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Title: Survival from Uveal Melanoma in Western Australia 1981-2005

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Abstract

Background: The survival rates for patients diagnosed with uveal melanoma in Australia are unknown. Few long-term studies of uveal melanoma are available, and it is unclear whether their results are applicable to the Australian population.

Design: Retrospective population-based study

Participants: Patients diagnosed with uveal melanoma between 1981 and 2005 in Western Australia.

Methods: 308 cases were included. Relative survival and Cox regression were performed. Variables tested for their predictive ability included patient age and sex, tumour-specific variables and treatment modality.

Main Outcome Measures: All cause survival rates and relative survival rates of patients with diagnosed uveal melanoma.

Results: Relative survival rates for the entire cohort were 88.2%, 81.4% and 71.4% at 3-, 5- and 10-years respectively. Predictors of worse survival included mixed-cell tumour morphology (HR = 2.1; p-value = 0.002), tumour location at the ciliary body (HR = 1.7; p-value = 0.029) and tumour apical height more than 5mm (HR 1.9, p-value = 0.026). Of all patients who underwent enucleation, those diagnosed in 1998-2005 died twice as fast (HR = 2.3; p-value = 0.004). In the 17 patients with metastasis median survival time from date of diagnosis of metastasis was 3.1 months.

Conclusions: These survival estimates are comparable to those reported for the United States, and more optimistic than those reported for most European-based studies. Tumour apical height, tumour site, tumour morphology and having an enucleation in certain calendar

periods of diagnosis were independent predictors of survival. Survival prognosis for patients with diagnosed metastatic uveal melanoma is very poor.

Key words: Uveal melanoma, Survival, Intraorbital malignancy

Background

Uveal melanoma (UM) is the most common primary intraocular malignancy.[1] with an incidence of 9.8 per million population per year in Australia .[2] This rate is higher than those reported from the USA[3] and Europe[4-6]

UM is most common in Caucasians, and is rare in pigmented races[7]. UM is fatal in approximately 50% of patients, due to metastatic disease, usually to the liver. Despite the many advances in diagnosis and treatment of the primary tumour in recent years, there has been no improvement in survival rates[8, 9] and median survival time following diagnosis with metastasis remains poor[10], even with adjuvant therapy.

Methods

This study was a retrospective population-based cohort study of all persons diagnosed with UM in Western Australia for the time period 1981-2005. Only patients who were residents of Western Australia at the time of diagnosis were included in the analysis. Ethics approval was obtained from two independent Human Research Ethics Committees.

Cases were sourced primarily from the Western Australia Cancer Registry (WACR) where all cases of cancers in Western Australia are legally required to be reported. Cases were identified the ICD-10-O Version 3 site and morphology code combinations specific for uveal melanoma. Only cases of UM (including iris, choroid and ciliary body) with a date of diagnosis from 1 January 1981 and 31 December 2005 were included.

The recruitment of cases was supplemented by review of medical physics files of all patients who had episcleral Cobalt-60- and Iodine-125-seeded radioactive plaque therapy between 1981 and 2005 at the Royal Perth Hospital Medical Physics department. Ophthalmic brachytherapy in Western Australia has been exclusively carried out at Royal Perth Hospital since its inception in Western Australia in the 1980s. Where available, accompanying clinical

information on size and location of the tumour were noted and entered into a Microsoft Access database. Tumours were grouped according to Callender's histological groupings[11]. This supplementary clinical data were crosschecked against the WACR and used to identify additional cases that were not adequately notified to the WACR and to record additional tumour details on notified cases where possible. Death information of the identified cases was extracted from the state based death registry by the Data Linkage Branch of the Western Australia Department of Health (WA Health).

Survival outcomes for the cohort were investigated using relative survival estimation and proportional hazards regression models. Analysis time was from date of diagnosis until date of death or the study censor date of 31 December 2008 for patients still alive at this date.

Relative survival analysis was performed to estimate tumour-specific survival. This method adjusts for competing causes of death by estimating the excess mortality associated with a cancer diagnosis over and above what mortality might be expected in a similar population who are assumed to be free of the cancer of interest.[12] Relative survival is estimated from life tables as the ratio of the observed survival of the patients to the expected survival in an age-, sex- and calendar period-matched population. Relative survival analysis using the Ederer II methodology was performed using the stnet command[13] based in Stata with life tables of the Australian population obtained from the Australian Bureau of Statistics. Stratified relative survival estimates and 95% confidence intervals were obtained by age group, sex, tumour histology, tumour site, treatment modality, tumour size and calendar period of diagnosis, and graphs produced.

Explanatory factors associated with all-cause mortality patients with UM were explored using multivariate Cox proportional hazards models.[14] Data were formatted using the counting process method with enucleation status entered as a time-dependent variable. Potential

predictors and confounders were age at diagnosis, calendar period of diagnosis, gender and all tumour-specific and treatment variables. Likelihood ratio tests were used to include or exclude covariates from the adjusted model and to identify any potential plausible interaction terms at the 5% significance level. A test for violation of the proportional hazards assumption was performed on the final model using Schoenfeld residuals. All analyses were performed using Stata 13 (StataCorp, College Station Tx).

Results

There were 309 Western Australian residents diagnosed with UM during the period 1981-2005. Of these, 299 cases were identified on the WACR and an additional 10 cases were identified from review of medical physics records that had not been notified to the WACR as UM. One case was excluded due to "zero survival"- that is, they were diagnosed with their UM at death, leaving 308 cases to be included.

The demographic and tumour characteristics of the cases are summarised in Table 1. There was an equal distribution of males and females amongst the cohort. The median age at diagnosis of UM was 61.6 years. Minimum and maximum ages at diagnosis were 16 years and 93 years respectively. Accurate tumour site sub-classification was achieved for 86% (n=266) cases. Details regarding the maximum diameter and apical height of the tumour were available in 148 cases and tumour histology was available for 151 cases. Most tumours were located in the choroid and around a quarter of the cohort had tumours greater than 1cm in diameter at time of diagnosis. There was a tendency for cases to be diagnosed in the more recent calendar periods.

Just over half of all cases (n = 158; 51%) died during the follow-up period. Median survival time for the entire cohort was 11.6 years (95% CI: 9.1, 14.1). Univariate Log –rank tests for equality of survivorship function showed that tumour histology was associated with all cause survival outcomes and there was evidence of a weak association of tumour apical height with

all-cause survival outcomes (Table 1). As expected, increasing age was associated with shorter overall survival.

The 3, 5 and 10 year overall survival proportions for the whole cohort were 83%, 73% and 56% respectively. When life tables were used to account for the baseline death rates in the general population, the relative survival rates at 3-, 5- and 10- years were 88% (95% CI: 83%-92%), 81% (95%CI: 76% - 87%) and 71% (95%CI 63% -78%) respectively. Relative survival proportions at 3, 5 and 10 years post diagnosis by demographic and tumour characteristics are shown in Table 2. After taking the background death rate of the general population, increasing age at diagnosis, having a ciliary location, a larger basal diameter and epithelial or mixed morphology were generally associated with poorer relative survival outcomes. No difference in relative survival outcomes were observed by gender. Cases diagnosed prior to 1990 tended to have better relative survival outcomes. Graphical representation of the relative survival outcomes by tumour morphology are shown in Figure` 1 and demonstrate a survival advantage of spindle cell melanomas compared to epitheliod or mixed cell type morphologies.

Multivariate survival regression models were constructed to determine if the survival advantage for spindle cell melanomas remained after taking other tumour information and patient demographic variables into account (Table 3). Spindle cell melanomas were found to have half the rate of dying compared to patients diagnosed with mixed cell morphology. There was a trend for spindle cell morphology to have a survival advantage compared with epitheliod cell types but this did not reach statistical significance in this study.

The multivariate model also showed that being diagnosed in more recent calendar periods was associated with poorer survival outcomes but only after a patient had undergone an enucleation. Patients diagnosed 1998-2005 and who underwent enucleation died more than twice as quickly as those who were diagnosed in 1981-1989 and had an enucleation. In

contrast, there was no difference in survival outcomes for patients diagnosed in 1981-1989 compared to those diagnosed in 1998-2005 for patients who had not undergone an enucleation. However, there was moderate evidence of poorer survival for patients who had not undergone enucleation if they were diagnosed in the middle period of the study.

Other clinical features found to be associated with survival outcomes and after adjusting for age and year and enucleation status were apical height and site. A recorded apical height greater than 5 mm was associated with 90% increased rate of death compared to patients with tumours less than 5 mm. Diagnosis of a ciliary body tumour bestowed a 70% increased hazard rate when compared to all other tumours. Patients who underwent brachytherapy showed no survival advantage compared to patients who did not receive brachytherapy. Basal diameter and patient gender were not associated with survival outcomes in this study.

In this patient series, there were 18 cases in which details regarding tumour metastasis were collected. One case had disseminated UM with liver involvement diagnosed at death, so was not included for analysis. Of the remaining 17 cases, 16 had died by the censor date. Liver involvement occurred in 16 of the 17 cases. The median time to metastasis was 3.3 years, but metastases were diagnosed up to 10.1 years after diagnosis of UM. Median survival time from date of diagnosis of metastasis was just 3.1 months in the 17 patients, with a range of 1 day to 14.3 years.

Discussion

This study's 5-year relative survival estimate of patients with UM is comparable to that reported in the United States[8], but more optimistic that the estimates provided in Danish[15], Finnish[16], European[17] and British[18] studies. The differences in the rates may be at least in part due to disparities between countries in the reporting practices to the relevant registries. Interestingly, in a worldwide population based study[19] comparing relative survival from major

cancers across 5 continents, Australian patients were found to have significantly better survival in all the studied cancers than Europe as a whole, and was found to have more favourable survival than the UK when it is considered in isolation. When compared to North America, Australia had very similar relative survival rates for all but one of the major cancers analysed. Hence the results and inter-country comparisons of survival estimates for UM in this study seem to parallel that for most major cancers.

The results from multivariate Cox models showed that tumours at the ciliary body bestowed a significantly increased rate of death from all causes when compared to all other tumours (including iris melanomas and those tumours for which site sub-classification was not achieved). Ciliary body involvement has been associated with increased mortality in a number of other studies[20]. When McLean et al.[21] investigated survivorship according to tumour location it was shown that in their series of patients, ciliary body involvement was determined by the location of the anterior tumour margin, and that the greater rate of tumour-related mortality was for the most part attributable to their larger size and more malignant cytology. Ciliary body tumours are more likely to be diagnosed later due to their location and hence, are larger at presentation.

Tumour apical height and histology exerted a demonstrable independent effect on survival. Tumour thickness was categorised as a high risk clinical prognostic factor in a review of prognostic parameters undertaken by Mooy and De Jong[20]. Tumour LBD was not a significant predictor in our multivariate analysis, which agrees with Mooy and De Jong's suggestion that tumour thickness is a more reliable prognostic parameter. Unfortunately, the limited number of cases for which tumour dimensions were obtained meant that categorisation according to the COMS criteria of tumour size would have rendered comparisons between the groups unreliable. This of course makes more extensive inter-study comparison difficult.

Any tumour that comprised a component of epithelioid-cell morphology appeared to be associated with increased mortality, with the relative survival table showing that spindle-cell melanomas were associated with better survivorship. However, the number of cases with histological data was too small to show that its trend towards better survival was significant.

On inspection of the survival data presented in our study the group of cases for which tumour diameter information was not obtained had similar relative survival trends to the >10mm tumour diameter group. An explanation for this is that accurate tumour measurements may have been less likely to be recorded for larger-sized tumours, particularly where enucleation is considered as the primary treatment. Unlike enucleation, conservative therapies including local excision or plaque brachytherapy require an accurate description of tumour dimensions. Thus tumour diameter information is more likely to be complete for smaller tumours as they are more likely to be treated by conservative methods. This would create in the "unknown" group, a profile of tumour diameter that would closer resemble that of the ">10mm" group.

The finding of poorer survival outcomes for patients diagnosed in more recent calendar periods and after undergoing enucleation is most likely a reflection of the use of enucleation as primary treatment in earlier time periods but more of a last resort treatment in more recent calendar periods. We could not confirm this hypothesis by estimating tumour stage at enucleation due to the lack of tumour details for a large number of patients, a limitation of this study. An interesting observation was that patients diagnosed 1990-1997 who did not undergo enucleation tended to have poorer survival outcomes. Most other comparable studies show little to no change in survival rates over time[8, 15, 17, 18], with the Swedish study[22] reporting an improvement in survival rates with diagnosis in more recent time periods.

In the 17 cases where metastasis was diagnosed before death, median survival time was 3.1 months. The identification of metastatic cases in our series of patients was somewhat crude

and incomplete such that our study probably identified more clinically obvious and progressive metastases. Thus it is not representative of survival in those patients with metastatic disease.

Case identification in this study is likely to have been incomplete, particularly for smaller melanomas of the uvea which are more likely to have been treated by more conservative methods including transpupillary thermotherapy and laser photocoagulation. Such treatments can be carried out as part of routine consultations in ophthalmology clinics across the state. This puts these cases at risk of non-notification to the Western Australia Cancer Registry and at risk of non-assessment at a major metropolitan teaching hospital. This may weaken the ability to extend the results of our study to those patients with a small UM.

Our data could not fully explain the survival disadvantage that was bestowed by being diagnosed in more recent time periods for patients who underwent enuclation. It is likely that enucleation has only been performed for more advanced tumours in the later years. More adequate completion of data fields for many of the covariates investigated in our study may reveal a time-dependent change that could explain the paradoxical trend over time. Another possible explanation for this observation is a change in notification practices over time.

In future, it is likely that clinicopathological features of uveal melanoma will assume lesser significance in clinical management. Recent developments in prognostic testing in uveal melanoma include the identification of cytogenetic markers, gene expression profiling, and the identification of specific driver mutations. Such discoveries offer the prospect of targeted therapy to those patients at greatest risk of metastatic disease and death.[23, 24]

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Table 1. Summary characteristics of the overall cohort (n=308) and tests for equality of survivorship function for each characteristic.

	Total cases		Alive		Died		Log-rank
	N	%	N	%	N	%	p-value
Age at diagnosis							
<50 years	82	26.6	65	43.3	17	10.8	<0.001
50-60 years	68	22.1	42	28.0	26	16.5	
61-70 years	78	25.3	29	19.3	49	31.0	
>70 years	80	26.0	14	9.3	66	41.8	
Year of diagnosis							
1981-1989	88	28.6	33	22.0	55	34.8	0.123
1990-1997	103	33.4	40	26.7	63	39.9	
1998-2005	117	38.0	77	51.3	40	25.3	
Sex							
Male	162	52.6	80	53.3	82	51.9	0.789
Female	146	47.4	70	46.7	76	48.1	
Tumour site							
Choroid	229	74.4	113	75.3	116	73.4	0.156
Ciliary	33	10.7	12	8.0	21	13.3	
Iris /Unknown	46	14.9	25	16.7	21	13.3	
Largest basal diameter							
<=10mm	69	22.4	40	26.7	29	18.4	0.083
>10mm	79	25.6	45	30.0	34	21.5	
Unknown	160	51.9	65	43.3	95	60.1	
Apical height							
<=5mm	59	19.2	36	24.0	23	14.6	0.187
>5mm	80	26.0	45	30.0	35	22.2	
Unknown	169	54.9	69	46.0	100	63.3	
Histology							
Epitheliod	15	4.9	2	1.3	13	8.2	<0.001
Spindle	87	28.2	40	26.7	47	29.7	
Mixed	49	15.9	16	10.7	33	20.9	
Unknown	157	51.0	92	61.3	65	41.1	
Brachytherapy							
No	240	77.9	99	66.0	141	89.2	0.027
Yes	68	22.1	51	34.0	17	10.8	
Enucleation							
No	133	43.2	78	52.0	55	34.8	0.003
Yes	103	56.8	72	48.0	103	65.2	
Total	308		150		158		

Table 2. Relative survival proportions alive at 3, 5 and 10 years post diagnosis for the uveal melanoma cohort (n=308) stratified by demographic and tumour characteristics and estimated using the Ederer II method.

	3 years		5 years		10 years	
	%	95% CI	%	95% CI	%	95% CI
Age at diagnosis						
<50 years	99	92 - 100	93	84 - 97	83	72 - 91
50-60 years	95	86 - 99	83	70 - 91	72	56 - 84
61-70 years	80	68 - 88	74	61 - 84	64	48 - 78
>70 years	78	65 - 89	74	59 - 87	62	42 - 83
Year of diagnosis						
1981-1989	91	81 - 97	88	78 - 96	85	71 - 95
1990-1997	86	76 - 93	76	64 - 85	62	49 - 74
1998-2005	88	79 - 94	80	70 - 88	67	50 - 81
Sex						
Male	87	80 - 93	80	72 - 87	71	60 - 81
Female	89	82 - 95	82	73 - 89	71	60 - 81
Tumour site						
Choroid	91	86 - 95	84	77 - 89	73	63 - 81
Ciliary	75	55 - 89	64	43 - 80	57	35 - 76
Iris /Unknown	83	66 - 94	79	61 - 92	73	51 - 90
Largest basal diameter						
<=10mm	100	90 - 103	103	92 - 107	89	72 - 103
>10mm	87	76 - 95	75	62 - 85	69	54 - 82
Unknown	84	76 - 90	75	66 - 82	65	54 - 75
Apical height						
<=5mm	97	86 - 102	95	82 - 103	82	62 - 98
>5mm	91	81 - 98	86	74 - 94	77	61 - 90
Unknown	83	76 - 89	74	65 - 81	65	55 - 74
Histology						
Epitheliod	75	42 - 95	58	26 - 85	34	8 - 72
Spindle	93	83 - 99	89	78 - 97	70	55 - 83
Mixed	75	59 - 86	59	43 - 73	50	34 - 66
Unknown	91	84 - 96	86	77 - 92	83	72 - 92
Brachytherapy						
No	85	75 - 90	77	70 - 83	68	59 - 76
Yes	96	85 - 100	92	79 - 99	70	49 - 87
Enucleation						
No	89	80 - 94	81	71 - 89	75	62 - 86
Yes	87	80 - 92	79	71 - 86	65	55 - 75

Figure 1: Relative Survival by Tumour Histology

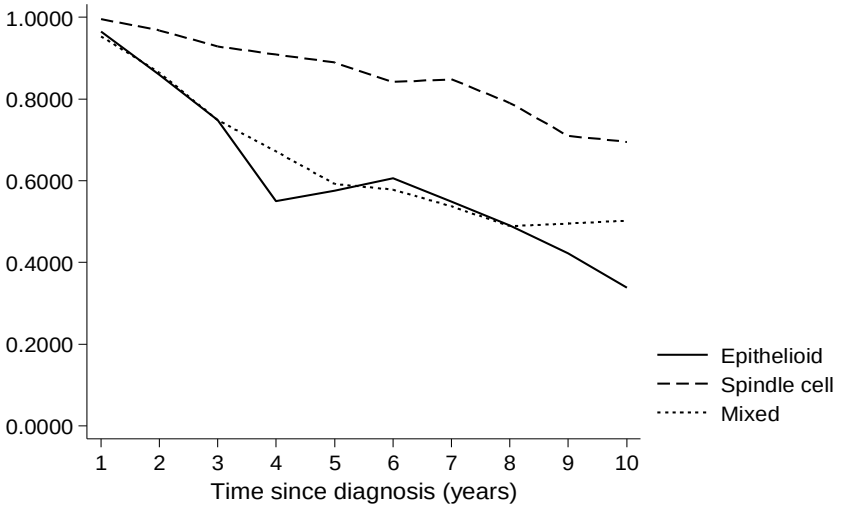

Table 3. Relative rates of death in the uveal melanoma cohort as estimated from a multivariate Cox regression model with enucleation status entered as a time-dependent covariate and as an interaction term with diagnosis period.

	Hazard ratio	95% CI	p-value
Age at diagnosis			
< 50 years	1	ref	
50-60 years	2.1	1.1-3.9	0.023
61-70 years	4.6	2.6-8.1	<0.001
>70 years	7.7	4.4-13.5	<0.001
Morphology			
Spindle	1	ref	
Epitheliod	1.6	0.8-3.1	0.204
Mixed	2.1	1.3-3.5	0.002
Unknown	1.1	0.7-1.8	0.574
Apical height			
<5 mm	1	ref	
>5 mm	1.9	1.1-3.3	0.026
Unknown	2.1	1.2-3.6	0.001
Site			
Choroid	1	ref	
Ciliary	1.7	1.1-2.9	0.029
Iris or unknown	1.0	0.6-1.6	0.945
Brachytherapy			
No	1	ref	
Yes	0.9	0.5-1.8	0.813
No enucleation			
1981-1989	1	ref	
1990-1997	2.0	1.1-4.0	0.036
1998-2005	1.0	0.4-2.4	0.955
After enucleation			
1981-1989	1	ref	
1990-1997	1.8	1.1-3.0	0.024
1998-2005	2.3	1.3-4.0	0.004