Prognostic factors following enucleation of 111 uveal melanomas

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Abstract
Follow up information was retrieved on 111 patients who underwent enucleation for uveal melanoma between 1964 and 1987, allowing a minimum postoperative period of 5 years. Univariate survival analysis was carried out using Kaplan-Meier curves and the differences between the curves were analysed with the Mantel-Cox test. Multivariate analysis used the Cox proportional hazards model. Univariate analysis isolated each of the following as significant prognosticators: largest tumour diameter (LTD) ($p<0.002$), presence of epithelioid cells ($p<0.03$), and glaucoma ($p<0.001$). A combination of cell type, glaucoma, and LTD ($p<0.0001$) had strong and independent prognostic significance in multivariate analysis. The results of this series are compared with previous studies and the value of cell type information and new quantitative parameters is discussed.
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melanomas are available from countries including Northern Ireland,⁵ Finland,⁶ Denmark,^{7,8} England^{9,10} and several different study groups in North America.^{3,11,12,13,14} The Collaborative Ocular Melanoma Study (COMS) is a set of multicentre prospective clinical trials established in North America and Canada in 1986, and is the first reported prospective study which has been designed to evaluate interventions used to treat patients with choroidal melanomas. The minimal follow up time is 10 years.¹⁵ However, because of the slow growth rate of some melanomas, it is expected that more than 30 years will elapse before all useful information is harnessed. Until then, survival analysis on as many different populations as possible may aid therapeutic decisions. With this in mind, we set out to evaluate survival following enucleation in 111 patients with uveal melanoma, and to compare our findings with published results.

Materials and methods
A total of 373 uveal melanomas were diagnosed in the National Ophthalmic Pathology Laboratory of The Royal Victoria Eye and Ear Hospital, Dublin, from January 1964 to July 1987. Enucleation was performed in each instance. Follow up information was collected by sending questionnaires to all referring ophthalmologists for the following information: survival, or date and cause of death; evidence of local spread; evidence of metastases; evidence of another neoplasm; and name of local physician. Questionnaires were also forwarded to the patient's physician where necessary and other doctors involved in the patient's care were contacted by telephone. It was decided that direct contact with relatives was not warranted for the purpose of this study. Full clinical information became available in 111 patients. The maximum follow up time was 24 years, the median was 11.5 years, and the minimum, 5 years. Distribution of age and sex was similar to the original group of 373. Pathology details were obtained from the original pathology reports. The site of the tumour was described as either anterior or posterior to the equator, equatorial, or involving the ciliary body. The largest tumour dimension (LTD) was recorded, but in some cases only qualitative data were available – for example, 'tumour fills globe', and in such cases the largest dimension from either preoperative clinical estimation or glass slide measurements was used. Ophthalmologically and pathologically assessed

Figure 1 Survival curve showing death from metastases following enucleation for uveal melanoma ($p<0.0001$).

Table 1 Summary of statistics on 111 uveal melanomas

Variable	n	Metastases n (%)	Alive n (%)	p Value	Mantel- Cox
Sex					
Male	53	15 (28)	38 (72)	0.69	0.2
Female	58	18 (29)	40 (71)		
Age (years)					
<60	60	17 (28)	47 (72)	0.16	2.0
≥60	51	16 (31)	35 (69)		
Age (years)					
<40	13	2 (15)	11 (85)	0.27	2.6
40–60	47	15 (32)	32 (68)		
>60	51	16 (31)	35 (69)		
Metastases					
Orbit	2	1 (50)	1 (50)	<0.0001	209.7
Lung	2	2 (100)	0		
Liver	24	24 (100)	0		
Other	4	4 (100)	0		
None	79	0	77 (100)		
Metastases					
Yes	32	32 (100)	0	<0.0001	113.0
No	79	0	77 (100)		
Other metastases					
Yes	11	11 (100)	0	<0.0001	54.7
No	91	16 (17)	75 (83)		
Unknown	9	6 (77)	3 (33)		
LTD					
<10 mm	42	8 (19)	36 (81)	0.002	12.8
10–15 mm	57	17 (30)	40 (70)		
>15 mm	12	8 (77)	4 (33)		
LTD					
<10 mm	42	8 (19)	36 (81)	0.03	4.7
≥10 mm	69	25 (36)	44 (64)		
Glaucoma					
Yes	36	19 (53)	17 (47)	0.001	10.5
No	75	14 (19)	61 (81)		
Detachment					
Yes	94	31 (33)	63 (67)	0.11	2.6
No	17	2 (92)	15 (88)		
Cell type					
Pure spindle	53	13 (25)	40 (75)	0.03	4.5
Part epith	55	20 (36)	35 (64)		
Cell type					
Spindle A	6	1 (17)	5 (83)	0.04	11.4
Spindle B	33	8 (24)	25 (76)		
Spindle A/B	14	4 (29)	10 (71)		
Spl/Epith	32	10 (31)	22 (69)		
Epith/Spl	23	10 (43)	13 (57)		
Necrotic	3	0	3 (100)		
Pigment					
None/low	21	4 (19)	17 (81)	0.73	0.63
Medium	71	24 (34)	47 (66)		
High	19	5 (26)	14 (74)		
Position					
Posterior	84	21 (25)	63 (75)	0.2	1.6
Other	27	12 (44)	15 (56)		
Position					
Iris	3	1 (33)	2 (67)	0.58	2.9
Ciliary body	12	5 (42)	7 (58)		
Posterior	84	21 (25)	63 (75)		
Anterior	7	3 (43)	4 (57)		
Equator	5	3 (60)	2 (40)		
Spread					
Yes	47	20 (43)	27 (57)	0.08	3.1
No	64	13 (20)	51 (80)		
Spread					
Optic nerve/extrascleral	17	7 (41)	10 (59)	0.27	1.2
Other	94	26 (28)	68 (72)		
Spread					
Optic nerve	9	4 (44)	5 (56)	0.36	3.2
Sclera	30	13 (43)	17 (57)		
Extrascleral	8	3 (37)	5 (63)		
None	64	13 (20)	51 (80)		
Eye					
Right	57	20 (35)	37 (65)	0.74	0.11
Left	54	13 (24)	41 (76)		
Vascularity					
Normal	98	28 (28)	70 (72)	0.5	0.43
Increased	13	5 (38)	8 (62)		

LTD=largest tumour dimension.

LTDs have been shown to be of equal prognostic significance.¹⁶ Where dimensions were available from more than one source – that is, pathology report or glass slide measurements, the largest reading was used. The extent of tumour spread was noted as follows: optic nerve, intrascleral channels, extrascleral, or orbital (noted at surgery). The presence or absence of retinal detachment or secondary glaucoma was also recorded.

The tumours were originally classified according to the first Callender classification¹⁷ by the

same pathologist (JM). The Callender classification has since been updated¹⁸ but still fails to distinguish between the different types of spindle cell or mixed cell tumours. In this study, the pathology reports were reviewed and the Callender classification modified as follows: spindle A, spindle B, spindle A and B mixed, predominantly spindle with a few epithelioid cells, and predominantly epithelioid, with or without the presence of a few spindle cells. Pigmentation was described as mild (including the amelanotic group), moderate, or heavy.

Data analysis

For survival analysis, patients dying without clinically evident metastases were censored at that date and corrected (tumour related) survival time was used as the follow up parameter. Grouping was performed according to the different subgroups for each non-continuous variable. For the two continuous variables (age and LTD) in the single variate analysis, cut off points were chosen according to the literature. These were at 40 years and 60 years for age, and at 10 mm and 15 mm for LTD. Kaplan-Meier curves were plotted, and differences between the curves were analysed with the Mantel-Cox test. Multivariate survival analysis was also performed to evaluate additional prognostic value of the variables studies, using the enter and remove limit of 0.01. The analysis was performed on all variables available at the time of surgery. All analyses were performed using the BMDP statistical package, with p values below 0.05 being regarded as significant.

Results

Patient survival is shown in Figure 1. General statistics are summarised in Table 1. There were 58 women (52%) and 53 men (48%). All patients were white. Age at enucleation ranged from 17 years to 91 years with a median age of 57.5 years. At the end of the study period, 45 (40.5%) patients had died, 31 (28%) with confirmed metastases as detected clinically before death. One patient was alive with orbital metastases. The possibility of metastases as a cause of death could not be ruled out in a further three patients and so, for statistical analysis, these were censored as being ‘well’. Of the 32 patients with metastases, 24 had secondaries in the liver, two in the lung, two in the orbit, and one each with metastases of bone, colon, and brain. It was not possible to confirm the site of metastases in one patient. Ten of the patients with liver metastases were subsequently found to have metastases at other sites, including lung, bone, brain, pancreas, chest wall, colon, and skin.

Univariate survival analysis provided significant results for the following: LTD, with cut off points of 10 mm and 15 mm (p<0.002) (see Fig 2) and glaucoma (p<0.001). When cell type was classified according to the presence or absence of epithelioid cells, significance was also reached (p<0.03) (see Fig 3). The presence of retinal detachment was not significant, but there was a trend (p<0.11). As these features came out as signs in the single variate survival analysis, the χ^2

Figure 2 Survival curve for patients with largest tumour diameter (LTD) less than 10 mm, between 10 and 15 mm, and more than 15 mm ($p < 0.002$).

Figure 3 Survival curve for patients with uveal melanomas with and without epithelioid cells ($p < 0.03$).

Table 2 Correlation of LTD (largest tumour dimension) with cell type, retinal detachment, and glaucoma (χ^2 test)

LTD	<10 mm	≥10 mm	p Value
Cell type*:			<0.12
Pure spindle	24	29	
Part epithelioid	17	38	
Detachment			<0.0001
Yes	28	66	
No	14	3	
Glaucoma:			<0.27
Yes	11	25	
No	31	44	

*Three cases were necrotic and so not evaluable.

Table 3 Multivariate analysis of uveal melanomas

Combination	n	Metastases n (%)	Alive n (%)	p Value	Mantel-Cox
OC MEL-1					
≤0.74	54	8 (15)	46 (85)		12.3
>0.74	57	24 (42)	28 (58)	<0.0005	
OC MEL-2					
<0.3	39	5 (13)	34 (87)		17.6
0.3-1.3	38	9 (24)	29 (76)	<0.0001	
>1.3	34	18 (53)	16 (47)		

Formula: $+0.0897 \times \text{LTD}$
 $+0.4449 \times \text{cell type}$ (1=spindle A, 2=spindle B, 3=spindle A/B, 4=spl/part epith, 5=epith/part spl, 6=necrotic)
 $-0.9977 \times \text{glaucoma}$ (1=yes, 2=no)

test was used to examine the correlation between LTD and cell type ($p < 0.12$), LTD and glaucoma ($p < 0.27$), and LTD and retinal detachment ($p < 0.0001$) (see Table 2). The occurrence of metastases ($p < 0.0001$) and presence of more than one metastatic site ($p < 0.0001$) were, as

expected, significantly correlated with shortened survival.

In multivariate survival analysis (see Table 3), a combination of LTD, cell type, and glaucoma emerged ($p < 0.0001$). Survival of patients according to this multivariate combination is shown in Figure 4. In order to allow a more accurate comparison of the significance of this combination with that of LTD, it was decided to attribute a similar number of cases to each group. A third set of cut off points was selected for LTD, dividing the patients into groups of 42, 40, and 29. This grouping also reached significance ($p < 0.04$ and Mantel-Cox 6.3), but the Mantel-Cox value and probability of the multivariate combination ($p < 0.0001$ and Mantel-Cox 17.6) are much better than that of any of the single variables.

Discussion

The purpose of this and other retrospective uveal melanoma survival studies has been to identify tumour characteristics that will help in deciding the most appropriate treatment and allow an accurate prognosis. This is the first survival analysis of uveal melanomas in the Republic of Ireland. Our 5-year survival rate of 72% is similar to that of the Northern Irish population (72%),⁵ the London study group (78.1%),⁹ and two American studies (71%¹¹ and 74%¹²). Raivio reported a survival of 65% in Finland.⁶ His was an epidemiological study with 99% follow up, and thus may represent the most realistic melanoma survival rates. Although these figures are for patients who eventually underwent enucleation, this was not always the immediate form of treatment in every case. Packard, for example, included 22 cases where surgery followed growth of the tumour after a period of observation, and 72 cases which were managed conservatively. He also reported better survival figures in the non-surgical managed group.⁹ A recent meta-analysis of melanoma reports between 1966 and 1988 implies that the above figures may be optimistic, and that the combined weighted estimates of 5-year mortality rates following enucleation were 16% for small (<10 mm) tumours, 32% for medium (10-15 mm) tumours, and 53% for large (>15 mm) tumours.¹³ This compares with the rates in the present study of 19% (small), 30% (medium), and 77% (large).

Of the four significant parameters in this series, information on only three – that is, LTD, glaucoma, and retinal detachment, was available before a decision to operate. We examined the usefulness of these signs as clinical guidelines (see Table 4). LTD has been the most important clinical characteristic to emerge from retrospective studies,¹³ but the cut off values, used by different investigators to predict optimal survival, vary.^{14-19,20} Furthermore, there is wide interobserver variation of clinical estimation of LTD despite the assistance of ultrasonography. Although the sensitivity of LTD as a prognostic parameter is good at 76%, the specificity of only 44% still allows for a 56% chance of a false positive prediction of outcome.

The presence of glaucoma as a preoperative predictor of metastasis may be more useful. Both

Figure 4 Survival curve for multivariate combination of largest tumour diameter (LTD), cell type, and glaucoma ($p<0.0001$).

the sensitivity and specificity were reasonable, with a predictive positive value of 53%. Although glaucoma is a frequent complication of uveal melanomas and is usually produced by large diffuse tumours,²¹ the correlation between LTD and glaucoma failed to reach significance ($p<0.27$). This points to mechanisms other than those occurring as a function of size. Microscopic tumour seeding of the trabecular meshwork will also raise intraocular pressure, and may be associated with concurrent haematogenous seeding and development of metastases.

Retinal detachment was a frequent finding, but was not a significant influence on survival.

Table 4 Predictive value of prognostic parameters for uveal melanomas

	LTD (%)	Glaucoma (%)	Cell type (%)	RD (%)	Multivariate (%)
Sensitivity	76	58	61	94	75
Specificity	44	78	53	19	58
Predictive (positive)	36	53	36	33	42
Predictive (negative)	81	81	76	88	85

LTD=largest tumour dimension
RD=retinal detachment

The sensitivity of this sign (94%) is naturally offset by a low specificity (19%). Its usefulness clinically is also limited by its strong correlation with LTD ($p<0.0001$). This is not surprising since expansion of the choroidal tumour, with inward bulging towards the vitreous, causes the retina to become stretched out over the summit of the mass.²² It would not, therefore, be expected to provide any additional information to LTD.

A summary of multifactorial analyses of other studies is given in Table 5. No two studies concur, but cell type and tumour size are significant variables in every group. Until recently, however, histology has been unavailable before enucleation. With the advent of safe tumour biopsy, both by excision²³ and fine needle aspiration,²⁴ this is likely to change, and knowledge of cell type could play a major role in clinical management. In this study, presence or absence of epithelioid cells had a reasonable sensitivity and specificity. Cell type did not correlate with LTD ($p<0.12$) and, with glaucoma, would be expected to contribute independently to the prediction of metastases. This is confirmed in the multivariate combination in Table 3, and is also supported by Gamel *et al* who demonstrated an even weaker correlation between LTD and cell type ($p<0.26$).²⁵

The prognostic significance of cell type has implications for the not always perfectly reproducible Callender system. The Callender classification scheme places the tumour into one of four¹⁸ to six¹⁷ subgroups, although the cells present in uveal melanomas actually represent a continuous spectrum of morphological change. The fact that this classification has repeatedly emerged as significant augurs well for the clinical value of an even better system, one that examines the characteristics of the cell as part of a continuum rather than limited subgroups. Such reproducible, quantifiable, and objective characteristics have been investigated over the past decade. The standard deviation of nucleolar area (SDNA) and mean area of the 10 largest nucleoli (MLN) have been equally and significantly correlated with malignancy of uveal melanomas.²⁵

Table 5 A summary of multivariate analysis in different studies

Study group	Methodology	Combinations	Independent variables (in order of significance)
Kidd <i>et al</i> (1986)	Cox proportional hazards Log-logistic model	Cell type and tumour extension correlated with tumour size	1 Tumour volume 2 Age 3 Tumour site
Seddon <i>et al</i> (1983)	Cox proportional hazards model		1 No of epithelial cells/HPF 2 LTD 3 Anterior to equator 4 Invasion to line of transection 5 Increased pigmentation
Packard (1980)	Stepwise discriminant analysis	1 Age and cell type 2 In spindle tumours, pigmentation 3 In mixed and epithelioid cell tumours, size	
Affeldt <i>et al</i> (1980)	Stepwise discriminant analysis	LTD, cell type and optic nerve spread	1 LTD 2 Cell type 3 Optic nerve invasion
(tumours with extrascleral spread)	Bayesian multifactorial analysis		
McLean <i>et al</i> (1977)	Discriminant function analysis	1 Cell type 2 LTD 3 Scleral extension 4 Mitotic activity	
(tumours <1400 mm)		LTD, glaucoma, and cell type	1 Glaucoma 2 Cell type 3 LTD
Coleman <i>et al</i> (1993)	Cox proportional hazards model		

DNA quantitation by flow cytometry has been shown in one study to be a better parameter than the inverse SDNA.²⁶ A study from our laboratory using DNA image analysis, and requiring a sample size of only 100 cells, has suggested that spindle A cells are, like most benign cells, non-cycling, and that tetraploid and aneuploid peaks are mainly occupied by the more pleomorphic spindle B and epithelioid cell types.²⁷

It is apparent that although important trends have emerged from retrospective prognosis studies, such as relevance of size and cell type, it is not possible to reach firm conclusions because of lack of uniformity of study designs. This is confirmed by Markowitz *et al* who noted the absence of information on study design and methods in 50% of 76 melanoma studies from 1966 to 1988.²⁸ Survival rates following enucleation are broadly similar in all study groups reported. The Collaborative Ocular Melanoma Study (COMS) in America is the first major prospective study designed to examine the natural history of patients with uveal melanomas following management by either enucleation or radiotherapy. We suggest a transcontinental approach and the creation of a strict European multicentre protocol for pooling of prospective clinical and pathological information. This is essential with the imminent availability of histological information before management, particularly now that many different forms of therapy are available, in order to ensure the best possible survival rates and lowest morbidity for our patients.

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