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Survival from uveal melanoma in England and Wales 1986 to 2001

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ABSTRACT

Purpose. To analyse survival from uveal melanoma diagnosed in England and Wales during 1986-1999 and followed up to 2001.

Methods. Data from the National Cancer Registry at the Office for National Statistics were analysed. The data were compiled from population-based cancer registries covering all of England and Wales for all adults (aged 15-99) diagnosed with primary ocular malignancy, excluding eyelid tumours. Level of poverty was based on the national classification of area of residence at time of diagnosis. Regression models explored the influence of sex, age and level of poverty on relative survival for patients diagnosed with uveal melanoma during successive calendar periods.

Results. Of 5,519 adults identified with primary ocular malignancy, 4,717 had melanoma, of which 4,308 (91%) were eligible for analysis. Two-thirds (67%) of the ocular melanomas were uveal, 5% conjunctival and 2% orbital; the sub-site was unspecified in 26%. Relative survival from uveal melanoma was 95% at one year and 72% at five years. There was no statistically significant variation in one-year or five-year survival by sex or poverty level, and no significant trend over time. Older patients had significantly worse survival ($P<0.001$).

Conclusions. This study provides national population-based survival estimates for England and Wales for uveal melanoma, the most common primary intraocular malignancy in adults. Five-year relative survival, an important indicator of the quality of cancer care, has not improved since the 1980s. Greater age, but not gender or level of poverty, is associated with a poorer prognosis. A standardised classification of uveal melanoma is required to improve reporting to cancer registries. Further research is required to explore reasons for lower relative survival in older persons.

BACKGROUND

Uveal melanoma is the most common primary ocular malignancy in adults. Worldwide, the highest incidence rates of uveal melanoma are observed in Northern Europe and Australia and the lowest in Asian, Hispanic and black populations.[1]

Uveal melanoma is important not only because of its uncertain prognosis - an estimated 40% of patients with posterior melanoma develop liver metastases within ten years, for which there is currently no effective treatment[2] - but also because loss of an eye and vision has a severe adverse impact on the quality of life.[3]

Epidemiological, clinical and histological indicators of poor prognosis for patients with uveal melanoma have been identified. These include older age, but not gender,[4] large tumour diameter, anterior location involving the ciliary body, extraocular extension, histopathological type and cytogenetic abnormalities, monosomy 3 being associated with a particularly poor prognosis.[5, 6]

Treatment for uveal melanoma has changed over the past twenty years. Current management favours preservation of the eye rather than enucleation, and includes brachytherapy, proton beam radiotherapy, trans-scleral local resection, endoresection, trans–pupillary thermotherapy and photocoagulation. The choice of treatment modality appears not to affect survival,[7-9] but quality of life may be improved by preserving the eye and useful visual function.

In the UK, four diagnostic, monitoring and treatment centres for ocular oncology were established in 1997 to provide specialised services for all suspected eye cancers, with the aim of improving survival and quality of life.[10]

The percentage of patients surviving at least five years is an important indicator of the outcome of cancer care.[11] The aim of this study was to examine population-based survival trends from uveal melanoma in England and Wales. A regional cancer registration system has covered these populations since 1962. The regional registries collect and collate data on individual patients from multiple sources, and a standard dataset is submitted to the national cancer registry at the Office for National Statistics. We have examined survival trends for patients diagnosed with uveal melanoma during 1986-1999 and followed up until 2001.

MATERIALS AND METHODS

We examined data compiled by the Office for National Statistics from the nine population-based cancer registries covering England and Wales for all adults (15-99 years) who were diagnosed with a primary invasive ocular cancer, excluding cancer of the eyelid, during the period 1986-1999. The Office for National Statistics provided information from the NHS Central Register on the vital status of each patient (alive, emigrated, dead, not traced) as at 31 December 2001. Among the 5,519 cases, 5000 (91%) were retained for analysis. Cases were excluded mainly because of unknown vital status (2.7%), 'zero survival' (3.3%), or previous primary cancer (2.7%). Almost all cases with 'zero survival' represent cancer registrations made solely from a death certificate, for which the date of diagnosis is not available. For "death certificate only" registrations, the date of death is taken as the date of diagnosis for incidence purposes, but survival time is then zero by definition, and such cases must be excluded from survival analysis.

Morphology was coded to the second revision of the International Classification of Diseases for Oncology (ICD-O-2,[12] codes 8720-8790). This category includes both microscopically verified and clinically diagnosed tumours. Anatomic localisation was coded to ICD-9[13] and ICD-10.[14] The ICD rubrics for 'eye' (190 in ICD-9 and C69 in ICD10) include adnexae such as lacrimal gland and duct, and orbital tumours as well as tumours of the globe. Tumours

were grouped by anatomic site as choroid (190.6, C69.3), ciliary body and iris (190.0, C69.4), retina (190.5, C69.2), conjunctiva (190.3, C69.0), cornea (190.4, C69.1), lacrimal gland (190.2-3; C69.5), orbit (190.1, C69.6), other (190.8, C69.8) and unspecified site (190.9, C69.9). Melanomas coded as retinal are most likely to have originated in the choroid and were therefore recoded as such, similarly tumours coded as corneal were recoded as of conjunctival origin. Uveal melanomas were defined as tumours coded to choroid, retina or ciliary body and iris, and with melanoma morphology. Tumours identified as conjunctival, lacrimal, orbital, or of other or unspecified site were not included in the analysis.

Poverty level (deprivation) and background mortality

Each patient was assigned to one of five categories of socio-economic deprivation based on the electoral ward of residence at diagnosis, the smallest geographic unit for which adequate data were available over the entire period 1986-99. For patients diagnosed during 1986-95, wards were assigned to quintiles of the Carstairs score, derived from the 1991 Census for both England and Wales. Not all the variables used to construct the Carstairs score (overcrowding, male unemployment, low social class, and no car) were available from the 2001 Census.[15] For patients diagnosed during 1996-99, wards were therefore assigned to quintiles of the income domain score, a sub-component of the Indices of Multiple Deprivation (IMD) 2000 for England,[16] combined with the comparable (although not precisely equivalent) version available for Wales.[17]

Background mortality was represented by life tables containing all-cause mortality rates by single year of age at death (up to 99 years), sex and level of poverty. The life tables were derived from the numbers of deaths in each electoral ward (England) or electoral division (Wales) for the periods 1990-92 and 1997-99. Population denominators for the 1990-92 life tables were derived from the 1991 census.[18] For 1997-99, estimated population counts for 1998 were used,[19] with the age-sex structure of the 2001 Census[20] in each Local Authority

applied to its constituent wards or divisions.[21] Each electoral ward or division was categorised by poverty level, and the data pooled by poverty level to enable construction of national life tables for each of five levels of poverty.

Statistical methods

Relative survival was used as the outcome measure. It is the ratio of the observed survival of the cancer patients and the survival that would have been expected if they had only had the same death rates by age, sex, poverty level and calendar period as the general population. Relative survival compensates for background mortality, the competing risk of death from other diseases, to which cancer patients are also subject,[22] and which differs widely by age, sex and poverty. It is the accepted method for reporting population-based cancer survival. It has the advantage of not requiring knowledge of the underlying cause of death, which is often inaccurate or contested.[4]

Relative survival estimates were derived with a maximum likelihood approach developed for individual data.[23] Differences or trends in survival across categories of covariates were assessed with variance-weighted least-squares regression, and their significance evaluated with two-tailed tests. Generalised linear regression[24] was used to model the excess mortality of the uveal melanoma patients over the background mortality, in order to explore the independent impact of age, sex and poverty level on relative survival. Such models enable us to compare the excess risk of mortality between patients with different covariate values, such as males and females, after adjusting for differences in their background mortality. Both approaches were applied with STATA algorithms.[25] Analyses were done both for the first year after diagnosis and, for those who survived at least one year, from the first to the fifth anniversary of diagnosis. The main and modifying effects of each factor were assessed with likelihood ratio tests.

RESULTS

Most malignant ocular tumours (4,308, 86%) were melanomas (Table 1); fewer than 8% of tumours were of unspecified clinical or histological diagnosis. Of the malignant melanomas, 2,876 (67%) were of uveal tract origin, 6% at other sites and 27% at an unspecified sub-site. Of the non-uveal melanomas, 197 (5% of the total) were conjunctival, 75 (2%) orbital and one lacrimal. The proportion of ocular melanomas of unspecified sub-site fell from 42% for those diagnosed during 1986-1990 to 19% for 1996-1999.

The median age at diagnosis for adults with uveal melanoma was 64 years (interquartile range 53-73). Men represented 52% of cases. For patients diagnosed with uveal melanoma over the entire period 1986-99, overall relative survival rates were 95% at one year and 72% at five years (Table 2). For uveal melanoma, there is a steep and significant decline in both one-year and five-year survival with age at diagnosis. Five-year survival ranged from 84% in the youngest adults (15-49 years) to 64% for the oldest (80-99 years). By contrast, survival did not vary significantly over time, between men and women or between poverty categories.

Age has a strong independent effect on the excess risk of death within five years of diagnosis of uveal melanoma, after adjustment for period of diagnosis, sex and level of poverty, and for the background risk of death (Table 3). Compared with patients aged 15-49 years at diagnosis (referent category) the relative excess risk for the first year of follow-up increases significantly from 2-fold in patients aged 50-59 to 5-fold in those aged 80 and over, and the risk increased by an average 1.44-fold between each of the five successive categories of age. This trend, using variance-weighted least-squares regression, was significant ($p<0.001$). After the first anniversary of diagnosis, the impact of age on the relative excess risk of death appears less marked, rising only to 2.6-fold in those aged 80 and over, and the average increase between successive age bands is also smaller, at 1.28-fold ($p<0.001$). However, the trend across age bands in the excess risk of death within the first year after diagnosis

compared with the trend in subsequent years is not statistically significantly different (p=0.72). Period of diagnosis, sex, and level of poverty had little independent association on either short-term or long-term relative survival.

DISCUSSION

Five-year relative survival for uveal melanoma in our study (72.4%) is lower than suggested for the USA by data from the Surveillance, Epidemiology and End Results (SEER) database which covered 14% of the USA population for this period. In the USA, survival was between 77% and 84% for cases diagnosed during the period 1973-1993 although, as in our study, survival did not vary by calendar period of diagnosis.[8] The differences may be partly attributable to how clinicians in different countries classify uveal melanoma and report to the cancer registries. It should be noted, however, that survival in the USA is higher than in the UK for most major cancers, with the exception of stomach cancer and childhood cancers.[26-29] Whilst case mix explains some of these differences for adult cancers, differences in the organisation of health care and in treatment are also contributing factors. Further, the SEER results may not be fully representative of the USA population. Our results are similar to those from Sweden, where five-year relative survival for patients diagnosed during 1990-1998 was 70.1%, but this was significantly higher than for those diagnosed 20 years earlier, between 1960-1969.[4] The incidence of uveal melanoma decreased during this period, so earlier detection is unlikely to be the explanation for the survival trend in Sweden.[4] Similar trends have been observed in England and Wales for all malignancies of the eye (not just uveal melanoma), with five-year relative survival increasing from 60% to 70% in both sexes between 1971-1975 and 1986-1990.[30]

Diagnosis of uveal melanoma relies on ophthalmoscopy and ultrasonography; tissue diagnosis is only available following enucleation or local resection, or if needle aspiration biopsy is undertaken to resolve diagnostic uncertainty. The proportion of uveal melanomas verified

histologically has decreased over the past three decades, due to the treatment changes favouring eye-preserving therapies and in such cases, cancer registration is perforce based on a clinical diagnosis.[1] Distinguishing benign large choroidal naevi from malignant melanoma can be difficult clinically, with misclassification occurring in some cases. If there are systematic differences in classification between regions and countries, the survival statistics may be misleading. Work is in progress to develop a standard international classification, and this will be valuable to all eye cancer registries allowing a more detailed analysis of survival according to tumour type. [31]

Greater age at diagnosis was associated with reduced relative survival, consistent with the results from Sweden,[4] and the excess risk of death associated with age at diagnosis is more marked within the first year of follow-up. For many cancers, relative survival is lower in older persons.[32] Delayed diagnosis with more advanced tumour at presentation and consequently delayed treatment may explain the excess mortality with increasing age. There may also be treatment differences for elderly patients. Co-morbidity may influence treatment decisions or make treatment less effective: greater age at diagnosis was associated with significantly worse five-year survival in a recent randomised controlled trial of iodine-125 brachytherapy versus enucleation for medium-sized choroidal melanomas.[9]

In the UK, most uveal melanomas are detected by optometrists.[33] The older patient may attribute visual symptoms to ageing and thus delay attendance at an optometrist. Melanomas may also be mis-diagnosed as macular degeneration and not referred for further investigation until it is too late.[34] Larger tumours are associated with worse survival after enucleation or brachytherapy.[35-37] Reports from two specialised ocular oncology centres in the UK indicate that current primary treatment for uveal melanomas is usually an eye-conserving treatment,[38,39] with older patients almost twice as likely to need primary enucleation.[38] If older age is associated with an increased likelihood of enucleation then the excessive mortality in

our study in the first year following treatment may support the Zimmerman-Mclean-Foster hypothesis that enucleation may accelerate the dissemination of tumour cells.[40] However, current evidence suggests that a more likely explanation for increased post-enucleation mortality is that occult metastases are present at the time of diagnosis.[41, 42] Thus, the apparent survival differences may reflect that, with increasing age at diagnosis, tumours are likely to have been present for longer and may already have metastasised by the time of diagnosis. Early referral to specialist ocular oncology centres of all suspect tumours would allow prognostic staging and identify those at risk of early death. Future developments in adjuvant systemic therapies may justify treatment and improve survival in people at high risk of metastatic disease.

Poverty has been implicated as a risk factor for reduced survival in other cancers, and for ocular cancer patients diagnosed in the early 1980s, but the level of poverty was no longer significant for patients diagnosed between 1986 and 1990.[30] We did not find an association between survival from uveal melanoma and level of poverty for patients diagnosed during the period 1986-99. The Carstairs score could not be used to classify poverty level for the late 1990s, but its replacement by the income domain of the Indices of Multiple Deprivation is not likely to have influenced survival patterns by level of poverty.[43] Access to ophthalmic care may have improved since 1986, with earlier diagnosis and treatment improving survival, although this has not been shown for the improved detection of other chronic eye diseases. [44]

The strength of our study is that it provides population based survival estimates based on data collected from multiple sources, which include hospital departments (mainly pathology), hospices, general practitioners and death certificates and collated by the regional cancer registries. The ascertainment rate of the England and Wales cancer registries is high, with an estimated 90-95% completeness of registration within five years of diagnosis.[45] Population-

based estimates avoid the selection bias associated with survival estimates reported from specialist centres.

There are several limitations to our study. Benign lesions, such as choroidal naevi, eccentric disciform macular degeneration or choroidal haemangiomas may be mis-classified as uveal melanomas resulting in some over-estimation of survival from uveal melanoma.

Cases of unspecified sub-site (27%) were not included in analyses, so survival estimates may not include all uveal melanomas. If large uveal melanomas are more likely to be classified as of unspecified site, relative survival from uveal melanoma may be lower than we report, because greater tumour diameter is associated with worse prognosis. In the England and Wales registry data, specification of ocular sub-site improved with time, possibly reflecting improved diagnostic and treatment facilities at specialised regional ocular oncology centres. Improved reporting of sub-site may have influenced survival trends. If the improvement affected mainly larger tumours, a trend towards improved overall survival would be under-estimated. Conversely, if improved specification affected mainly smaller tumours, with a better prognosis, any survival trend would be overestimated.

Standardised coding and reporting to cancer registries of the anatomic localisation and stage for all uveal melanomas, particularly for tumours treated conservatively, for which tissue is not available for histological classification, would allow more reliable monitoring of trends in incidence and survival over time and between different geographic areas, and social groups.

Early referral of suspicious tumours to specialist oncology centres for accurate tumour staging, and if necessary, early treatment, should optimise outcomes following a diagnosis of uveal melanoma. Further research is required into the reasons for the relatively poor prognosis

in older persons, to confirm whether earlier diagnosis and treatment would indeed improve survival.

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Table 1: Distribution of malignant ocular tumours diagnosed in adults (15-99 years), England and Wales, 1986-1999[*]

	Morphology							
	Melanoma[†]		Non-melanoma		Unspecified		Total	
Localisation	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Uveal[‡]	2,876	66.8	30	9.7	191	50.1	3,097	61.9
Non-uveal[§]	292	6.8	230	74.0	81	21.3	603	12.1
Unspecified[‖]	1,140	26.5	51	16.4	109	28.6	1,300	26.0
Total	**4,308**	**100.0**	**311**	**100.0**	**381**	**100.0**	**5,000**	**100.0**

[*] 5000 (92%) malignant ocular tumours retained for survival analysis

[†] ICD-O2 codes 8720-8790

[‡] ICD-9 codes 190.0 (ciliary body and iris), 190.5 (retina), 190.6 (choroid);
ICD-10 codes C69.2 (retina), C69.3 (choroid), C69.4 (ciliary body and iris),

[§] ICD-9 codes 190.1 (orbit), 190.2 (lacrimal gland), 190.3 (conjunctival), 190.4 (cornea), 190.7 (lacrimal duct), 190.8 (other);
ICD-10 codes C69.0 (conjunctiva), C69.1(cornea),
C69.5 (lacrimal), C69.6 (orbit), C69.8 (other)

[‖] ICD-9 code 190.9 (unspecified); ICD-10 code C69.9 (unspecified)

Table 2: Relative survival (%) and 95% confidence interval (CI) up to 2001, uveal melanoma, adults (15-99 years) diagnosed 1986-99, England and Wales

	No. (%) of cases	One year	95% CI	p-value*	Five years	95% CI	p-value*
All patients	2,876 (100)	94.6	93.5 - 95.5		72.4	70.2 - 74.5	
Period of diagnosis							
1986-90	955 (33.2)	96.1	94.5 - 97.6	0.2	74.2	70.7 - 77.4	0.3
1991-95	1,076 (37.4)	93.1	91.3 - 95.0		69.7	66.1 - 73.0	
1996-99	845 (29.4)	94.8	92.9 - 96.7		72.9	65.8 - 77.4	
Men	1,482 (51.5)	94.0	92.3 - 95.3	0.3	72.3	69.1 - 75.2	0.7
Women	1,394 (48.5)	95.1	93.6 - 96.3		73.0	69.9 - 75.8	
Age group (years)							
15-49	556 (19.3)	98.2	96.6 - 99.1	<0.001	83.8	80.2 - 86.8	<0.001
50-59	587 (20.4)	96.5	94.4 - 97.8		74.5	70.2 - 78.2	
60-69	758 (26.4)	95.8	93.6 - 97.2		70.2	66.0 - 73.9	
70-79	678 (23.6)	94.3	91.4 - 96.2		66.6	61.2 - 71.5	
80-99	297 (10.3)	91.7	85.4 - 95.3		63.7	52.2 - 73.2	
Income quintile							
Most affluent	474 (16.5)	94.9	91.8 - 96.8	0.6	73.2	67.9 - 77.8	0.3
2	510 (17.7)	93.4	90.1 - 95.6		74.5	69.2 - 79.0	
3	584 (20.3)	95.1	92.3 - 96.8		72.3	67.4 - 76.6	
4	643 (22.4)	95.5	93.0 - 97.2		72.0	67.1 - 76.3	
Most deprived	665 (23.1)	93.7	91.0 - 95.5		70.5	65.6 - 74.9	

* for difference (two categories) or trend: variance-weighted least-squares regression

Table 3: Relative excess risk of death (RER)[*] within five years of diagnosis (and 95% CI), uveal melanoma, England and Wales, adults diagnosed 1986-99

	First year since diagnosis			p-value[†]	2nd-5th year since diagnosis			p-value[†]
	RER	95%	CI		RER	95%	CI	
Period of diagnosis								
1986-90	1.00				1.00			
1991-95	0.94	(0.56	- 1.59)		1.12	(0.91	- 1.39)	
1996-99	1.00	(0.59	- 1.72)	0.97	0.86	(0.67	- 1.11)	0.09
Men	1.00				1.00			
Women	0.84	(0.55	- 1.30)	0.41	0.90	(0.74	- 1.08)	0.25
Age at diagnosis (years)								
15-49	1.00				1.00			
50-59	2.00	(0.89	- 4.48)		1.67	(1.23	- 2.26)	
60-69	2.45	(1.12	- 5.36)		2.11	(1.59	- 2.81)	
70-79	3.38	(1.55	- 7.35)		2.42	(1.79	- 3.28)	
80-99	5.19	(2.19	- 12.31)	<0.001	2.57	(1.64	- 4.01)	<0.001
Income quintile								
Most affluent	1.00				1.00			
2	1.83	(0.91	- 3.69)		0.79	(0.58	- 1.09)	
3	1.11	(0.52	- 2.38)		0.84	(0.62	- 1.13)	
4	0.91	(0.40	- 2.06)		0.92	(0.69	- 1.23)	
Most deprived	1.19	(0.56	- 2.52)	0.28	0.95	(0.71	- 1.27)	0.57

[*] Adjusted for all variables in the table

[†] Likelihood ratio test