Impact of enucleation versus plaque radiotherapy in the management of juxtapapillary choroidal melanoma on patient survival

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Abstract

The records of 265 consecutive patients with juxtapapillary choroidal melanoma were reviewed and a statistical non-randomised retrospective study was performed to evaluate the risk for metastasis and compare the survival rate of patients treated with plaque radiotherapy or enucleation. To obtain sufficient overlap between the enucleation and plaque radiotherapy, the statistical analysis was limited to an adjusted subgroup of 127 patients who met eligibility criteria for plaque radiotherapy and who had a minimum of 3 years of follow up after treatment. In the adjusted subgroup of 127 patients, 92 patients (72%) were initially treated with enucleation and 35 (28%) with plaque radiotherapy. In both univariate and multivariate logistic analysis models, the age of the patient (>50 years), tumour thickness (>3 mm), and treatment by age interaction were found to be significant factors for development of distant metastasis. In patients younger than 50 years, the method of treatment (enucleation versus plaque radiotherapy) did not significantly affect the risk of metastasis. For those older than 50 years, there was a non-significant trend for patients in the enucleation group to be at a higher risk for metastasis than those in the plaque group. In the enucleation group, patients older than 50 years had a significantly higher incidence of distant metastasis than those younger than 50 years. In the plaque radiotherapy group, there was no significant higher incidence of metastasis in patients younger than 50 years than in those older than 50 years. When a Cox proportional hazards model was used to evaluate the survival rate, there was the same statistically significant effect of treatment by age interaction as was found in the multivariate logistic model on survival time. Moreover, there was a significant effect of treatment by tumour thickness interaction on survival time. Patients in the enucleation group had a better survival rate when the thickness of the tumour was less than 3 mm compared with a tumour of more than 3 mm. There were no apparent effects of tumour thickness on survival for patients treated with plaque radiotherapy. From these results, the authors currently recommend plaque radiotherapy as a viable option to enucleation in patients with juxtapapillary choroidal melanoma.

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enucleation, radiotherapy, local tumour resection, or photocoagulation.¹⁻⁶ Although the trend away from enucleation and the increasing use of radiotherapy is recognised for management of choroidal melanoma,¹ little information is available regarding the role of plaque radiotherapy for melanomas that are located adjacent to the optic disc (juxtapapillary choroidal melanoma). Moreover, the risk factors for metastasis and the survival rate of patients with juxtapapillary choroidal melanoma treated with enucleation have never been compared with those of a properly matched group of patients treated with plaque radiotherapy.

To assess the risk factors for metastasis and evaluate the prognosis of patients with juxtapapillary choroidal melanoma, we performed a non-randomised retrospective study as defined by Mausner and Bahn⁷ and covariable adjustment using logistic regression⁸ and Cox proportional hazards analysis.⁹ The visual outcome and clinical course of patients managed with plaque radiotherapy was not analysed in this series and will be evaluated in another study.

Patients and methods

PATIENTS

We reviewed the records of all patients with choroidal melanoma who were evaluated and managed in the Oncology Service at Wills Eye Hospital between April 1972 and June 1991. This review of 3706 patients with choroidal melanoma revealed that 265 (7%) of these tumours were immediately adjacent to the optic disc. Those 265 tumours were classified as juxtapapillary choroidal melanoma and were the subjects of this study.

Our methods of clinical examination, diagnosis, and treatment have been described previously.¹ The patients were not randomised to one or another treatment but were managed selectively on the basis of clinical factors including visual status of involved eye and the fellow eye, tumour size, degree of tumour surrounding the optic disc, clinical signs of optic disc invasion (that is, optic disc oedema, congestion of retinal vessels), extent of retinal detachment, presence of vitreous haemorrhage, age and general health of the patient, and patient preference for a particular treatment. Patients with preoperative or intraoperative demonstrable extraocular extension of their juxtapapillary melanoma, with less than 6 months of follow up or without available follow up were excluded from this study.

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The treatment of choroidal melanoma includes

DATA COLLECTION

The clinical variables were recorded for each patient at the time of examination in the Oncology Service just before initial treatment. They included:

- (1) Age (years)
- (2) Sex (male or female)
- (3) Symptoms: symptoms due to the tumour (asymptomatic or symptomatic)
- (4) Visual status: best corrected Snellen visual acuity
- (5) Tumour data: size of the tumour, including maximal and minimal basal diameters (estimated in millimetres from ophthalmoscopic examination, fundus drawings, ultrasonographic measurements, and fundus photographs), thickness (estimated in mm from A and B scan ultrasonographic measurements); shape of the tumour defined by the B scan ultrasonographic features; colour of tumour (described as non-pigmented, minimally pigmented, or pigmented); and location of tumour described the degree of the optic disc surrounded by the tumour (0–180°, 181°–360°, non-assessable due to the overhanging of the tumour hiding the optic nerve head).
- (6) Associated ocular features: visualisation of the optic nerve head described as the percentage of optic disc overhung by tumour (100%, 99–50%, 49–0%); retinal detachment (present or absent); retinal haemorrhage (present or absent).
- (7) Treatment: method of treatment (enucleation, cobalt-60, ruthenium-106, iodine-125 or iridium-192 plaque radiotherapy, and argon laser photocoagulation). The date of treatment constituted the start of the study.
- (8) Metastasis: development of distant metastasis (present or absent) evaluated by systemic evaluation, liver functions tests, chest radiography, liver computed tomographs, or ultrasonography). The survival status of each patient was determined by follow up examination in the Oncology Service, data from referring ophthalmologists; family physicians, internists or oncologists who saw regularly in follow up the patients unable to return to Wills Eye Hospital. Occasionally, telephone interviews with the patient or family members were also used. The date of death constituted the end of the study.

METHODS OF ANALYSIS

Univariate analyses were performed on all clinical variables in Table 2 to detect the significant different variables between the enucleation and plaque radiotherapy groups.¹⁰ Univariate logistic regression was performed to assess the relation between each individual clinical variable in Table 2 and the development of metastasis.⁸ Multivariate logistic regression was then performed to determine the effect of treatment after adjusting for (1) variables which were significantly different between the enucleation and plaque radiotherapy groups, and (2) variables which were significantly related to the development of metastasis.⁸

The univariate Cox proportional hazard model was used to determine the variables that were significantly related to survival time (death from all causes).⁹ A multivariate Cox proportional

hazard model was then fitted to evaluate the effect of treatment on survival adjusting for (1) variables that differed significantly between the enucleation and plaque radiotherapy groups, and (2) variables that were significantly related to survival time.⁹ All tests were two tailed.

Results

A total of 265 patients corresponding to the criteria described above were diagnosed clinically with juxtapapillary choroidal melanoma. All of the patients were white. Of the 265 juxtapapillary choroidal melanomas, 129 (49%) involved the right eye and 136 (51%) the left eye. Among the 265 patients with juxtapapillary choroidal melanoma, 180 patients (68%) were treated with enucleation, 73 (28%) with plaque radiotherapy, and 12 (4%) with argon laser photocoagulation. Of the 73 patients managed by brachytherapy, 41 (57%) were treated with an iodine-125 plaque, 17 (23%) with an iridium-192 plaque, 11 (15%) with a cobalt-60 plaque, and four (5%) with ruthenium-106. The mean follow up post-treatment was 6.2 years (medium, 5.8 years, range 0.5 to 19.1 years).

None of our patients had recognisable metastatic disease at the time of initial treatment. Of the 265 patients, 50 (19%) had developed distant metastasis after a mean interval post treatment of 35 months (range 1 to 79 months). Sixty two patients (23%) died during the total mean follow up period of 6.2 years. Forty six (17%) died from metastatic melanoma and 16 (6%) died from unrelated causes. Eleven patients died from myocardial infarction, three from stroke, one from pneumonia, and one in a car accident. The mean interval between the diagnosis of metastatic melanoma and death was 10 months (range 0.5 to 31 months).

COMPARISON OF TREATMENT GROUPS

Because of the small number of patients with juxtapapillary choroidal melanoma treated with photocoagulation we elected to exclude this group of patients from our statistical study. Clinical variables regarding the two groups of treatment (enucleation versus plaque radiotherapy) are presented in Table 1.

Comparison of the enucleation group (180 patients) and the plaque radiotherapy group (73 patients) by univariate analysis shows that patients selected for enucleation tended to be younger and male, to have more overall symptoms and a worse visual acuity before treatment, a larger and thicker tumour, more extensive retinal detachment, and a tumour with a greater amount surrounding the optic nerve head and less visualisation of the optic disc due to the extent of the juxtapapillary tumour.

IDENTIFICATION OF THE ADJUSTED TREATMENT GROUPS

Inspection of Table 1 reveals that some clinical variables overlapped incompletely in range of values of the variable between the treatment groups. The following clinical variables were present in the enucleation group but were absent

Table 1 Distribution of clinical variables by treatment groups in 253 patients with juxtapapillary choroidal melanoma

Clinical variables	Treatment groups		Test statistics	p Value
	Enucleation (n=180)	Plaque (n=73)		
Age (years):				
≤40	30	8		
>40 to ≤50	24	8		
>50 to ≤60	44	15		
>60 to ≤70	60	24		
>70	22	21		
Mean age	55	61	t Test	0.01
Sex:				
Male	108	33		
Female	72	40	Fisher's exact test	0.004
Symptoms:				
Asymptomatic	21	19		
Symptomatic	159	54	Fisher's exact test	0.007
Visual acuity:				
≤20/40	55	45		
20/50 to 20/100	49	17		
≥20/200 to HM	58	11		
LP to NLP	18	0	Ordered χ^2	0.0001
Maximal basal diameter (mm):				
≤6	18	10		
>6 to ≤10	59	37		
>10 to ≤14	52	26		
>14	51	0	Ordered χ^2	0.0001
Minimal basal diameter (mm):				
≤6	35	21		
>6 to ≤10	75	41		
>10 to ≤14	49	11		
>14	21	0	Ordered χ^2	0.0004
Thickness (mm):				
≤3	38	25		
>3 to ≤6	76	42		
>6	66	6	Ordered χ^2	0.0001
Cross sectional shape:				
Ovoid	122	60		
Mushroom	58	13	Fisher's exact test	0.02
Colour of tumour:				
Amelanotic	28	12		
Minimally pigmented	12	5		
Pigmented	140	56	χ^2	1.0
Degree of optic disc circumferential:				
≤180°	80	60		
>181° to ≤360°	44	9		
No view (overhanging)	45	4		
No view of fundus	11	0	Ordered χ^2	0.0001
Optic disc visualisation:				
100%	64	53		
99% to ≥50%	33	13		
<49% to 0%	61	7		
Optic disc invasion	11	0		
No view of fundus	11	0	Ordered χ^2	0.0001
Retinal detachment:				
No	20	17		
Surrounding	152	56		
Total bullous	8	0	Fisher's exact test	0.003
Retinal haemorrhage:				
No	149	67		
Yes	31	6	Fisher's exact test	0.08
Distant metastasis:				
No	137	67		
Yes	43	6	Fisher's exact test	0.005

HM=hand movements; LP=light perception; NLP=no light perception.

in the plaque radiotherapy group. These clinical variables were considered as ineligible for plaque radiotherapy and included: visual acuity less than hand motion; tumour basal diameter greater than 14 mm; total retinal detachment; no view of the fundus due to cataract or total vitreous haemorrhage; and clinical optic nerve invasion suspected when there was optic disc oedema and congestion of retinal vessels. To ensure that there was sufficient overlap of the clinical variables in the enucleation versus the plaque radiotherapy groups, we limited our statistical analysis to an adjusted group of patients in which the patients with the above clinical variables were eliminated from the enucleation group. This made the comparison between the enucleation and the plaque radiotherapy groups more reliable. After these exclusions, we were left with an adjusted group of 189 patients. Of those 189 patients, 116 (61%)

were treated with enucleation and 73 (39%) with plaque radiotherapy.

In addition, to ensure an adequate survey, we limited our logistic regression analysis to patients with a minimum of 3 years of follow up after treatment. Therefore, we were left with an adjusted subgroup of 127 patients. Of these 127 patients with juxtapapillary choroidal melanoma, 92 (72%) were treated with enucleation and 35 (28%) with plaque radiotherapy. Table 2 summarises the distribution of clinical variables by adjusted treatment groups in 127 patients with juxtapapillary choroidal melanoma.

The median follow up after treatment in the subgroup of 127 patients was 6.8 years (range 3 to 16 years). The median follow up post treatment in the adjusted enucleation group was 7.2 years (range 3 to 16 years) and in the adjusted plaque radiotherapy group was 6.3 years (range 3 to 11 years). Of this adjusted subgroup of 127 patients with a follow up of at least 3 years, 26 (20%) had developed distant metastasis. None of the patients from the original adjusted group of 189 patients who were excluded because of follow up of less than 3 years developed metastasis.

Among the 26 patients who developed distant metastasis, 20 (77%) were treated initially with enucleation and six (23%) with plaque radiotherapy. Of these 127 patients, 31 (24%) died from all causes during the mean follow up of 6.8 years. Twenty four (19%) died from metastatic melanoma and seven (5%) died from unrelated causes. Five patients died from myocardial infarction and two from stroke.

Among the 35 patients treated with plaque radiotherapy, seven patients (20%) developed local recurrence which was treated with enucleation in three cases, repeated plaque radiotherapy in three cases, and laser photocoagulation in one case. Among these seven patients, three (43%) developed distant metastasis. Of the 28 patients (80%) who did not develop local recurrence, three (11%) developed metastasis. Patients treated initially with plaque radiotherapy and who developed local recurrence showed a non-significantly higher risk of distant metastasis than those who did not develop local recurrence ($p=0.08$, Fisher's exact test).

COMPARISON OF THE ADJUSTED TREATMENT GROUPS

Comparison of clinical variables of the two adjusted matched treatment groups of 127 patients (92 patients treated with enucleation and 35 patients treated with plaque radiotherapy) are presented in Table 2. The significant variables different between the enucleation and plaque radiotherapy group that were identified by the univariate analysis included age ($p=0.05$), sex ($p=0.03$), visual acuity ($p=0.007$), degree of circumference around the optic disc ($p=0.003$), and percentage of visualisation of the optic nerve head ($p=0.002$). This table showed that patients selected for enucleation tended to be younger and male, to have worse pretreatment visual acuity, to have

Table 2 Distribution of clinical variables by adjusted treatment groups in 127 patients with juxtapapillary choroidal melanoma

Clinical variables	Adjusted treatment groups		Test statistics	p Value
	Enucleation (n=92)	Plaque (n=35)		
Age (years):				
≤40	15	5		
>40 to ≤50	17	1		
>50 to ≤60	19	5		
>60 to ≤70	29	16		
>70	12	8		
Mean age	55	61	t Test	0.05
Sex:				
Male	53	12		
Female	39	23	Fisher's exact test	0.03
Symptoms:				
Asymptomatic	15	9		
Symptomatic	77	26	Fisher's exact test	0.3
Visual acuity:				
≤20/40	33	24		
20/50 to 20/100	27	7		
≥20/200	32	4	Ordered χ^2	0.007
Maximal basal diameter (mm):				
≤6	10	3		
>6 to ≤10	40	18		
>10 to ≤14	42	14	Ordered χ^2	0.7
Minimal basal diameter (mm):				
≤6	22	8		
>6 to ≤10	53	22		
>10 to ≤14	17	5	Ordered χ^2	0.8
Thickness (mm):				
≤3	25	8		
>3 to ≤6	39	25		
>6	28	2	Ordered χ^2	0.2
Cross sectional shape:				
Ovoid	60	28		
Mushroom	32	7	Fisher's exact test	0.1
Colour of tumour:				
Amelanotic	14	4		
Minimally pigmented	6	1		
Pigmented	72	30	χ^2	1.0
Degree of optic disc circumferential:				
≤180°	50	29		
>181° to ≤360°	18	3		
No view (overhanging)	24	3	Ordered χ^2	0.003
Optic disc visualisation:				
100%	43	25		
99% to ≥50%	19	4		
<49% to 0%	30	6	Ordered χ^2	0.02
Retinal detachment:				
No	13	8		
Yes	79	27	Fisher's exact test	0.6
Retinal haemorrhage:				
No	80	8		
Yes	12	27	Fisher's exact test	1.0
Distant metastasis:				
No	72	29		
Yes	20	6	Fisher's exact test	0.6

a tumour with a larger amount surrounding and overhanging the optic nerve head.

With the presence or absence of metastasis as a dependent variable, univariate logistic regression was performed on each clinical variable to assess its individual effect on the development of metastasis. In our univariate logistic analysis model, variables with a p value ≤0.25 were

suggestive in predicting metastasis and were subsequently included in the multivariate logistic model.⁸ Variables that were predictors of metastasis included age of patient [>50 years] (p=0.22) and tumour thickness [>3 mm] (p=0.04).

In order to assess the effect of treatment (enucleation versus plaque radiotherapy) while adjusting for other variables from the univariate analysis, a multivariate logistic regression was performed.

Firstly, the effect of treatment was tested when controlling for age of the patient and tumour thickness which were predictive of development of metastasis on a univariate level. Results of the first step multivariate logistic model (Table 3) showed that age of patient [>50 years old] (p=0.05), tumour thickness [>3 mm] (p=0.04), and the treatment by age interaction (p=0.03) were significant factors in the prediction of development of metastasis. The main effect of treatment just missed statistical significance, and was modified by the significant treatment by age interaction. In patients ≤50 years old, the method of treatment (enucleation versus plaque radiotherapy) did not significantly affect the risk of metastasis (p=0.14). For patients >50 years old, there was a non-significant trend (p=0.08) for patients in the enucleation group to be at a higher risk for metastasis than patients in the plaque group. However, in the enucleation group, those patients older than 50 years had a significantly higher incidence of distant metastasis than patients younger than 50 years (p=0.05). In the plaque radiotherapy group, there was no significant difference in incidence of metastasis in patients >50 years old compared with patients <50 years old (p=0.18) (Fig 1).

Secondly, the effect of treatment was tested while controlling for all variables that: (1) showed significant differences between the enucleation and plaque radiotherapy groups (univariate analysis); and (2) were related to the development of metastasis on a univariate level. The age of the patient [>50 years] (p=0.05), tumour thickness [>5 mm] (p=0.009), treatment [enucleation] (p=0.03), and treatment by age interaction (p=0.04) were significantly predictive of development of metastasis (Table 3). No other variables were significantly predictive of metastasis.

Cox proportional hazards regression was used

Table 3 Risk factors assessment on development of metastasis for the adjusted subgroup of 127 patients with juxtapapillary choroidal melanoma

Clinical variables	Analysis models			
	Multivariate logistic regression (1st step)* (n=127)	Multivariate logistic regression (2nd step)† (n=127)	Multivariate Cox model (1st step)* (n=189)	Multivariate Cox model (2nd step)† (n=189)
Age	0.05	0.05	0.002	0.0004
Thickness	0.04	0.009	0.2	0.05
Treatment	0.06	0.3	0.02	0.006
Sex	—	0.26	—	0.73
Visual acuity	—	0.98; 0.36‡	—	0.91; 0.09‡
Degree of optic disc surrounding	—	0.21; 0.65‡	—	0.47; 0.58‡
Percentage of optic disc visualisation	—	0.22; 0.21‡	—	0.58; 0.73‡
Treatment by thickness	0.25	0.1	0.05	0.02
Treatment by age	0.03	0.04	0.09	0.03

*The first step indicates the evaluation of the effect of treatment when controlling clinical variables that were predictive of development of metastasis on a univariate level.

†The second step indicates the evaluation of the effect of treatment when controlling all clinical variables.

‡Two p values given for the two design variables used for ordinal categories with three levels.

Figure 1 Proportion of metastasis versus mean age for the adjusted group of 127 patients with juxtapapillary choroidal melanoma. Age was grouped into four quantile groups and logit transformation was used for proportion of metastasis. Differences between the two respective curves were not statistically significant ($p>0.05$) for both end points. (Enucleation group = □; plaque radiotherapy group = ■.)

to measure the effect of treatment (enucleation versus plaque radiotherapy) on length of survival from treatment to death from all causes. The 62 patients not used in the logistic regression analysis because of a follow up <3 years were included in the survival analysis. There was no difference in the number of deaths from all causes in the adjusted group of 189 patients compared with the adjusted subgroup of 127 patients who had at least 3 years' follow up post treatment. Variables with a p value <0.25 in the univariate analysis were included in the subsequent multivariate Cox regression model. Variables which were predictive of survival on a univariate level included age of patient [>50 years] ($p=0.09$) and tumour thickness [>3 mm] ($p=0.16$).

In order to look at whether treatment influenced survival when adjusting for all predictive factors, a multivariate Cox regression was performed using variables which were related to survival on a univariate level. Results in Table 3 indicated that factors which influence survival were age of patient [>50 years] ($p=0.002$), treatment [enucleation] ($p=0.02$), and treatment by tumour thickness interaction ($p=0.05$). Treatment by age interaction showed a non-significant trend ($p=0.09$). Note that development of metastasis was highly predictive of survival ($p=0.001$) but was not included in any multivariate model.

A second analysis included factors which reflected pre-existing differences between groups (sex, pretreatment visual acuity, degree of surrounding the optic disc, percentage of visualisation of optic disc). Results showed that the following factors were significantly related to survival (Table 3). They included age of patient [>50 years] ($p=0.0004$), tumour thickness [>3 mm] ($p=0.05$), treatment [enucleation] ($p=0.006$), treatment by age interaction ($p=0.03$), and treatment by tumour thickness interaction ($p=0.02$).

Subsequent post hoc analyses investigating the nature of the treatment by age interaction indicated that for the enucleation group, there was a significant decrease in survival time for patients older than 50 years compared with those younger than 50 years ($p=0.03$). No such analogous effect was found for the patients in the plaque radiotherapy group. Post hoc analyses also indicated that for patients in the enucleation group, survival was increased for tumours less

than 3 mm compared with tumours larger than 3 mm ($p=0.03$). Again, no such analogous effect was found in the plaque radiotherapy group. However, these results should be interpreted with caution, as a small number of deaths was used in these survival curves (enucleation, 25 deaths; plaque radiotherapy, six deaths). The similar statistical effects of treatment by age interaction and thickness interaction were found in the adjusted subgroup of 127 patients.

Discussion

Posterior uveal melanoma is an uncommon tumour. It is generally accepted that the annual incidence estimate for uveal melanoma in the United States is six cases per million population.¹¹ The incidence of posterior uveal malignant melanoma has been estimated at approximately 1500 new cases per year.¹² In our study among 3706 patients with uveal malignant melanoma, 265 (7%) were juxtapapillary choroidal melanoma.

Although enucleation has been the main treatment for posterior uveal melanoma, this treatment has become controversial.¹³ Consequently, other therapeutic options have been used more frequently in recent years.¹⁻⁶ Radiotherapy has become more widely accepted in the management of posterior uveal melanoma.¹ Juxtapapillary choroidal melanoma poses an especially challenging situation for treatment since most of these tumours are small in size and one would like to avoid enucleation if possible. A common misconception for a long time was that radiotherapy could not be used for choroidal melanoma touching the optic disc. On the contrary, specially designed notched plaques have been effectively employed to surround the optic nerve and irradiate the tumour in that location.¹⁴ We have employed such plaques for almost 15 years.¹

Few articles written about radiotherapy provide statistical information about the survival rate of treated patients and survival data for a comparable group of patients treated with enucleation. An observational study of 237 patients with posterior uveal melanoma treated with enucleation versus cobalt plaque radiotherapy demonstrated that the adjusted risk of death from metastatic melanoma following enucleation was not significantly different from the risk of death following plaque radiotherapy.¹⁵ Seddon and associates reported from a Cox model adjusted analysis that patients treated with proton beam irradiation experienced a higher adjusted survival rate than patients treated with enucleation.¹⁶

Our non-randomised study identified clinical variables best predictive of development of metastasis and analysed the relative effectiveness of plaque radiotherapy versus enucleation on survival rate in patients with juxtapapillary choroidal melanoma. Logistic regression analysis showed that the clinical risk factors for metastasis are the age of patient (>50 years) and tumour thickness (>3 mm). On a multivariate level, the effect of treatment modality on development of metastasis was significantly modified by its interaction with age. For

example, in the enucleation group, patients older than 50 years had a significantly higher incidence of distant metastasis than patients younger than 50 years. In the plaque radiotherapy group, there was no higher incidence of metastasis in patients older than 50 years than in patients younger than 50 years.

Multivariate Cox modelling showed that age of patient (>50 years), tumour thickness (>3 mm), treatment (enucleation), treatment by age interaction, and treatment by thickness interaction were the most significant risk factors for death. In fact, the main effect of treatment was modified by its interaction with age and thickness. Specifically, in the plaque radiotherapy group, there was no effect on survival in patients younger than 50 years compared with patients older than 50 years. In the enucleation group, there was significantly better survival for patients younger than 50 years compared with patients older than 50 years. Patients in the enucleation group had also a better survival when the thickness of the tumour is smaller than 3 mm compared with tumour with a thickness greater than 3 mm. In the plaque radiotherapy group there was no apparent effect of tumour thickness on survival.

Although our study does not represent a randomised clinical trial, three features support the validity of our observations. Firstly, there was a follow up period of 3 years in the adjusted treatment subgroups of patients was exceptionally complete for a study of this type. Patients with less than 3 years of follow up were excluded from the study for the logistic regression analysis. Furthermore, there were no patients who developed metastasis in the group that had less than 3 years of follow up. Secondly, the clinical variables were assessed by the same examiners using objective examination techniques in all patients. Thirdly, the statistical technique of logistic regression and Cox modelling was used to adjust for differences in the composition of the groups being compared.

This study also has several identifiable limitations. Firstly, despite the fact that this statistical analysis was limited to patients with at least 3 years of follow up, the follow up time is still relatively short for a study of uveal melanoma. Secondly, the results of multivariate Cox proportional hazards regression model should be interpreted with caution as a fairly small number of deaths were used in these survival curves. Thirdly, our analysis did not include the histopathological variables in the two groups, since there is no histopathology on tumours treated by plaque radiotherapy. The distribution of cell type, mitotic activity, and other histopathological parameters in the enucleated group could possibly have differed from the distribution of these histological variables among tumours in the plaque radiotherapy group.

We are not concluding that enucleation as management of juxtapapillary choroidal melanoma poses a greater risk of metastatic death than plaque radiotherapy. What the results indicate are older patients (>50 years old) treated with enucleation to have a risk of significantly

worse survival than younger patients (<50 years old). The absence of any effect of age for the plaque radiotherapy group may be due to the smaller number of patients in this group.

We realise that some patients with juxtapapillary choroidal melanoma treated with plaque radiotherapy will eventually lose their useful vision and some will eventually require enucleation as a result of radiation complications or tumour recurrence. However, there is no doubt that the visual outcome of those patients treated with plaque radiotherapy is better than that of patients treated by enucleation. We also found that the incidence of local tumour recurrence in juxtapapillary choroidal melanoma treated with plaque radiotherapy does not appear to significantly affect the incidence of metastasis. Furthermore from our study, because enucleation as treatment for patients with juxtapapillary choroidal melanoma older than 50 years carries a higher risk of metastasis, the benefits of an eye preserving therapy is legitimate. We currently recommend plaque radiotherapy as a viable option to enucleation in many patients with juxtapapillary choroidal melanoma. However, it remains for a randomised clinical trial to ascertain more definitely whether the risk of metastasis is similar for enucleation versus plaque radiotherapy.

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