Risk factors for metastatic uveal melanoma after trans-scleral local resection

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Abstract

Aims—This study reports the metastatic death rate after trans-scleral local resection of uveal melanoma and identifies relevant risk factors.

Methods—Local resection was performed in 332 patients (mean age 51 years), with follow up ranging to 20.9 years (median for living patients 33 months). The tumours had a mean largest basal diameter of 13.1 mm and mean thickness of 7.5 mm, with 135 containing epithelioid cells. Risk factors were identified by Cox analysis and metastatic rates demonstrated using Kaplan-Meier curves.

Results—There were 52 deaths from metastatic melanoma. The significant risk factors were (i) age more than 60 years at treatment ($p=0.001$), (ii) mixed/epithelioid tumours ($p=0.003$), (iii) superior location of mixed/epithelioid tumours (over and above (ii)) ($p=0.001$), (iv) largest basal tumour diameter of 16 mm or more ($p<0.001$), (v) lack of adjunctive radiotherapy ($p=0.031$), (vi) secondary enucleation for bulky residual/recurrent tumour ($p=0.002$), and (vii) secondary enucleation for small residual/recurrent tumour extraocularly ($p=0.019$). Metastatic death was not significantly associated with (i) incomplete tumour excision ($p=0.163$), and (ii) small residual/recurrent tumour treated by enucleation ($p=0.855$).

Conclusions—Survival diminished from 92% at 15 years if less than two risk factors were present to less than 30% in 3.5 years if more than three risk factors were present.

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Uveal melanoma is the commonest primary malignancy in the eye. Despite successful eradication of the primary tumour, about 50% of all patients ultimately develop metastatic disease,¹ which is invariably fatal.² Factors reported to be associated with an increased risk of metastatic disease include tumour size,³ number of epithelioid cells per high power field,⁴ nucleolar size,⁵ hyperploidy,⁶ lymphocytic infiltration,⁷ tumour pigmentation,^{8–10} presence of closed microvascular loops,¹¹ acoustic tissue characteristics,¹² extrascleral tumour extension,^{8 10 13} ciliary body involvement,¹⁴ old age at diagnosis,⁹ rapid tumour regression after radiotherapy,^{15 16} and others.

In specialist centres, enucleation is avoided whenever possible in favour of less mutilating forms of treatment, which are aimed at

conserving vision and the eye and which include brachytherapy,^{17–19} teletherapy,^{20 21} and trans-scleral local resection.^{22–25} Previous studies suggest that survival after enucleation is not significantly better than after radiotherapy²⁶ or local resection.²⁷ Sight conserving treatment has been encouraged by a widely shared belief that treatment does not influence survival in patients with medium sized and large tumours because fatal tumour dissemination has already occurred by the time the patient first presents.^{28 29}

The aims of this study were to (i) identify predictive risk factors for metastasis after trans-scleral local resection, and (ii) establish whether the prognosis for survival is affected by incomplete tumour resection and by adjunctive plaque radiotherapy.

Patients, materials, and methods

PREOPERATIVE ASSESSMENT

Our methods of preoperative assessment are described elsewhere.^{25 30} The following data were obtained at the time of treatment or subsequently by reviewing photographs and records: (i) patient age and sex; (ii) Snellen visual acuity measured with spectacles, pin-hole, or unaided, as clinically indicated; (iii) tumour height and largest and smallest basal tumour diameters as measured by B-scan ultrasonography; (iv) location of anterior and posterior margins of the tumour; and (v) coronal and sagittal location of the tumour. The tumour was said to have 'posterior tumour extension' if its posterior margin was situated at or within 1 disc diameter of the disc margin or fovea. The coronal location of the tumour was categorised as 'vertical' if the 'centre of gravity' of the tumour was located on a vertical line passing through the fovea, and 'nasal' or 'temporal' if the tumour was placed medial or lateral to the fovea.

SURGICAL TECHNIQUE

The surgical techniques are described in detail elsewhere.²⁵ Briefly, a rectangular lamellar scleral flap, was dissected over the tumour, after defining the tumour margins by transpupillary transillumination. The deep sclera and choroid were divided some 3–5 mm from the tumour, which was removed avoiding retinal damage whenever possible. Since 1986, partial ocular decompression was routinely performed, either before the dissection of the scleral flap by three port vitrectomy (WSF), or after preparation of the flap via a single sclerotomy and without infusion (BED).

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Haemorrhage was minimised by lowering the systolic blood pressure to approximately 40–60 mm Hg.³¹ The sclera was closed with interrupted 8-0 virgin silk, nylon, or vicryl sutures. Any small extraocular tumour nodule was excised with a surround of full thickness sclera and the defect in the lamellar flap was closed with a lamellar graft taken from a healthy part of the same eye. Adjunctive plaque radiotherapy was applied routinely and indiscriminately (that is, as often as possible) between the years of 1986 and 1989, but before and after this period such radiotherapy was administered only if there was definite or probable residual tumour. A ruthenium plaque was used, except in five cases treated before 1981, when only a cobalt plaque was available. External plombage and/or internal tamponade with gas or silicone were used to prevent retinal detachment if a large retinal defect was created.

PATHOLOGICAL EXAMINATION

Tumours were categorised as spindle cell, mixed, or epithelioid but the latter two types were considered together for this study because of the small number of purely epithelioid tumours. Surgical clearance was considered adequate if normal choroid was present beyond the tumour margin, uncertain if tumour extended close to the excision edge, and inadequate if tumour was present at the resection edge. Residual and recurrent tumours in enucleated eyes were categorised as 'large' if they measured approximately 10 mm³ or greater.

PATIENT FOLLOW UP

After the local resection, patients were reviewed after 1 month, 6 months, and then annually, if possible, unless more frequent visits were indicated because of complications. The following data were recorded: (i) visual acuity, measured with a Snellen chart either unaided, or with current spectacles, or pinhole as appropriate; and (ii) ocular and systemic complications together with the date of their diagnosis. Persistent intraocular tumour after local resection was categorised as (i) 'residual tumour' if present from the time of the operation (that is, diagnosed within the first 40 postoperative days), or (ii) 'recurrent tumour' if the tumour regrew from invisible microscopic deposits after apparently complete resection. Residual tumour and recurrent tumour were categorised as 'possible' when pigmentation could not be differentiated from retinal pigment epithelial hyperplasia and 'definite' when the diagnosis was certain. During most of the study, postoperative laser photocoagulation was applied only to 'possible' or 'definite' residual and recurrent tumours, whereas in the latter part of the study a double row of confluent photocoagulation burns was routinely applied to margins of the coloboma in all patients irrespective of whether or not residual tumour was suspected.

STATISTICAL METHODS

During the 18 months preceding the close of the study or the date of death, follow up data were obtained on 93% of all the 272 live patients, with all patients lost to follow up living overseas. The data were derived from examinations performed by one of the clinical authors (BED or WSF) or by the referring ophthalmologists, who returned questionnaires.

Information about the cause of death was obtained from family practitioners, referring ophthalmologists, and cancer registries. If a post mortem was not performed, the cause of death was assumed to be metastatic melanoma unless an alternative diagnosis had been confirmed. Follow up for patients still alive at the close of the study varied from 7 days to 20.9 years, with a median of 33 months. Ninety six patients were followed up for more than 5 years and 24 of these were followed up for more than 10 years.

In relation to metastatic death, *p* values for the univariate comparisons of time to death between different groups were derived by fitting Cox's proportional hazards model³² to the data. Estimates of relative event rates were obtained in the same way. A forward stepwise procedure (*p* to enter=*p* to remove=0.05) was used in conjunction with Cox's proportional hazards model to identify those factors influencing metastatic death most profoundly. A backward stepwise procedure was also used and gave the same model as the forward procedure and is therefore not referred to specifically in the results section. As with the outcome of any statistical analysis, the findings presented should be interpreted critically taking into account both the statistical and the clinical levels of significance. Such caution is all the more necessary with stepwise procedures as they produce exaggerated *p* values. In the analysis of the effect of various postoperative events on the risk of metastatic death, Cox's proportional hazards model was again used together with techniques for modelling the effect of time dependent covariates.³² Such techniques allow the influence of postoperative events to be estimated properly by including them only after the time that they occur for each patient. In these models the pretreatment and treatment variables already shown to be of prognostic importance were also included. Kaplan-Meier estimates³³ were used to draw survival curves. These curves were terminated when there were fewer than five patients at risk.

Patients were included in the study if they had primary choroidectomy, cyclochoidectomy (with or without iridectomy) or iridocyclectomy. They were excluded from the study if the operation was abandoned in favour of another form of conservative therapy or enucleation.

For the statistical analysis, persistent tumour in enucleated eyes was categorised as showing extraocular extension only if the extraocular extension was diagnosed at the same time as the recurrent tumour.

Table 1 Metastatic death after local resection. Univariate analysis

Variable	Categories	No of patients	Relative rate of metastatic death	95% Confidence interval for RR		p Value
				Lower limit	Upper limit	
Sex	Female	163	1.00	—	—	0.541
	Male	169	1.19	0.69	2.05	
Age at diagnosis (years)	<40	70	1.00	—	—	<0.001
	40–60	172	1.19	0.48	3.00	
	>60	90	4.86	1.99	11.87	
Eye	Right	146	1.00	—	—	0.232
	Left	186	0.72	0.42	1.24	
Initial vision	6/6–6/12	192	1.00	—	—	0.967
	6/18–6/36	81	1.08	0.55	2.13	
	6/60 or worse	59	1.06	0.53	2.13	
Anterior tumour margin (in relation to ora serrata)	Posterior	166	1.00	—	—	0.091
	Anterior	166	1.63	0.92	2.90	
Posterior tumour margin (in relation to disc or fovea)	≥1 DD	290	1.00	—	—	0.391
	<1 DD	42	0.64	0.23	1.78	
Coronal tumour position	Nasal to fovea	136	1.00	—	—	0.063
	Vertical midline	39	2.64	1.14	6.12	
	Temporal to fovea	157	1.61	0.85	3.06	
Sagittal tumour position	Superior to fovea	119	1.00	—	—	0.324
	Horizontal meridian	67	0.97	0.47	2.00	
	Inferior to fovea	146	0.65	0.35	1.20	
Operation type	Iridocyclectomy	37	1.00	—	—	0.033
	Choroidectomy	206	2.57	0.77	8.55	
	Cyclochoroidectomy	89	4.03	1.21	13.50	
Adjunctive brachytherapy	No	282	1.00	—	—	0.111
	Yes	50	0.40	0.12	1.29	
Ocular decompression	No	165	1.00	—	—	0.828
	Yes	167	0.54	0.23	1.23	
Surgical clearance (on histology)	Yes	125	1.00	—	—	0.163
	Uncertain	43	0.27	0.06	1.15	
	No	164	0.94	0.53	1.65	
Tumour thickness (mm) (pathology measurement)*	<5	52	1.00	—	—	0.058
	5–8	152	1.73	0.59	5.05	
	>8	108	2.91	1.00	8.41	
Tumour diameter (mm) (pathology measurement)†	<11	71	1.00	—	—	<0.001
	11–15	179	2.93	1.02	8.43	
	>15	72	7.40	2.54	21.58	
Cell type	Spindle	197	1.00	—	—	<0.001
	Mixed/epithelioid	135	5.91	3.13	11.15	

*Pathological height not recorded for 20 patients; †pathological diameter not recorded for 10 patients.

Results

SAMPLE

The study included 332 patients (169 male, 163 female; mean age 51 years) (Table 1). The tumours had a mean largest tumour diameter (LTD) of 13.1 (SD 4.1) mm and a mean thickness of 7.5 (SD 3.0) mm, as measured by the pathologist. The tumours extended anterior to the ora serrata in 166 cases and to within 1 disc diameter (DD) of the optic disc margin or fovea in 42 cases. Epithelioid cells were noted in 135 tumours. A total of 50 patients received adjunctive plaque radiotherapy at the time of the local resection. As reported more fully in a parallel study, residual tumour diagnosed immediately after the local resection occurred in 24 eyes and delayed tumour recurrence from microscopic deposits occurred in another 56 eyes.³⁴ Thirty three eyes were enucleated because of residual tumour, which was categorised as 'large'

in nine cases (with or without extraocular extension), and 'small' in 24 patients, nine of whom were classified as having extraocular tumour extension. Fifty two patients died of metastatic disease and another eight patients died of other causes, which included carcinoma of the bronchus (two), pneumonia (two), myocardial infarction (two), suicide (one), and gastroenteritis (one).

PREDICTIVE FACTORS

Univariate analysis showed that the variables predicting metastatic death were (i) age greater than 60 years at the time of diagnosis ($p<0.001$), (ii) presence of epithelioid cells ($p<0.001$), (iii) largest tumour diameter of 16 mm or more ($p<0.001$), (iv) choroidectomy and cyclochoroidectomy types of local resection ($p=0.033$) (Table 1). A forward stepwise Cox regression indicated in a multivariate setting that the statistically significant predictors

Table 2 Metastatic death after local resection. Multivariate analysis

Variable	Categories	No of patients	Relative rate of metastatic death	95% Confidence interval for RR		p Value
				Lower limit	Upper limit	
Age at diagnosis (years)	≤60	235	1.00	—	—	<0.001
	>60	87	3.14	1.75	5.62	
Sagittal tumour position (with respect to fovea)	Superior/horizontal	181	1.00	—	—	0.004
	Inferior	141	0.40	0.22	0.75	
Adjunctive brachytherapy	No	274	1.00	—	—	0.029
	Yes	48	0.26	0.08	0.87	
Tumour diameter (mm) (pathology measurement)*	<16	250	1.00	—	—	0.001
	≥16	72	2.87	1.58	5.22	
Cell type	Spindle	191	1.00	—	—	<0.001
	Mixed/epithelioid	131	5.48	2.76	10.90	

*Total number of patients is adjusted to 322 because pathological diameter is not recorded for 10 patients.

Figure 1 Kaplan-Meier curves showing the percentage of live patients according to age at the time of treatment. Patients older than 60 years showed were more likely to die of metastatic disease than younger patients.

Figure 3 Kaplan-Meier curves showing the percentage of live patients according to largest tumour diameter. Patients with larger tumours showed poorer survival.

for metastatic death were (i) patient age more than 60 years at diagnosis ($p < 0.001$), (ii) presence of epithelioid tumour cells ($p < 0.001$), (iii) largest tumour diameter of 16 mm or more ($p = 0.001$), (iv) superior tumour location within the eye ($p = 0.004$), and (v) lack of adjunctive plaque radiotherapy ($p = 0.029$) (Table 2). Adjunctive plaque radiotherapy tended to be applied to large tumours having a poorer prognosis; 25% of patients with a largest tumour diameter greater than 15 mm received adjunctive plaque radiotherapy compared with 15% of those with 11–15 mm tumours and 6% of those less than 11 mm in diameter. Because the multivariate analysis took account of the effect of tumour size, the advantage of plaque radiotherapy therefore became apparent statistically at this stage of the analysis. Figures 1–4 show the Kaplan-Meier survival curves giving an indication of time to metastatic death according to age, presence of epithelioid cells, largest tumour diameter, and adjunctive plaque radiotherapy.

All two way interactions between variables in the above multivariate model were examined and this suggested that an interaction existed between sagittal location and tumour cell type, with mixed/epithelioid cell tumours being associated with a higher rate of metastatic death if located superiorly in the eye ($p = 0.053$). Although this interaction did not reach the conventional level of statistical significance ($p < 0.05$), it was included as an extra term in the final statistical model (Table 3) because it accounted for the strong significance of sagittal tumour location in the multivariate model compared with non-significance in the univariate setting. In the final multivariate model, the predictive factors were therefore (i) patient age greater than 60 years at diagnosis ($p < 0.001$), (ii) largest tumour diameter of 16 mm or more ($p = 0.001$), (iii) mixed/epithelioid cell type ($p = 0.002$), (iv) superior tumour of mixed/epithelioid cell type (over and above (iii)) ($p = 0.002$), and (v) lack of adjunctive plaque radiotherapy ($p = 0.021$) (Table 3).

Figure 2 Kaplan-Meier curves showing the percentage of live patients according to tumour cell type. Patients with mixed or epithelioid cell tumours were more likely to die of metastatic disease than those with spindle cell tumours.

Figure 4 Kaplan-Meier curves showing the percentage of live patients according to adjunctive plaque radiotherapy. Patients receiving adjunctive plaque radiotherapy showed improved survival.

Table 3 Metastatic death after local resection. Multivariate analysis after adjusting for interaction between cell type and sagittal tumour location

Variable	Categories	No of patients	Relative rate of metastatic death	95% Confidence interval for RR		p Value
				Lower limit	Upper limit	
Age at diagnosis (years)	≤60	235	1.00	—	—	<0.001
	>60	87	2.93	1.62	5.32	
Superior tumour with epithelioid cells	No	279	1.00	—	—	0.002
	Yes	43	3.07	1.53	6.17	
Tumour diameter (mm) (pathology measurement)*	<16	250	1.00	—	—	0.001
	≥16	72	2.94	1.59	5.45	
Cell type	Spindle	191	1.00	—	—	0.002
	Mixed/epithelioid	131	3.22	1.53	6.77	
Adjunctive brachytherapy	No	274	1.00	—	—	0.021
	Yes	48	0.24	0.07	0.81	

*Total number of patients is adjusted to 322 because pathological diameter is not recorded for 10 patients.

The predictive factors were each given a score of +1 and patients were allocated into risk groups according to the sum of these risk factors. Figure 5 shows the Kaplan-Meier survival curves which give the time to metastatic death according to the risk group. Approximately 92% of 142 patients survived 15 years if less than two risk factors were present. At the other end of the scale, only 27% of 31 patients survived 3.5 years if more than three risk factors were present. Six years postoperatively, 76% of patients were alive if two risk factors were present compared with 57% of patients with three risk factors.

POSTOPERATIVE EVENTS

A forward stepwise regression procedure was performed to determine whether metastatic death was statistically related to (i) residual or recurrent tumour, (ii) subsequent enucleation for residual or recurrent tumour, and (iii) enucleation for retinal detachment or phthisis. This showed that the only subsequent event showing a statistically significant association with the relative rate of metastatic death was enucleation for persistent intraocular tumour ($p=0.017$) (Table 4).

The regression procedure was repeated after categorising the persistent intraocular tumour in the enucleated eye according to size and extraocular extension. This showed that metastatic death was associated with enucleation for large persistent tumour ($p=0.002$) and

with small persistent tumour with extraocular extension ($p=0.019$) but not with small persistent tumour without extraocular extension ($p=0.855$) (Table 5).

Discussion

This is the largest study on survival after local resection performed to date, because it includes 332 patients, with maximum follow up of up to almost 21 years, few losses to follow up, and documentation of a large number of variables.

Many of the adverse prognostic factors after local resection have previously been shown to be important in patients treated by enucleation or radiotherapy. These include presence of epithelioid cells, large tumour size and old age at time of treatment. Similarly, the lack of significance of sex has previously been noted after other forms of treatment.³⁵

There are a few notable differences between our results and those of other workers. Unlike other studies,⁹ our data do not show a statistically increased risk of metastatic disease in patients with anterior tumour extension, although there does seem to be a trend in this direction. This is perhaps because few of the tumours we resected were located entirely behind the equator of the eye. Our finding that mixed and epithelioid cell tumours are particularly associated with a poorer prognosis if located superiorly has not been reported previously. Whether other workers have not studied sagittal tumour location or whether they have found this variable to be insignificant is uncertain. This surprising statistical result may be due to chance or to previously unrecognised factors. In any case, the combined effect of sagittal tumour location and tumour cell type on survival merits further study.

An important finding is that the risk of metastatic death is higher in patients who undergo secondary enucleation for persistent tumour that is large or that extends extraocularly. The numbers of patients with these adverse features are small so that these results are only tentative and need to be confirmed by further studies; however, data published by other workers indicate that failure of local tumour control is associated with a significantly increased risk of metastatic death after plaque radiotherapy^{36 37} and with a non-significant increase in mortality after proton beam radiotherapy.³⁸ There are two possible

Figure 5 Kaplan-Meier curves showing the percentage of live patients according to the number of adverse prognostic features.

Table 4 Metastatic death after local resection. Multivariate analysis including postoperative events

Variable	Categories	No of patients	Relative rate of metastatic death	95% Confidence interval for RR		p Value
				Lower limit	Upper limit	
Age at diagnosis (years)	≤60	235	1.00	—	—	0.002
	>60	87	2.68	1.45	4.96	
Superior tumour with epithelioid cells	No	279	1.00	—	—	0.001
	Yes	43	3.13	1.57	6.25	
Tumour diameter (mm) (pathology measurement)*	<16	250	1.00	—	—	0.002
	≥16	72	2.65	1.42	4.95	
Cell type	Spindle	191	1.00	—	—	0.003
	Mixed/epithelioid	131	3.13	1.48	6.55	
Adjunctive brachytherapy	No	274	1.00	—	—	0.040
	Yes	48	0.27	0.08	0.95	
Subsequent enucleation for persistent tumour	No	299	1	—	—	0.017
	Yes	33	2.25	1.15	4.39	

*Total number of patients is adjusted to 322 because pathological diameter is not recorded for 10 patients.

explanations for such results. It is possible that in a proportion of cases metastatic death after local resection (and indeed after radiotherapy) is caused by malignant cells which disseminate from viable tumour persisting in the eye after inadequate treatment. An alternative explanation is that large size and extraocular extension of recurrent tumours are indicators of aggressive tumour behaviour, with tumour dissemination occurring before treatment and with microscopic tumour deposits in the liver behaving in the same aggressive manner as microscopic deposits in the eye. In other words, the question is whether persistent viable tumour after unsuccessful conservative treatment causes metastatic death or whether persistent tumour and metastatic death are both indicators of adverse prognostic factors that were not included in predictive statistical models.

In this study, (i) histologically incomplete tumour resection, and (ii) small persistent tumours treated by enucleation were not associated with an increased risk of metastatic disease. This is possibly because prompt and successful secondary treatment prevented growth and dedifferentiation of residual tumour cells in the eye, or because many of the persistent tumours had a low metastatic potential, or both of these reasons. Treatment of known residual or recurrent disease may also have inadvertently prevented metastatic spread from unrecognised microscopic tumour deposits, as implied by the efficacy of adjunctive plaque radiotherapy (see

below). Some patients with apparently complete excision on histology and ophthalmoscopy developed local tumour recurrence and this suggests that microscopic tumour seedlings and extensions were sometimes missed both by the pathologist and the surgeon.

Adjunctive plaque radiotherapy was introduced in 1986 as a routine procedure to reduce the incidence of local tumour recurrence, and indeed in a parallel study, we show that adjunctive plaque radiotherapy is effective at preventing local tumour recurrence after trans-scleral local resection (Cox multivariate analysis, $p=0.018$).³⁴ In 1989, we adopted more aggressive resection with wider clearance margins, and adjunctive laser photocoagulation to reduce the incidence of radiational complications. The finding that adjunctive plaque radiotherapy is associated with a better prognosis for survival is serendipitous. Our results suggest that in eradicating microscopic tumour deposits left in the eye after local resection, adjunctive plaque radiotherapy prevents not only local tumour recurrence but also metastasis. The effect of adjunctive plaque radiotherapy on metastasis was not studied in a randomised and prospective fashion so that further investigation is necessary. Nevertheless, it is noteworthy that patients treated with adjunctive plaque radiotherapy tended to have larger tumours and would therefore have been expected to have a higher incidence of metastatic disease not lower.

Table 5 Metastatic death after local resection. Multivariate analysis adjusting for size of persistent tumour in enucleated eyes and extraocular extension

Variable	Categories	No of patients	Relative rate of metastatic death	95% Confidence interval for RR		p Value
				Lower limit	Upper limit	
Age at diagnosis (years)	<60	235	1.00	—	—	0.001
	≥60	87	2.92	1.57	5.45	
Superior tumour with epithelioid cells	No	279	1.00	—	—	0.001
	Yes	43	3.50	1.72	7.13	
Tumour diameter (mm) (pathology measurement)*	<16	250	1.00	—	—	<0.001
	≥16	72	3.59	1.83	7.01	
Cell type	Spindle	191	1.00	—	—	0.003
	Mixed/epithelioid	131	3.03	1.45	6.34	
Adjunctive brachytherapy	No	274	1.00	—	—	0.031
	Yes	48	0.25	0.07	0.88	
Enucleation for persistent tumour	No	299	1	—	—	0.002
	Yes, for large tumour	9	5.98	1.95	18.34	
	Yes, for small tumour with extraocular extension	9	3.65	1.24	10.74	
	Yes, for small tumour without extraocular extension	15	1.10	0.40	3.00	

*Total number of patients is adjusted to 322 because pathological diameter is not recorded for 10 patients.

Lack of adjunctive plaque radiotherapy seemed to be associated with an increased mortality even in patients without residual or recurrent disease (28/206 14% versus 2/44 5%). This crude estimate is in keeping with the results of our multivariate analyses, which show adjunctive plaque radiotherapy to be an independent prognostic indicator even when enucleation for persistent tumour is included in the model ($p=0.031$) (Table 5). These results would seem to suggest that adjunctive plaque radiotherapy may prevent metastatic disease in some cases because it prevents seeding from microscopic deposits. We, therefore, share the concerns expressed by Robertson and associates about residual tumour after local resection, although we find that deposits in uveal tissue are more troublesome than deposits in sclera or retina.³⁹ On the basis of these findings, we now excise tumours with wider clearance margins than before and routinely perform adjunctive treatment, which consists either of (i) ruthenium plaque radiotherapy or, if this is not technically possible, (ii) laser photocoagulation and cryotherapy to the margins and bed of the coloboma.

The 5 year mortality rates for patients with largest basal tumour diameters of <11 mm, 11–15 mm, and >15 mm were approximately 3%, 20%, and 44% (Fig 3). These results seem better than those reported in a meta-analysis: by Diener-West and associates, which shows the 5 year mortality rates after treatment of uveal melanoma to be 16% for small tumours (large tumour diameter <10–11 mm and tumour thickness <2 mm–3 mm), 32% for medium tumours (large tumour diameter <15 mm–16 mm and tumour thickness 3–8 mm), and 53% for large tumours (large tumour diameter >15 mm–16 mm or tumour thickness ≥ 8 mm).³ If we had classified our tumours according to both height and diameter, then 103 of our tumours would have been placed in a less favourable category so that our survival figures would have been even better than those of Diener-West and associates. The most likely explanation for better survival after local resection is selection bias related to the need for good general health for hypotensive anaesthesia. In view of the hazards of comparing apparently similar data from different publications we would prefer to assess only our own data. We have previously shown that survival in 220 patients treated by local resection was not significantly different from that in a matched series of 239 patients treated by enucleation.⁴⁰ On the basis of our findings, we continue to regard trans-scleral local resection as a reasonable alternative to enucleation, especially if some form of adjunctive local treatment is administered, and this applies to all tumours irrespective of size and location.

Overall 5 year survival figures have been reported as approximately 75–85% after helium ion radiotherapy,²¹ proton beam radiotherapy,²⁰ cobalt plaque radiotherapy,⁴¹ and ruthenium plaque radiotherapy.⁴² These results do not seem markedly different from our own data, although as mentioned above there are severe limitations inherent in comparing results

from different studies. Because we reserve local resection for patients we consider to be unsuitable for radiotherapy, there would not seem to be much scope for performing comparisons between these two treatments in a randomised prospective fashion.

The results of the present study with regard to the influence of adjunctive plaque radiotherapy on survival are only tentative as they were not obtained in a randomised prospective fashion. If survival is indeed improved by adjunctive treatment, this would imply that (i) residual tumour can cause metastatic disease, (ii) fatal tumour dissemination can occur after the patient presents, even if the tumour is of medium size or large, and that (iii) all patients without evidence of metastasis should receive urgent and total tumour destruction.

In the present study, differences in survival rates according to adjunctive radiotherapy seem to appear as early as the fourth year after treatment (Fig 4). This tentative result is not in keeping with the views expressed by others that (i) metastatic death within the first 7 years postoperatively is always due to tumour dissemination before treatment and that (ii) a minimum follow up interval of 7 years is essential to allow any comparisons between different forms of treatment.⁴³ In this respect, it is noteworthy that (i) factors predicting metastatic death within the first 2 years may be different from those that predict more delayed onset of metastatic disease and death,¹⁶ and that (ii) the prognostic values of pretreatment variables may decline with time.⁴⁴

In conclusion, this study confirms the findings of other workers that epithelioid cell type, largest basal tumour diameter, and old age are useful predictors of metastatic death and, in addition, identifies other adverse prognostic factors, such as lack of adjunctive plaque radiotherapy, delayed or inadequate treatment of residual or recurrent tumour, and superior tumour location within the eye of mixed and epithelioid tumours. These tentative results appear to contradict some general beliefs about the natural history of uveal melanomas and imply that these tumours should be treated aggressively and urgently. The prognostic score developed in this study allows survival after local resection to be described in a more meaningful manner than has hitherto been possible and in future may facilitate the selection of patients for adjunctive systemic immunotherapy or chemotherapy.

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