were measured using the Functional Assessment of Cancer Therapy scale (FACT-G) (also known at FACIT [Functional Assessment of Chronic Illness Therapy]).[35] Each symptom was scored as 'not at all', 'a little bit', 'somewhat', 'quite a bit' and 'very much'. Higher scores indicate better wellbeing. Mean scores for each of these four aspects of QoL have been published for the adult general and cancer populations in the United States, with scores exceeding 0.5 standard deviation below the mean for each subscale indicating low wellbeing in that specific domain.[36]

Social support was measured using a 7-item questionnaire, which was abbreviated from a 50-item 'Interview Schedule for Social Interaction (ISSI), developed by Henderson and Byrne.[37,38] Each question prompted a 'yes/no' answer. Social support was categorized as 'poor' if the total score was less than 6, 'borderline' if the score was 6 and 'good' if the score was 7.

CLINICAL DATA

Baseline clinical data included: age at primary ocular treatment; gender; affected eye; pre-treatment visual acuity; uveal locations of anterior and posterior tumor margins; tumor meridian; largest basal tumor diameter; tumor thickness; type of ocular treatment; melanoma cell type; extravascular matrix pattern, mitotic count per 40 high power fields, and genetic tumor type (i.e., presence of absence of chromosome 3 loss).

Follow-up data included: time between initial ocular treatment and completion of questionnaire; age at completion of questionnaire; and times to loss of good vision, loss of moderate vision, local tumor recurrence, and enucleation, if these events occurred, so as to determine whether such events developed before or after completion of the questionnaire.

If a patient died by the close of the study, we determined the cause of death and the time interval between completion of the questionnaire and the end of life. The National Health Service Cancer Registry automatically informed us of the date and cause of death of all deceased patients, having been notified by us of every patient at the time of initial diagnosis.

STATISTICS

Clinical and QoL data were computerized prospectively using a database (Revelation Software, Westwood, NJ, USA), which was customized for our ocular oncology service and maintained by Sprezzatura (Sprezzatura Ltd, London, UK). Statistical analyses were performed with Stata/IC 14.1(StataCorp, Texas, USA) and IBM SPSS Statistics, Version 22 (IBM Corp, New York, USA).

Between-group differences for categorical variables were examined with the Pearson chi-square test of independence, and with ordinal logistic regression for ordinal categorical data. Continuous variables were analyzed with the two-sample t-test with unequal variance, using the bootstrap (with 1000 replications) for skewed variables. Factors associated with QoL were examined with multivariable analysis using backwards stepwise regression with bootstrapping (with 1000 replications). Inferences from bootstrapped analyses were made using the bootstrapped nonparametric, bias-corrected confidence intervals. Positive observed coefficient scores indicate better quality of life and wellbeing but more anxiety and repression after enucleation.

RESULTS

DEMOGRAPHICS

A total of 1596 patients completed a QoL questionnaire at least once between 1993 and 2013. These comprised 442 patients who had undergone primary enucleation and 1154 patients who had received radiotherapy, which consisted of ruthenium plaque radiotherapy in 730 patients and proton beam radiotherapy in 424. The patients included 771 females with a median age of 62.5 years (range, 21.6 – 94.4) and 825 males with a median age of 62.0 years (range, 25.9 – 91.7). The time between primary ocular treatment and first completion of a questionnaire had a median of 59.1 months (SD, 58.7; interquartile range, 23.7 – 107.9; range, 3.6 – 252.3).

Participants vs Non-Participants

The patients participating in this study comprised 79.4% of 2804 eligible patients (Appendix B). The number of non-participants increased until around 2001 then diminished as more patients were recruited to this study (Table B1 & Figure B1). Primary enucleation was performed in 27.7% of participants and 43.6% of eligible non-participants (Pearson $\chi 2$, $P<.001$) (Table B1). In patients treated with radiotherapy, there were no significant differences between study participants and non-participants except for visual acuity, which was better in participants, and tumor thickness, which tended to be greater in non-participants (Table B2). With regards to patients undergoing primary enucleation, study participants were more likely to be younger, with better vision in the treated eye and with a smaller tumor, which was more likely to be medial and less likely to show epithelioid cells and chromosome 3 loss (Table B3).

COMPARISON BETWEEN IRRADIATED AND ENUCLEATED PATIENTS

Demographics and Clinical Features

Compared to patients undergoing enucleation, those receiving radiotherapy were more likely to be female, younger and to have better visual acuity in the treated eye (Table 1). Further, their tumor was more likely to be smaller, more posterior and temporal, also less likely to show extraocular spread, epithelioid cells and chromosome 3 loss (Table 1). The time between primary treatment and the first completion of the QoL questionnaire was longer in patients who had received primary radiotherapy than those who had undergone primary enucleation (Table 1 & Figure 1).

Social Factors

Marital Status

At the time of completion of the first QoL questionnaire, there were no significant differences between enucleated and irradiated patients with respect to: being married/living with partner (65.2% vs 69.8%); divorced/separated (9.3% vs 7.8%); widowed (17.8% vs 16.6%) or single (7.7% vs 5.8%) respectively (Pearson $\chi 2$, $P=.250$).

Employment Status

At completion of the first QoL questionnaire, 19.3% of enucleated patients were employed as compared to 29.8% of those who had received primary radiotherapy (Pearson $\chi 2$, $P<.001$), with 71.8% and 61.3% reporting themselves to be retired (Pearson $\chi 2$, $P<.001$), 2.6% and 3.2% as homemaker (Pearson $\chi 2$, $P=.505$), 2.4% and 1.0% as unemployed (Pearson $\chi 2$, $P=.04$), 3.8% and 4.5% as invalid (Pearson $\chi 2$, $P=.522$) and .2% and 0% as student, respectively.

Social Support

At completion of the first QoL questionnaire, social support was categorized as ‘poor’, ‘borderline’ and ‘good’ in 19.5%, 14.8%, and 65.7% of patients who underwent enucleation, respectively, as compared to 22.2%, 14.7%, and 63.1% respectively among patients who received primary radiotherapy (Pearson $\chi 2$, $P=.501$).

Survival

Metastatic death occurred in 106 (24.0%) of patients after enucleation and 85 (7.4%) after radiotherapy (Pearson $\chi 2$, $P=.001$) with death from other causes occurring in 51 (11.5%) and 100 (8.7%) of patients respectively. Death from any cause occurred within 6 months of completion of the questionnaire in 37 (8.4%) patients who underwent primary enucleation and 47 (4.1%) of patients treated with radiotherapy (Pearson $\chi 2$, $P=.001$).

Ocular Outcomes

After radiotherapy, the last known visual acuity before completion of the questionnaire was 20/40 or better in 664 (57.6%) of patients, 20/60 to 20/200 in 251 (21.8%), Count Fingers in 131 (11.6%), and Hand-Motions to Light Perception in 63 (5.5%) with 44 (3.8%) patients having undergone secondary enucleation. In all patients, the binocular vision was 20/40 or better in 1099 (95.3%) patients, 20/60 to 20/200 in 43 (3.7%), Count Fingers in 7 (.6%), Hand Motions to Light Perception in 3 (.3%) with one patient (.1) having binocular enucleation. After radiotherapy, local tumor recurrence before completion of the questionnaire occurred in 30 (2.6%) patients.

Patient-Reported Outcomes

EORTC-QLQ-OPT30

Compared to enucleated patients, those undergoing radiotherapy were less likely to complain of ocular discomfort (grittiness, itching, watering, discharge) (Table 2 & Figure 2). They also reported less visual difficulty (driving in the dark, pouring drinks, walking in crowds, seeing steps, walking on uneven ground, judging distance) (Table 2 & Figures 3 & 4). They were also less likely to report worry about their appearance and about future poor health, their risk of metastatic disease and of losing the eye (Table 2 & Figure 5). They were more likely to complain of headache or diplopia and to worry about local

tumor recurrence. There were no significant differences between the two forms of treatment with respect to reported pain, visual field loss, interference of vision in the untreated eye, difficulty driving during the day and difficulty reading. As many as 41.2% of enucleated patients reported that they were not driving, as compared to 31.4% of those who had received primary radiotherapy ($\chi 2$, $P<.001$). A total of 30.4% of enucleated non-drivers reported that they did not drive because of visual loss as compared to 22.9% of irradiated non-drivers ($\chi 2$, $P=.113$).

Metamorphopsia, photopsia, floaters, and photophobia with the treated eye were reported by 263 (24.9%), 206 (19.3%), 259 (24.3%) and 329 (30.5%) of patients who had received primary radiotherapy whereas in those treated by enucleation, ptosis, poor prosthetic motility and sagging of lower eyelid were reported by 80 (18.7%), 42 (10.0%) and 68 (15.9%) of patients respectively.

Quality of Life

Univariable Analysis

Patients who had received radiotherapy had significantly better physical, functional and emotional wellbeing and less depression than those who had undergone primary enucleation, with no significant differences in anxiety, self-reported quality of life, self-reported general health, social wellbeing, and overall FACT-G score (Table 3 & Figures 6 & 7).

Multivariable Analysis

After adjusting for ocular factors (i.e., visual acuity with the affected eye, laterality, TNM prognostic group, and chromosome 3 loss), radiotherapy was significantly associated with higher functional wellbeing (Table 4). After adjusting for demographic and social factors (i.e., age, gender, follow-up time, general health, marital status, employment status and social support), radiotherapy was significantly associated with higher functional and emotional wellbeing and with a better FACT-G score (Table 5b).

ASSOCIATIONS BETWEEN QUALITY OF LIFE AND FACTORS UNRELATED TO TYPE OF TREATMENT.

The results of multivariable analysis are listed in Tables 4 and 5. Female gender was associated with greater anxiety and better emotional wellbeing. Older age at primary treatment was significantly associated with reduced anxiety as well as increased physical and emotional wellbeing. Chromosome 3 loss was associated with higher levels of anxiety. Better social support was associated with reduced anxiety, reduced depression, higher self-reported QoL as well as better physical, functional, emotional and social wellbeing. Being married or living with a partner was associated with better functional wellbeing. Being employed or a homeworker was associated with less depression, better self-reported QoL as well as better physical, functional and emotional wellbeing. Better self-reported general health was associated with less anxiety and depression, better self-reported QoL as well as better physical, functional, emotional and social wellbeing.

Poor self-reported QoL was attributed mostly to the ocular disease by 57 (21.1%) enucleated patients and 120 (20.0%) of patients who had received primary radiotherapy ($\chi 2$, $P=.938$).

Poor self-reported general health was mostly attributed to the ocular disease by 57 (26.3%) enucleated patients and by 125 (12.8%) of patients who had received primary radiotherapy ($\chi 2$, $P=.073$).

A total of 705 patients reported health problems unrelated to their uveal melanoma, which were: predominantly cardiovascular in 185 (mostly systemic hypertension, ischemic heart disease and cardiac arrhythmia); rheumatic/musculoskeletal in 124 (e.g., arthritis, spinal problems); oncological in 71 (mostly cancers affecting prostate, breast and lung); diabetological in 64; pulmonary in 52 (mostly asthma and chronic obstructive pulmonary disease); gastrointestinal in 37 (e.g., gallstones, diverticular disease); psychiatric in 29 (e.g., depression, dementia); neurological in 28 (e.g., parkinsonism, migraine, paresis); genitourinary in 24 (mostly prostatic); endocrine in 20 (mostly hypothyroidism); and a variety of other conditions in the remainder.

Major events in the previous year were reported by 181 patients. The most common types of event were concurrent illness in 49 patients, bereavement in 46, severe illness in close relatives or friends in 26, other malignancy in 20, employment issues in 7, moving home in 5, and relationship issues in 8 (e.g., divorce, emigration of child).

DISCUSSION

MAIN FINDINGS

Many patients with choroidal melanoma experienced ocular discomfort, visual difficulties, concerns about future health, dissatisfaction with appearance, anxiety, and depression, as well as reduced physical, functional, emotional and social wellbeing. QoL was associated with factors such as age, gender, general health, risk of metastasis, marital status, employment status, social support and follow-up time. After taking these factors into account, enucleation was associated with reduced functional and emotional wellbeing. Enucleated patients were more likely than irradiated patients not to drive a car. Only a fifth of patients with poor self-reported QoL attributed this to their ocular condition, irrespective of type of treatment;

however, enucleated patients were twice as likely to attribute poor general health to their ocular condition and were also twice as likely to die within six months of completing their first QoL questionnaire.

STRENGTHS AND WEAKNESSES OF STUDY

The main strengths of our study are the large number of patients and the long follow-up period for some patients.

The main inferential weakness is that the patients were not randomized between enucleation and radiotherapy. However, such randomization would have been unethical in view of the patients' preference for ocular conservation and the lack of evidence indicating better survival after enucleation.[39] Such randomization would also have diminished the relevance of our results to clinical practice, because treatment is selected according to each patient's ocular condition, general health status, and personal preferences.

Another limitation is the lack of a pre-treatment assessment of psychological symptoms and QoL. Patients were not asked to complete a QoL questionnaire before treatment because, having just been informed of the presence of an intraocular tumor, patients tended to be more anxious during this time. Therefore, it was felt that any questionnaire responses would not have represented their normal 'baseline' status.

A weakness of this study is that we added un-verified questions to the EORTC OPT-QLQ30 instrument to assess self-reported QoL and self-reported general health and the degree to which these were determined by the ocular condition. Although these were not evaluated formally, the statistical correlations with outcomes appeared meaningful. There is scope for further studies investigating the validity of these additional questions.

Another weakness is that not all patients completed QoL questionnaires, which may have limited our ability to detect important patterns. As mentioned, participation was higher among patients who attended the ocular oncology clinic during the study, especially if they did so several times, which was more likely after radiotherapy. Although there were no significant differences between participants and non-participants within treatment groups, patients who repeatedly attended the ocular oncology clinic were more likely to receive psychological support and this may have improved their outcomes in comparison with those who had been discharged from our care but who were nevertheless completing questionnaires. It would have been ideal if all patients had been evaluated indefinitely in our clinic, to improve data quality; however, this would have been unethical without reimbursing patients for their travel and accommodation expenses and for lost income. Such funding was not available as the collection of QoL data was incorporated into our routine clinical practice and was not undertaken as a part of a formal clinical trial.

Although it would have been ideal to measure a wider range of patient-reported outcomes (e.g., decisional regret), we chose to limit the number of questions to reduce the burden placed on patients, particularly as they were being asked to complete our questionnaires repeatedly.

DISCUSSION OF METHODS

The EORTC QLQ-OPT30 was selected because it was developed specifically for patients with an ocular tumor, measuring visual function, ocular discomfort and concerns. Most questions proved to be informative, except for those pertaining to diplopia looking ahead, visual field loss, and concerns about losing the eye (see below).

The FACT-G was deployed because it is widely used for assessing QoL after treatment of cancer, allowing comparison of our patients with the adult general and cancer populations in the United States.

The HADS instrument was useful in demonstrating the degree of anxiety and depression in our patients and comparing our results with those of other studies, having been validated elsewhere.[40]

The questions on self-reported QoL, self-reported general health and the extent to which these were influenced by the ocular condition were devised by the first author (BD). Although not previously validated by formal analyses, significant associations with other QoL indicators supported their use as a means of obtaining summary statistics.

The abbreviated version of the Interview Schedule for Social Interaction, which we used to measure social support, has been shown to have reliability, validity and predictive capacity.[38] We found this to correlate well with several aspects of QoL.

DISCUSSION OF RESULTS

Demographics

Participants vs Non-Participants. Patients were less likely to participate in our study if they had undergone enucleation than if they had received radiotherapy. This is because enucleated patients tended to be discharged from our care soon after treatment whereas after radiotherapy they attended our clinic for several months or years so that they were more likely to be invited and to participate.

Radiotherapy vs Enucleation. Patients undergoing primary enucleation tended to have more advanced disease, which reflects our preference for radiotherapy unless the chances of conserving what the patient considered to be a useful eye were insufficient (for the patient). Males and older patients were more likely to have primary enucleation; this suggests variation in patients' stage of disease at presentation and risk tolerance according to age and gender.

Social Factors

The enucleated and irradiated patients were similar with respect to being married/living with partner, divorced/separated, and widowed or single, at least when the first QoL questionnaire was completed. It would have been interesting to know the marital status at the time of initial ocular treatment, but this information was not collected.

Compared to patients who received primary radiotherapy, enucleated patients were more likely to be retired or unemployed. This is likely because they tended to be older and probably because they experienced more visual and psychological problems than patients who had radiotherapy.

Social support was similar in both groups of patients, which is in keeping with the finding that social wellbeing was not adversely affected by enucleation, despite more anophthalmic patients being concerned about their appearance.

Clinical Outcomes

The higher mortality in patients who underwent primary enucleation corresponds to their older age and more advanced disease at the time of primary treatment. Approximately 5% of patients completed the questionnaire in the last six months of life when they were likely to have been suffering from terminal illness. The proportion of such patients was higher in patients who had undergone enucleation and this may have biased the QoL results.

Patient-Reported Outcomes

Visual difficulties were more severe after enucleation than radiotherapy, with the exception of diplopia, which was more common after radiotherapy. Although monocular patients were more likely to report difficulty walking in crowds there was no significant difference in their complaint about defects in peripheral vision, and this is because most individuals are only aware of the impact of visual field loss and not the field loss itself. The two groups of patients showed no significant difference in difficulty driving during the day and this is probably because many patients had stopped driving because of their visual loss.

It is noteworthy that visual function was better in the radiotherapy treatment group than the enucleation group despite the fact that many irradiated patients had lost vision by the time they completed their questionnaire. Some had also experienced failure of local tumor control and/or secondary enucleation, but such patients were too few to have influenced overall results significantly. Because of their rarity, it was not possible to examine statistically the impact of these adverse outcomes on QoL although this is likely to have been considerable. In irradiated patients, metamorphopsia, photopsia, floaters and photophobia were common and may therefore have affected the results. Grittiness, discharge, watering and other forms of discomfort were more common after enucleation than after radiotherapy. Conversely, headache was more troublesome after radiotherapy. Fears about future health and metastasis were more common in patients who had undergone enucleation. This is consistent with the worse prognosis they were given, which was based on large tumor size and/or monosomy 3.

Some enucleated patients reported interference of vision in the fellow eye by the treated eye as well as diplopia, fear of local tumor recurrence and fear of losing the eye. There are several explanations for such responses. The questions may have been answered incorrectly. Also, patients may have forgotten the advice that local tumor recurrence is rare after enucleation, which suggests that this information should be repeated several times and that patients' understanding of the information should be assessed by the clinical team. At every follow-up visit, all patients were routinely asked how worried they were about local tumor recurrence and fatal illness. A printed list of items ensured that these questions were not omitted. We strongly reassured patients if the risk of local tumor recurrence was minimal, as after enucleation. It is possible, therefore, that patients expressing fears of local recurrence after enucleation were no longer attending our clinic and so were not being reminded about the low risk of local recurrence.

As diplopia was more common when looking straight ahead than when looking sideways, this term may have been confused with astigmatism. The question about fear of losing the eye was, in retrospect, ambiguous, with some patients possibly understanding this question to refer to having lost the eye and others perhaps expressing fears about the possibility of losing the fellow eye. As for patients reporting that the enucleated eye interfered with vision in the remaining eye, some patients may have taken this to mean that the loss of one eye adversely affected their visual function, especially if this was impaired in the remaining eye. Also, it is known that patients can experience the phantom eye syndrome after enucleation with some even reporting that they can see better when they close the enucleated eye.[41]

Some patients reported symptoms peculiar to the type of treatment they had received (e.g., photopsia after radiotherapy and poor motility of prosthesis after enucleation). These outcomes may have influenced QoL or may have been amplified by anxiety, depression or other psychological problems.

QoL after Radiotherapy vs Enucleation

There are several explanations for the finding that physical wellbeing, functional wellbeing and depression were worse after enucleation than after radiotherapy. First, enucleated patients reported higher rates of ocular discomfort, visual difficulty and concerns about health and appearance. Second, these patients tended to be older and to have a more advanced tumor so that they were more likely to have other disease and a greater risk of metastasis. Third, their advanced ocular disease and the need for enucleation may have been the consequence of delays in presentation caused by reduced wellbeing or depression. In other words, poor wellbeing may have been the cause as well as the result of enucleation. Fourth, almost a quarter of patients report that their tumor was missed when they presented to a medical practitioner with symptoms and these patients were more likely to require enucleation than those whose tumor was detected without delay.[42] It is possible that the wellbeing of some of these patients was diminished by regret that their tumor was not detected and treated in a timely manner. Finally, enucleated patients were also more likely to be experiencing terminal illness when completing the questionnaire.

QoL according to Other Factors

Women tended to report more anxiety than men, as found elsewhere in the general US and UK populations, in patients with uveal melanoma and those with cutaneous melanoma.[43-45] However, they also reported better emotional wellbeing. These seemingly contradictory findings would suggest that it is possible to be anxious and to enjoy good emotional wellbeing at the same time. Holterhues and associates have reported high levels of both positive and negative indicators of QoL in women.[44]

Patients who were younger at the time of primary treatment showed more anxiety, less depression, better functional wellbeing and worse emotional wellbeing than older patients. Increase in depression with age has been reported previously.[46,47] A German study of 664 patients with localized cutaneous melanoma reported reduced role functioning and reduced global QoL with older age, but improved emotional functioning and body image.[48]

Patients indicating poor social support showed more anxiety and depression and lower physical, functional, social and emotional wellbeing. Other studies support these results.[13,14,48,49]

As one might expect, QoL was better in patients reporting good general health and good social support, as indeed was reported elsewhere.[14,48]

As reported previously, patients who described themselves as being employed or as homemakers showed better QoL[14]; this is probably because of the benefits provided by such activity and also because patients were more likely to be active if they had better physical and emotional health.

Only 20.3% of patients with poor self-reported QoL attributed this to their ocular condition. Similarly, only 17.0% of patients with poor general health reported that this was mostly caused by their ocular disease. Wiley and associates have reported similar findings.[50] Patients reported a wide variety of general health problems and adverse events experienced during the previous year. Detailed analysis of these influences is beyond the scope of the present study. Nevertheless, such results indicate the importance of taking non-ophthalmic disease and social factors into account when analyzing the QoL of patients with uveal melanoma and when managing these patients clinically.

After adjusting for these factors, enucleated patients showed reduced functional and emotional wellbeing and hence a lower overall FACT-G score. As mentioned, this is probably because they had more discomfort, more visual difficulties, more concerns about their health and appearance, older age, poorer health and worse survival probability.

COMPARISON WITH PREVIOUS STUDIES ON UVEAL MELANOMA

Cruickshanks and associates (1999)[19]

QoL in 82 patients treated with radiotherapy was compared with that of 65 patients who had undergone enucleation. This cohort represented 40% of 370 invited patients. Patients who had received radiotherapy had better scores in the vitality scale of the MOS (Medical Outcome Study) SF (Short Form)-36 questionnaire but there were no statistical differences in the estimated Quality of Well-being score, NEI_VFQ (National Eye Institute Visual Function Questionnaire) or the TTO (Time-Tradeoff) questionnaire. The authors concluded that there were minimal differences between the two treatment groups and that the overall QoL among choroidal melanoma patients was comparable to others in their age range. These results differ from those of the present study, possibly because of the small number of patients studied by Cruickshanks and associates and therefore the lack of sufficient statistical power.

Brandberg and associates (2000)[16]

In this study, 38 patients treated by enucleation were compared with 47 who had received ruthenium plaque radiotherapy two months previously, with 32 and 46 of these respectively completing questionnaires one year after treatment. With the EORTC-QLQ-Q30 scale, most patients reported reduced QoL, emotional functioning, cognitive functioning, fatigue and insomnia but there were no statistically significant differences between treatment groups with respect to QoL. This negative result probably occurred because of the small cohort size. 'Role functioning' improved during the first year after surgery.

With the HAD Scale, mean scores for anxiety in enucleated and irradiated patients respectively were 8.7 and 6.6 before treatment, 5.6 and 4.5 two months after treatment and 5.8 and 5.0 one year after treatment, the decrease in these values reaching statistical significance. The authors report that mean scores for depression did not change significantly over time and were 4.3 and 3.6 respectively before treatment, 4.3 and 3.7 two months after treatment and 4.5 and 4.0 one year after treatment. These negative findings probably occurred because of the small number of patients and the short follow-up. Differences between treatment groups were not considered to be statistically significant, in contrast to the present study.

With the IES (Impact of Event) Scale, which measured stress, there were no significant differences between the two treatment groups.

With the EORTC QLQ-OPT30, the percentages of patients treated by enucleation and radiotherapy respectively showed statistically significant differences with respect to concerns about appearance (55% vs 15%), difficulty walking on uneven ground (85% vs 50%) and 'difficulty seeing to side' (55% vs 83%). These differences were statistically different in our study also but the prevalences of these symptoms in our study were lower, possibly because we were able to select between plaque and proton beam radiotherapy according to the tumor size and location.

In their Discussion, Brandberg and associates reported that 'compared with patients with other cancer diagnoses, and with normative data, high proportions of patients reported reduced QoL and substantial emotional problems 1 year after the surgery.' The authors remarked on the high level of anxiety before treatment, which vindicates our decision not to measure psychological indicators during this stressful time.

Chabert and associates (2004)[17]

This group evaluated QoL in 49 patients treated with stereotactic external beam irradiation (LINAC), 21 treated with the Leksell Gamma Knife and 19 with ruthenium plaque radiotherapy.

The mean HAD scores were 5.7 for anxiety (SEM $\pm$4.0) and 4.9 for depression (SEM $\pm$4.3) as compared to 4.9 and 3.5 respectively in our study, with HAD scores indicating pathological levels of anxiety and depression in 12% and 14% of patients respectively in comparison with 10% and 6% in our patients. These comparisons are not meaningful because of limitations of Chabert and associates' study, which include: not describing the patient population; not reporting follow-up times; and not reporting any statistical values. Chabert and associates listed a number of severe complications that developed in their cohort, such as scleral and corneal necrosis, optic neuropathy, retinal detachment and glaucoma, which suggest that they had attempted to conserve eyes with advanced tumors. Our results indicate that some or many of their patients would perhaps have experienced less psychological morbidity if there had been a lower threshold for primary enucleation at their hospital.

The Collaborative Ocular Melanoma Study (COMS) Group (2006)[18]

QoL after iodine-125 brachytherapy was compared with that after enucleation for choroidal melanoma, with 103 patients randomized to each kind of treatment. The COMS and our study differed with respect to inclusion and exclusion criteria and in the reporting of baseline and outcomes data so that only the conclusions drawn by the two studies can be compared.

The COMS showed that patients receiving radiotherapy had better visual function in the early post-treatment period as compared to enucleation but this difference diminished over time as radiation-induced complications developed. This is probably because of the use of iodine-125 plaques, which emit long-range gamma rays and which are more likely to cause collateral damage to healthy ocular tissues than beta-emitting ruthenium-106 plaques and proton beam radiotherapy. The design of iodine plaques has since improved so that visual loss may now be less than that experienced in the COMS.[51] The COMS also found more anxiety after radiotherapy because of increased fear of metastasis, although this difference between treatment groups diminished once the COMS reported that survival following radiotherapy was not worse than after enucleation. In contrast, although in our study irradiated patients were more concerned about the risk of local recurrence than enucleated patients, we found no significant difference in the level of anxiety between the two treatment groups and this was probably because we were able to confidently reassure most patients that they had a good prognosis, thanks partly to the genetic tumor typing that we offered to patients.

The COMS reported no difference in concerns about appearance more than two years following treatment; however, in our cohort enucleated patients reported more concern than those receiving radiotherapy. The prevalence of dissatisfaction with appearance in our study was low (i.e., 9% following enucleation and 3% after radiotherapy). In the COMS, social functioning in the first post-operative year was worse after enucleation than after radiotherapy, with this difference no longer being significant by the fourth post-treatment year.

Hope-Stone and associates (2016)[20]

This group of researchers (which included some of the authors of this article) measured QoL during the first two years after treatment for uveal melanoma between 2008 and 2011. The patients were treated at the Liverpool Ocular Oncology Centre and were also included in the present study, except for those treated by some form of primary local resection or phototherapy. Anxiety, depression and QoL, assessed using the HADS and FACT-G, were correlated with age, gender, type of ocular

treatment (i.e., enucleation vs radiotherapy or local resection), and genetic tumor type (i.e., monosomy 3 vs disomy 3). Compared to 195 patients whose eye was conserved, the 66 patients who had undergone primary enucleation showed no significant difference in any QoL measures, unlike our study, which indicated better QoL after radiotherapy than after enucleation. The present study is likely to be more sensitive because it includes a larger number of patients and relies on multivariable analysis adjusting for a wide variety of factors. As in the present study, younger patients and females showed higher levels of anxiety, which diminished over time, especially in younger patients. The study by Hope-Stone and associates also showed that within six months of treatment patients had regained a level of QoL that was similar to that of the general population.

Schuermeyer and Associates (2016)[9]

Depression, anxiety and decision regret were assessed in 96 patients before and after informing patients of survival probability after treatment of uveal melanoma.[9] At baseline, 49% and 9% of patients had possible/probable anxiety or depression respectively. Decision regret at baseline was found in 10% of patients and was associated with depression, which decreased with time, as did anxiety; however, the follow-up time was only 12 months. Unlike our study, anxiety was not associated with prognosis.

Wiley and Associates (2013)[50]

In this study, QoL questionnaires were completed by 99 patients, 82 of whom had received radiotherapy with 16 undergoing primary enucleation. The follow-up averaged 2.05 years. As in our study, enucleated patients had worse scores on role difficulties but QoL was primarily determined by recent stressful life events, other physical co-morbidities and perceived unmet cancer needs (i.e., physical and daily living needs, psychological support, communication, information, patient care and support needs).

Reimer and Associates (2003)[52]

This study sample comprised 93 patients with choroidal melanoma who had undergone radiotherapy an average of 5.5 years previously. QoL was compared with that of 93 matched controls. Patients reported better emotional support and support from confidants than controls but worse social support and poorer QoL. Clinically relevant distress was found in 36% of patients, who suffered significantly more 'bodily pain', poorer 'mental health' and worse visual acuity. These results are similar to those found in the present study.

COMPARISON WITH PREVIOUS STUDIES ON ENUCLEATION

Morgan-Warren and Associates (2013)[53]

The cohort comprised 36 patients treated by evisceration (64%) or enucleation (36%) for a variety of conditions other than malignancy (e.g., trauma, glaucoma and retinal detachment). Pathology in the fellow eye was present in 28% of patients, with visual loss in several of these. Troublesome symptoms experienced in the previous month included pain (33%), watering (50%), discharge (i.e., 'stickiness') (61%), concerns about appearance (50%), some degree of self-consciousness (78%) and activities limited because of poor vision (44%). These rates are higher than those of the present study, possibly because of previous inflammation, trauma and other morbidity. About 33% had stopped driving, with almost half of these having poor vision in the fellow eye.

Rasmussen and Associates (2012)[54]

This study included 120 patients, who had been treated by enucleation (55), evisceration (63) or exenteration (2). Although the reason for enucleation was not specified, another article by the same group suggests that about a third of patients had surgery because of a neoplasm.[55] Approximately 12.5% of the patients were divorced or separated, as compared to 6.3% of the general Danish population. In our study, 9.3% vs 7.8% were divorced or separated after enucleation or radiotherapy respectively. Cessation of leisure activities such as ball games was reported by 39.5% of patients and about 25% of patients had retired or moved to part-time work because of their ocular condition. The authors attributed these changes in lifestyle to emotional problems caused by altered body image and poor self-confidence. In the present study, 19.3%, 71.8% and 2.4% of enucleated patients described themselves respectively as employed, retired and unemployed, as compared to 29.8%, 61.3% and 1.0% of those who had received primary radiotherapy. Although enucleated patients tended to be older in our study, it is likely that some retired because of their illness, as in the study by Rasmussen and associates. As in the Danish study, we found that many patients reported that their activities had been limited and some had stopped driving. In the study by Rasmussen and associates, patients also had poorer health-related QoL and self-rated health as well as more anxiety than the general population.

Ye and Associates (2015)[56]

This Chinese study investigated 195 enucleated patients, after excluding patients with poor vision in the fellow eye, severe systemic disease and/or patients with facial disfigurement as a result of trauma. The authors found that 23.1% were dissatisfied with their facial appearance, as compared to less than 10% in our study. They reported anxiety and depression in 11.8% and 13.8% of patients. Anxiety was associated with younger age, visual difficulties, and concerns about appearance. Depression was associated with lower level of education, visual difficulties, concerns about appearance and anger about condition.

Kondo and Associates (2013)[57]

This study compared 29 enucleated patients with 25 binocular controls. The patients had undergone enucleation a mean of 23.6 years before participating in this study. As in the present study, the authors found the patients to have reduced peripheral vision and role difficulties.

COMPARISON WITH GENERAL AND CANCER POPULATIONS

Compared with the general adult US population, patients in our study showed better social wellbeing, which is perhaps more indicative of the response of family and friends to the patients' condition than that of the patients themselves (Table 6).[36,58] Enucleated patients showed poorer emotional wellbeing than the general population, for the reasons already discussed.[36,58] In comparison with adult cancer patients in the US, enucleated patients showed better physical wellbeing whereas those who received radiotherapy showed better physical wellbeing and better FACT-G scores.[36,58]

Crawford and associates determined normative HAD values in the general adult UK population reporting female anxiety, male anxiety, female depression and male depression score means of 7.0, 5.8, 3.8 and 3.6 respectively.[59] In our study, these scores were 5.7, 4.4, 3.6 and 3.6 respectively, possibly suggesting lower levels of anxiety in our patients. Other studies have shown QoL indicators of patients facing cancer and other adversities to compare favorably with those of the general population.[60] Such unexpectedly good QoL may be the result of coping mechanisms such as benefit finding and meaning making.[61]

FURTHER RESEARCH

Relevance to Other Ocular Oncology Centers

There is scope for further studies to determine whether our results are relevant to other centers and countries. For example, few centers have such a wide choice of therapeutic modalities and few are able to provide patients with so many resources, such as emotional support from specialist nurses and a health psychologist. In Liverpool, many patients avoided some of the financial burdens they might have experienced in some other countries. This is because the UK National Health Service provided medical care that was free of charge at the point of delivery so that patients were not required to pay for any clinic visits, investigations or treatments at our hospital or at their local health center. Further, when patients traveled to our center from afar, our hospital reimbursed them and one accompanying person for their travel expenses and for accommodation at a nearly hotel. In many other countries, patients incur considerable medical costs unless they are fully covered by medical insurance.

Impact of Clinical Interventions on Wellbeing

It would be useful to include patient-reported outcomes in studies evaluating rival forms of treatment, as happens with other cancers and diseases. For example, although radiotherapy and surgical excision of iris melanoma may have similar outcomes in terms of visual acuity and ocular conservation, there may be great differences in symptoms such as photophobia and satisfaction with appearance.[62] A few studies have already investigated the psychological effects of genetic tumor typing of uveal melanoma[9]; however, there is still much to learn about the influence of accurate prognostication on QoL, both in patients with a good prognosis and those at high risk of metastasis. Similarly, surveillance for systemic metastases is stressful for patients, unnecessarily so when false positive results occur, but such investigation also provides patients with reassurance when the results are normal. A better understanding of the psychological impact of imaging studies should result in improved counseling and better care. Conversely, many patients are denied the opportunity of prognostic tumor biopsy, possibly because their doctor considers such an intervention to be futile or risky. It would be useful to understand how such patients feel, especially if they were not given any say in the matter.

Change over Time

There is scope for further studies to determine how patient-centered outcomes and quality of life change over time so as to predict long term outcomes according to findings in the early post-operative period.

Possible Interventions to Enhance Wellbeing of Patients and Relatives

There are several interventions that merit development and evaluation. For example, there is scope for investigating a protocol for telephoning patients at regular intervals, if they have been discharged from the ocular oncology clinic, to answer any questions as well as to reiterate important and reassuring information (e.g., if the chances of local tumor recurrence are small after enucleation or if the risk of metastasis is minimal because the tumor shows disomy 3 or a class 1 genotype).

Further studies are needed to understand how best to provide information, support, and assistance to patients' relatives and friends, who can and do serve as valuable resources to patients with ocular melanoma. Attention tends to be focused on patients; however, their wellbeing is greatly influenced by the support that they receive from those who are close to them and who are also likely to be distressed by the patient's illness.[63]

The development of the Internet has enabled the formation of several patient advocacy groups. As well as championing higher standards of care, these organizations can be helpful in providing patients and relatives with useful information and encouragement. It would seem worthwhile evaluating how these affect patients' wellbeing as well as identifying and enhancing the activities that are most beneficial while recognizing and rectifying any measures that might be counter-productive, however well-intentioned they may be.

CLINICAL IMPLICATIONS

Initial Counseling and Treatment Selection

When counseling patients on therapeutic options and prognosis, it is important to discuss not only the chances of retaining vision and conserving the eye, according to tumor size and location, but also the likelihood of visual difficulties, ocular discomfort, and dissatisfaction with appearance. It is also useful to discuss the possible impact of these outcomes on wellbeing, alerting patients and relatives to the possibility of psychological morbidity, especially if the prognosis for survival is guarded. Such discussions should help patients choose the treatment that best suits their needs and may allow some of them to obtain support from a health psychologist even before serious emotional problems develop. This counseling can also alert close relatives to functional and psychological difficulties that the patient may experience so that they are better able to understand the disease caused by uveal melanoma and to provide assistance. The data provided by this study should be useful in these conversations.

Detection of Psychological Morbidity

The first author has found that when patients are asked how they are, many simply say they are 'fine', when in fact they are experiencing considerable worries and difficulties (unpublished data). It has long been his practice, therefore, to ask patients explicit questions about any visual difficulties, discomforts, moods, concerns about appearance, and fears about developing visual handicap, local tumor recurrence and metastatic disease. This questioning often reveals problems that can be addressed in a straightforward manner, for example, by reassuring patients with a disomy 3/class 1 melanoma that they have an excellent survival probability, or reminding enucleated patients that their chances of developing local tumor recurrence are remote. Not infrequently, such questioning helps to identify patients who may benefit from referral to a psychologist. By enhancing awareness of the emotional difficulties that may develop and the risk factors for such problems, this study should help detect and predict psychological morbidity so that comprehensive biopsychosocial care can be provided more widely.

Psychological Support

Informal feedback from patients and from psychologists at the Liverpool Ocular Oncology Center suggests that protocols aimed at predicting, detecting and addressing psychological morbidity enhance patients' wellbeing. It is not only the health psychologist who can provide emotional support, but also other members of the ocular oncology team, particularly the specialist nurse and the ocular oncologist. This study demonstrates how patients' wellbeing is greatly enhanced by any support they receive from close relatives and friends, as has been found in other studies. It is helpful to include such individuals in any discussions, with the patient's permission (as opposed to leaving them in the waiting area during consultations). It is also important to give relatives and friends all possible encouragement, not only because of the assistance they are providing, but also because they may themselves be experiencing distress as a result of the patient's illness.[64]

CONCLUSIONS

This study gives an indication of the disease burden experienced by patients with uveal melanoma, according to the type of primary treatment. We found that many patients experience discomfort, visual difficulties, concerns about appearance and worries about their future health. A significant minority of patients experience considerable anxiety, depression and reduced wellbeing; however, these are usually the result of factors unrelated to the ocular disease (e.g., bereavement, poor general health).

The findings of this study should make it easier to select between radiotherapy and enucleation according to the likely impact of these treatment modalities on QoL, taking into account age, gender and social factors as well as tumor size and location. With the exception of some individuals with a large tumor, patients undergoing radiotherapy for uveal melanoma have a better QoL than those who undergo primary enucleation for this disease. To some extent, this is because enucleated patients tend to experience more visual difficulties, discomfort and concerns about appearance. There is a tendency to discharge patients after enucleation, with the advice to return should they ever develop socket or eyelid problems; however, this study indicates that there is scope for evaluating such patients regularly in order to address visual and psychological difficulties.

Negative influences unrelated to the ocular disease may precede the diagnosis of uveal melanoma, contributing to delays in presentation so that opportunities for conserving vision and the eye are missed. Poor QoL may therefore be both the result and the cause of enucleation. QoL tends to deteriorate over time, especially after enucleation. This is not only because age-related problems are more common in patients requiring enucleation but also because enucleation makes it more difficult to cope with such problems. Conversely, anxiety tends to be more common and severe in young patients, especially in women. All these findings indicate the importance of taking age, gender, social support, general health and other factors into account when selecting treatment for uveal melanoma and when predicting, detecting, and treating psychological morbidity.

This study provides a reminder that treatment of the ocular tumor constitutes only a small part of the comprehensive care that needs to be provided to patients and those who are close to them. Despite high-quality specialist ophthalmic treatment and extensive emotional support from ophthalmologists, specialists and nurses, many patients continue to experience considerable functional and psychological difficulties. There is scope for improvement and, therefore, a need for more research in this field.

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Time form treatment to first QoL questionnaire, according to type of treatment. This time interval was shorter in patients who underwent enucleation because these patients were discharged to their local hospital for long-term management (Table 1b).

Ocular comfort according to type of treatment. Grittiness (upper left), discharge (upper right) and watering (lower left) were more common after enucleation whereas headache (lower right) was more common after radiotherapy (Table 2).

Visual function according to type of treatment. Difficulty walking in crowds (upper left), activities limited by vision (upper right) and difficulty driving at night (lower left) were more common in enucleated patients whereas double vision on looking to side (lower right) was more common in patients who had received radiotherapy. The number of patients reporting on difficulty driving was small, suggesting that many had stopped driving because of their ocular condition. Some enucleated patients reported diplopia, either because they confused this symptom with astigmatism or poor vision or because they misunderstood the question (Table 2).

Stereoscopic visual function according to type of treatment. Difficulty pouring drinks (upper left), difficulty with steps (upper right), difficulty with stairs and uneven ground (lower left) and difficulty judging distance (lower right) were more common after enucleation with most patients reporting visual difficulties after this kind of treatment (Table 2).

Health concerns according to type of treatment. Concerns about appearance (upper left), risk of metastasis (upper right) and future health (lower left) were more common after enucleation whereas worry about the risk of local tumor recurrence (lower right) was more common after radiotherapy. Few patients had serious concerns about their appearance, even after enucleation. Some enucleated patients expressed unwarranted concerns about the possibility of local tumor recurrence, despite having received reassurance that this risk was small (Table 2).

Association of type of treatment with anxiety (upper left), depression (upper right), self-reported QoL (lower left) and total FACT-G score (lower right). Only FACT-G score showed a significant association, with irradiated patients having a better FACT-G score (Tables 4a & 4b).

Association between type of treatment and wellbeing. Patients who received radiotherapy showed better functional (upper right) and emotional (lower right) wellbeing than those who underwent enucleation whereas there was no difference in physical (upper left) and social wellbeing (lower left) (Table 5b).

TABLE 1a. IRRADIATED VS ENUCLEATED PATIENTS: CATEGORICAL VARIABLES

Variable	Number	Enucleation N (%)	Radiotherapy N (%)	Statistic
Sex				
Female	771	188 (42.5)	583 (50.5)	$\chi2$=8.16, *P*=.004
Male	825	254 (57.5)	571 (49.5)	
Tumor-affected Eye				
Left	790	228 (51.6)	562 (48.7)	$\chi2$=1.063, *P*=.303
Right	806	214 (48.4)	592 (51.3)	
Visual Acuity				
20/15-20/40	1106	171 (38.7)	935 (81)	$\chi2$=292.65, *P*<.001
20/60-20/200	322	148 (33.5)	174 (15.1)	
20/400-Count Fingers	92	56 (12.7)	36 (3.1)	
Hand Motions - No Light Perception	76	67 (15.2)	9 (.8)	
Anterior Tumor Margin				
Post-Equatorial Choroid	595	102 (23.1)	493 (42.8)	$\chi2$=101.25, *P*<.001
Pre-Equatorial Choroid	645	170 (38.6)	475 (41.2)	
Ciliary Body	271	120 (27.2)	151 (13.1)	
Anterior Chamber	83	49 (11.1)	34 (3)	
Posterior Tumor Margin				
Pre-Equatorial Uvea	200	41 (9.3)	159 (13.8)	$\chi2$=57.16, *P*<.001
Post-Equatorial Uvea	689	169 (38.2)	520 (45.1)	
1-2 Disc Diameters from Disc/Fovea	187	28 (6.3)	159 (13.8)	
<1 Disc Diameters from Disc/Fovea	309	70 (15.8)	239 (20.7)	
Involving Disc	211	134 (30.3)	77 (6.7)	
Coronal Tumor Location				
Nasal	582	225 (50.9)	357 (30.9)	$\chi2$=68.38, *P*<.001
Midline	318	92 (20.8)	226 (19.6)	
Temporal	696	125 (28.3)	571 (49.5)	
Sagittal Tumor Location				
Superior	572	143 (32.4)	114 (25.8)	$\chi2$=2.26, *P*=.133
Horizontal	386	114 (25.8)	272 (23.6)	
Inferior	638	185 (41.9)	453 (39.3)	
Extraocular Tumor Spread				
No	1520	379 (85.8)	1141 (98.9)	$\chi2$=121.4302, *P*<.001
Yes	76	63 (14.3)	13 (1.1)	
Epithelioid Cytomorphology				
No	371	165 (37.6)	206 (58.5)	$\chi2$=34.3876, *P*<.001
Yes	420	274 (62.4)	146 (41.5)	
Chromosome 3 Status				
Disomy 3	322	169 (43.4)	153 (59.8)	$\chi2$=16.4505, *P*<.001
Monosomy 3	323	220 (56.6)	103 (40.2)	

TABLE 1b. IRRADIATED VS ENUCLEATED PATIENTS: CONTINUOUS VARIABLES

Variable	Enucleation				Radiotherapy				Difference				Statistics
	N	Mn	Med	SD	N	Mn	Med	SD	Mn	SD	95% CI		
											Lower	Upper	
Age (Yrs)	442	.56	64.63	11.78	1154	60.99	61.54	13.04	3.33	.68	1.99	4.66	t(877.913)=4.898; *P*<.001
Basal Tumor Diameter (mm)	439	15.08	15.30	3.33	1150	10.99	10.80	2.99	4.08	.18	3.73	4.44	t(724.294)=22.481; *P*<.001
Tumor Thickness (mm)	440	7.74	7.90	3.46	1154	3.31	2.80	1.89	4.42	.18	4.07	4.79	Bias-Corrected Bootstrap
Follow-up (Months)	442	61.09	37.91	51.95	1154	76.61	60.04	60.56	-15.52	3.05	-21.50	-9.54	t(923.834)=-5.094; *P*<.001

Mn Mean, Med Median, SD Standard Deviation, SE Standard Error, CI Confidence Interval

TABLE 2. PREVALENCE AND SEVERITY OF ADVERSE PATIENT-REPORTED OUTCOMES ACCORDING TO PRIMARY TREATMENT

Variable	Enucleation				Radiotherapy				Statistic	OR	95% CI	
	N	Symptoms (%)	Mn	SD	N	Symptoms (%)	Mn	SD			Lower	Upper
Grittiness	426	17.4	1.75	.83	1136	12.0	1.61	.76	z=3.19, *P*=.001	1.41	1.14	1.74
Pain	422	11.1	1.56	.76	1126	10.3	1.56	.74	z=-.33, *P*=.742	.96	.77	1.20
Itching	423	14.4	1.69	.81	1127	10.2	1.55	.71	z=2.67, *P*=.008	1.34	1.08	1.66
Watering	421	15	1.74	.80	1131	8.5	1.44	.70	z=7.86, *P*<.001	2.39	1.92	2.97
Discharge	419	17	1.79	.84	1127	2.5	1.16	.46	z=16.88, *P*<.001	9.08	7.03	11.73
Dryness	422	9.7	1.47	.77	1131	13.3	1.54	.82	z=-1.49, *P*=.137	.84	.67	1.06
Headaches	422	7.8	1.37	.70	1133	10.5	1.48	.76	z=-2.79, *P*=.005	.71	.55	.90
Field defects	400	17.8	1.74	.91	1113	21.4	1.77	.96	z=-.04, *P*=.966	1.00	.80	1.23
Diplopia ahead	411	2.2	1.13	.42	1114	6.7	1.28	.65	z=-4.19, *P*<.001	.48	.34	.67
Diplopia to side	408	2.2	1.13	.39	1115	7.2	1.31	.67	z=-4.92, *P*<.001	.42	.29	.59
Interference with other eye	400	8.8	1.34	.74	1110	6.9	1.33	.69	z=-.62, *P*=.536	.92	.70	1.21
Driving during day	252	3.2	1.28	.56	793	3.4	1.24	.55	z=1.3, *P*=.194	1.25	.89	1.76
Driving at night	249	20.1	1.95	.88	789	16.6	1.74	.88	z=3.85, *P*<.001	1.67	1.29	2.17
Difficulty pouring	434	18.9	1.89	.84	1135	6.8	1.34	.67	z=13.75, *P*<.001	4.76	3.81	5.95
Difficulty in crowds	431	27.2	2.12	.88	1124	10.2	1.47	.77	z=14.45, *P*<.001	4.95	3.99	6.16
Difficulty with steps	433	28.9	2.15	.87	1131	13.5	1.62	.82	z=11.5, *P*<.001	3.43	2.78	4.23
Difficulty on uneven ground	433	28.9	2.16	.87	1133	14.9	1.66	.83	z=10.7, *P*<.001	3.12	2.53	3.84
Difficulty judging distance	428	33.6	2.25	.90	1129	14.6	1.64	.84	z=12.42, *P*<.001	3.81	3.08	4.70
Activities limited by vision	433	23.8	1.86	.96	1135	11.6	1.49	.82	z=8.08, *P*<.001	2.42	1.95	2.99
Difficulty reading	431	20.9	1.78	.97	1140	18.2	1.76	.93	z=.02, *P*=.986	1.00	.81	1.24
Worries about health	423	29.1	2.13	.91	1130	22.4	1.96	.88	z=3.36, *P*=.001	1.42	1.16	1.75
Worries about local recurrence	402	17.7	1.71	.96	1130	22.1	1.92	.93	z=-4.88, *P*<.001	.58	.46	.72
Worries about metastasis	417	36	2.31	1.00	1133	28.8	2.10	.99	z=3.84, *P*<.001	1.49	1.22	1.83
Worries about losing eye	359	37.1	2.21	1.16	1087	25.4	1.87	1.08	z=5.17, *P*<.001	1.78	1.43	2.22
Worries about appearance	436	8.7	1.47	.72	1136	3.1	1.20	.52	z=8.38, *P*<.001	2.90	2.26	3.73
Dissatisfied with cosmesis	431	8.6	1.34	.74	1090	3.3	1.13	.50	z=6.93, *P*<.001	3.06	2.23	4.19

Mn Mean, SD Standard Deviation, SE Standard Error, OR Odds Ratio, CI Confidence Interval. Data were obtained using the EORTC QLQ-OPT30 questionnaire. Patients were dichotomized as having the symptom 'not at all/a little' (i.e., 'minimal') or 'quite a bit/very much' (i.e., 'severe') during the previous week. The percentages indicate the prevalence of patients reporting severe symptoms according to the type of treatment with the *P* values indicating the significance of any differences between the two groups as measured with Pearson's $\chi 2$ test. The non-dichotomized scores were measured with ordered logistic regression to provide the Odds Ratio and hence an impression of the extent of any differences between the two groups. Figures 2-5 provide more information on the most important of these outcomes.

TABLE 3. QUALITY OF LIFE ACCORDING TO TYPE OF OCULAR TREATMENT: UNIVARIABLE ANALYSIS

Variable	Enucleation				Radiotherapy				Statistic	95% CI	
	N	Symptoms (%)	Mn	SD	N	Symptoms (%)	Mn	SD		Lower	Upper
Self-Reported Quality of Life	439	13.0	5.23	1.46	1146	10.7	5.30	1.40	z=-.81, *P*=.420	-.22	.10
Self-Reported Overall Health	440	13.2	5.15	1.38	1146	10.9	5.21	1.31	z=-.70, *P*=.486	-.19	.11
Physical Well Being	430	13.7	24.53	4.81	1133	9.8	25.13	3.86	z=-2.36, *P*=.018	-1.10	-.11
Functional Well Being	432	24.1	20.48	6.79	1134	16.8	21.64	6.18	z=-3.0, *P*=.003	-1.89	-.29
Social Well Being	422	11.9	22.73	5.93	1121	11.4	22.84	5.88	z=-.31, *P*=.755	-.79	.53
Emotional Well Being	430	27.4	18.9	4.70	1125	23.6	19.56	4.00	z=-2.51, *P*=.012	-1.14	-.16
FACT-G	412	17.2	86.74	16.64	1100	11.8	89.46	14.96	z=.76, *P*=.447	-.12	.23
Anxiety	414	13.3	5.21	4.37	1109	9.9	4.92	4.08	z=1.17, *P*=.243	-.18	.81
Depression	415	7.5	4.07	3.83	1115	5.7	3.47	3.69	z=2.68, *P*=.007	.09	1.00

Mn Mean, CI Confidence interval. The percentages indicate the prevalence of significant symptoms in enucleated and irradiated patients respectively (i.e., the percentages of patients with poor quality of life, poor self-reported general health, reduced wellbeing, anxiety or depression, as defined in the Methods section). These were measured with the modified EORTC QLQ-OPT30, FACT-G and HAD. The mean difference between these two types of treatment was estimated using the t-test with unequal variance, using the nonparametric bootstrap (with 1000 replications) and was significant if the 95% bias-corrected CI did not include zero. The negative FACT-G values indicate poorer physical, functional and emotional wellbeing after enucleation whereas the positive HAD values indicate more depression after enucleation.

TABLE 4. QUALITY OF LIFE ACCORDING TO OCULAR FEATURES: MULTIVARIABLE ANALYSIS

	Obs. Coeff.	Bias	SE	*P* VALUE	95% CI	
					Lower	Upper
Anxiety						
Treatment	.08	.01	.36	.810	-.61	.79
Monosomy 3 Melanoma	.75	-.01	.36	.039	.01	1.45
Depression						
Treatment	-.53	.02	.35	.127	-1.22	.10
Self-Reported QoL						
Treatment	.04	-.00	.12	.715	-.20	.26
Physical Well Being						
Treatment	.11	-.01	.38	.784	-.67	.82
Functional Well Being						
Treatment	1.18	.01	.55	.030	.09	2.21
Emotional Well Being						
Treatment	-.02	.01	.40	.954	-.73	.76
Monosomy 3 Melanoma	-.86	.01	.37	.019	-1.54	-.10
Social Well Being						
Treatment	.50	.01	.47	.293	-.43	1.41
FACT-G						
Treatment	2.31	-.07	1.39	.096	-.53	4.85

SE Standard Error, CI Confidence interval. Multivariable linear regression was performed with nonparametric bootstrap (with 1000 replications) to estimate the Observed Coefficient, which indicated a significant influence if the 95% bias-corrected CI did not include zero. The model included treatment, pre-treatment visual acuity, eye laterality, TNM size category, melanoma cytomorphology and cytogenetic tumor type. In this table, monosomy 3 melanoma was significantly associated with greater anxiety and worse emotional wellbeing whereas radiotherapy was associated with better functional wellbeing,

TABLE 5a. ANXIETY, DEPRESSION AND SELF-REPORTED QUALITY OF LIFE ACCORDING TO SOCIAL FACTORS

	Obs. Coeff.	Bias	SE	*P* Value	95% CI	
					Lower	Upper
Anxiety						
Treatment	-.30	.01	.22	.184	-.73	.13
Age at treatment	-.07	-.00	.01	<.001	-.09	-.06
Male gender	-1.30	.01	.19	<.001	-1.68	-.95
Follow-up	-.01	-.00	.00	<.001	-.01	-.01
Self-reported gen. health	-1.30	.00	.09	<.001	-1.48	-1.13
Social support	-.36	.00	.07	<.001	-.51	-.22
Depression						
Treatment	-.29	-.00	.17	.085	-.61	.04
Employment status	.81	-.00	.17	<.001	.46	1.13
Social support	-.51	-.00	.07	<.001	-.63	-.37
Self-reported gen. health	-1.42	-.00	.08	<.001	-1.58	-1.27
Self-Reported QoL						
Treatment	.04	-.00	.05	.411	-.05	.13
Social support	.06	.00	.02	<.001	.03	.09
Employment status	-.17	-.00	.04	<.001	-.24	-.08
Self-reported gen. health	.83	.00	.02	<.001	.79	.86

SE Standard Error; CI Confidence Interval. Multivariable linear regression measuring the influence of social factors on anxiety, depression and self-reported QoL was performed with nonparametric bootstrap (with 1000 replications) to estimate the Observed Coefficient, which indicated a significant influence if the 95% bias-corrected CI did not include zero. The model included type of treatment, age at primary treatment, gender, time between treatment and completion of questionnaire, self-reported general health, marital status, employment status and social support.

TABLE 5b. PHYSICAL, FUNCTIONAL, EMOTIONAL AND SOCIAL WELLBEING AND FACT-G SCORE ACCORDING TO SOCIAL FACTORS

	Obs. Coeff	Bias	SE	*P* Value	95% CI	
					Lower	Upper
Physical Wellbeing						
Treatment	.37	.00	.20	.063	-.02	.77
Age at treatment	.05	.00	.01	<.001	.03	.07
Employment status	-1.01	.00	.23	<.001	-1.48	-.55
Follow-up	.01	-.00	.00	<.001	.00	.01
Self-reported gen. health	1.80	.00	.10	<.001	1.59	1.99
Social support	.17	.00	.08	.035	.02	.32
Functional Wellbeing						
Treatment	.61	-.01	.29	.037	.05	1.21
Social support	.72	.00	.09	<.001	.56	.91
Employment status	-2.01	.01	.24	<.001	-2.51	-1.54
Follow-up	.01	.00	.00	<.001	.01	.01
Self-reported gen. health	2.51	.00	.11	<.001	2.28	2.75
Marital status	-.29	-.00	.14	.037	-.56	--.02
Emotional Wellbeing						
Treatment	.44	.00	.22	.051	.00	.90
Age at treatment	.06	.00	.01	<.001	.04	.08
Gender	1.08	.00	.20	<.001	74	1.50
Follow-up	.01	.00	.00	<.001	.01	.02
Self-reported gen. health	1.12	.00	.09	<.001	.95	1.30
Social support	.31	-.00	.08	<.001	.14	.45
Employment status	-.72	.00	.24	.002	-1.20	-.26
Social Wellbeing						
Treatment	.29	.00	.30	.334	-.30	.82
Social support	1.91	.00	.10	<.001	1.71	2.08
Self-reported gen. health	.49	-.00	.11	<.001	.28	.70
FACTG						
Treatment	1.71	.02	.72	.018	.37	3.24
Age at treatment	.09	-.00	.03	.004	.03	.16
Male gender	1.60	.00	.61	.009	.42	2.78
Follow-up	.03	.00	.00	<.001	.17	.04
Self-reported gen. health	5.86	.01	.28	<.001	5.31	6.41
Social support	3.12	-.01	.26	<.001	2.68	3.68
Employment status	-3.75	.01	.76	<.001	-5.21	-2.33

SE Standard Error; CI Confidence Interval. Multivariable linear regression measuring the impact of social factors on wellbeing was performed with nonparametric bootstrap (with 1000 replications) to estimate the Observed Coefficient, which indicated a significant influence if the 95% bias-corrected CI did not include zero. The model included type of treatment, age at primary treatment, gender, time between treatment and completion of

questionnaire, self-reported general health, marital status, employment status and social support. Radiotherapy was significantly associated with higher functional and emotional wellbeing and with a better FACT-G score.

TABLE 6. COMPARISON OF WELLBEING AND OVERALL FACT-G WITH ADULT GENERAL AND CANCER POPULATIONS IN THE US

Variable	Enucleation		Radiotherapy		Gen. Adult Pop.		Cancer Pop.	
	N	Mean	N	Mean	Mean+SD/2	Mean-SD/2	Mean+SD/2	Mean-SD/2
Physical Well Being	430	**24.53**	1133	**25.13**	25.4	20.0	**24.3**	18.3
Functional Well Being	432	20.48	1134	21.64	21.9	15.1	22.3	15.5
Social Well Being	422	**22.73**	1121	**22.84**	**22.5**	15.7	24.75	19.45
Emotional Well Being	430	**17.34**	1125	17.75	22.3	**17.5**	20.95	16.45
FACT-G	412	86.74	1100	**89.46**	89.15	71.1	**89.4**	72.4

SD Standard Deviation. Significant differences are printed in bold.

Time from Treatment to Questionnaire