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CLINICAL STUDY

Differences in uveal melanomas between men and women from the British Isles

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Abstract

Purpose **The purpose of this study is to compare uveal melanomas (UMs) in men and women.**

Methods **The Liverpool Ocular Oncology Centre (LOOC) database was reviewed. Patients treated for UM at the LOOC between 1993 and 2010 were selected. Differences between sexes were identified using the χ^2-test for categorical variables and the Mann–Whitney test for continuous variables.**

Results **The 3380 patients comprised 1685 women and 1695 men. The tumours were considered clinically to have arisen in choroid in 89.5%, ciliary body in 5.3%, and iris in 5.2%. Tumours in women were less likely to originate in choroid (87.2 *vs* 91.7%; $P<0.001$) and showed more circumferential spread in ciliary body ($P<0.001$) and iris ($P=0.003$). Tumours in men were more likely to extend to within 3 mm of optic disc or fovea (46.3 *vs* 39.0%, $P<0.001$), showing more extensive optic-disc involvement ($P<0.001$). The median largest basal tumour diameter was 12.2 mm in men and 11.9 mm in women ($P=0.001$). The tumour thickness had a median of 4.4 mm and 3.8 mm in men and women, respectively ($P=0.015$). The 180 ciliary body tumours occurred in 112 women and 68 men. In these, the prevalence of extraocular spread was higher in women (19.6 *vs* 8.8%; $P=0.052$). The 175 iris melanomas were more common in women than men (103 *vs* 72, respectively).**

Conclusions **In men, UMs tend to be larger and more posterior than in women.**

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Keywords: uveal melanoma; gender; sex; histology; genetics

Introduction

Uveal melanomas (UMs) are rare, with an incidence of approximately six per million per year.[1] More than 90% of UMs involve the choroid. The age at diagnosis peaks at approximately 60 years.[1] Most patients present with visual symptoms.[2] In a significant minority of patients, the tumour is asymptomatic and detected on routine examination (eg, screening for diabetic retinopathy).[2]

Ocular treatment is aimed at conserving the eye and useful vision, and consists of various forms of radiotherapy, phototherapy, and surgical resection, which are administered individually or in combination.[3] About 30–40% of patients require enucleation.[4]

Approximately 50% of patients develop metastatic disease, which almost always involves the liver, and which is usually fatal within a year of becoming symptomatic. Predictors of metastatic death include the following: advanced clinical stage, histological features indicating high grade of malignancy, and genetic abnormalities, such as chromosome 3 loss.[5,6]

UMs affect both sexes in equal numbers, but males have been reported to show higher disease-specific mortality.[7,8] Lower survival rates in males have also been reported in cutaneous melanoma.[9] This is believed to correlate with more aggressive histology in males.[10] Males show higher rates of rhegmatogenous retinal detachment after trans-scleral local resection, and are more likely to require enucleation after proton-beam radiotherapy.[11,12] In view of such differences, there would seem to be scope for comparing UMs in males and females. Such investigation may provide insights into the biology of UMs and may help design outcomes analyses taking gender into account.

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The aims of this study were to compare UMs in men and women in terms of age at presentation, clinical features, histological findings, and genetic abnormalities.

Patients and methods

Inclusion and exclusion criteria

Patients were included in this study if diagnosed clinically as having a UM, if assessed at the Liverpool Ocular Oncology Centre (LOOC) between January 1993 and December 2010, and if they resided in the British Isles. The patients were identified by searching the LOOC database. Some patients with a clinically suspected UM were excluded because they were not treated, for example, if they were observed because of an uncertain diagnosis or if they declined therapy. These patients were excluded to reduce the chances of including naevi in the sample. A few patients (ie, less than 20) were excluded because they had received treatment before referral to the LOOC, and the primary method of treatment for their UM was not known. This problem tended to occur when the initial surgical procedure was recorded as biopsy. Eleven patients were excluded because of missing data on anterior or posterior extent, and two patients were excluded because they had bilateral UMs.

Clinical assessment

Clinical assessment included full ocular and systemic history and examination, including ocular B-scan ultrasonography. The likelihood of a clinical diagnosis of melanoma increased with the number of features suggestive of malignancy. For choroidal tumours, these were as follows: thickness exceeding 2 mm, basal tumour diameter exceeding 10 mm, serous retinal detachment, lipofuscin (ie, 'orange pigment'), and/or a collar-stud shape. In the case of ciliary body tumours, malignancy was suspected if the tumour exceeded 2 mm in diameter and/or showed invasion into the anterior chamber or extraocularly (although these features can occur with melanocytoma). With iris melanocytic tumours, signs of malignancy were considered to be as follows: basal diameter exceeding 3 mm, thickness exceeding 1 mm, tumour vascularity, seeding, and diffuse spread. With all tumour locations, documented growth was considered indicative of melanoma. In some cases, the diagnosis was established by aspirational, incisional, or excisional biopsy.

Tumours were classified clinically according to their most likely site of origin within the uvea, which was determined by their 'centre of gravity'. As the site of origin was not always identifiable, we also analysed anterior and posterior tumour margins. Choroidal tumours were categorised as involving the ciliary body if they extended anterior to the ora, and any tumour was categorised as involving the anterior chamber if visible in the iris or angle on slit-lamp examination.

With few exceptions, all patients were assessed at LOOC by the first author (BED), who also performed the ultrasonography. Ethics Committee approval was obtained (Number 11/NW/0179). The study was conducted in accordance with the 'Declaration of Helsinki'.

Histological assessment

Histological examination was performed on all eyes that were treated by enucleation or local resection, and those that were biopsied. Until 2002, tumour specimens were routinely fixed in glutaraldehyde. After that date, buffered formalin was used. Histology was performed using sections stained with haematoxylin and eosin and, if necessary, immunohistochemistry using Melan A. Melanomas were categorised as being of spindle-cell, epithelioid, or mixed type, using the modified Callender system. They were recorded as having epithelioid cells irrespective of the proportion of such cells in the tumour. From 1994 onwards, extravascular matrix patterns were assessed so as to identify closed connective tissue loops, and this was done using the periodic-acid-Schiff reagent, without counterstaining. Mitoses were counted in 40 high-power fields ($\times$ 40 objective) in haematoxylin and eosin sections. Extraocular extension was recorded as being present whether this was noted clinically or on pathological examination.

Genetic studies

We analysed tumours for chromosome 3 loss, chromosome 6p gain, and chromosome 8q gain. These studies were performed using microsatellite analysis between 1999 and 2000, fluorescence *in situ* hybridisation between 1999 and 2007, and with multiplex ligation-dependent probe amplification from 2006 onwards, with some overlap of techniques during transition periods.[5,13,14] These tests were routinely performed on fresh tumour samples.

Statistical methods

Clinical, histological, and genetical data were documented synoptically on paper forms in the patients' casenotes and were computerised prospectively using a customised database. Data analysis was performed using a statistical programme (SPSS, SPSS Inc., Chicago, IL, USA). Correlations between baseline factors and sex

were analysed using the χ^2-test (without Yates's adjustment) for categorical variables, and with the Mann–Whitney test for continuous variables. A *P*-value of less than 0.05 was considered to be statistically significant. All statistical tests were two-sided.

Results

All tumours

The 3380 patients comprised 1685 (49.9%) women and 1695 (50.1%) men, with a median age of 61.4 years (range 7.3–96.9; Table 1). Referral was from England in 2458 patients, Ireland in 294 patients, Wales in 293 patients, Scotland in 215 patients, and Northern Ireland in 120 patients. In men, the tumour was considered to originate in choroid in 1555 (91.7%) patients, the ciliary body in 68 (4.0%) patients, and in the iris in 72 (4.2%), whereas in women, the tumour appeared to originate in choroid in 1470 (87.2%) patients, the ciliary body in 112 (6.6%), and the iris in 103 (6.1%; χ^2-test, $P<0.001$). The anterior tumour margin extended anterior to ora serrata in 33.8% of women and in 26.3% of men (χ^2-test, $P<0.001$), with women showing greater involvement of ciliary body (Mann–Whitney, $P<0.001$) and iris (Mann–Whitney, $P=0.004$; Table 2). The posterior tumour margin extended to within 3 mm of optic disc or fovea in 39.0% of women and 46.3% of men (χ^2-test, $P<0.001$), with the extent of optic-disc involvement being greater in men than women (Mann–Whitney, $P<0.001$). The median largest basal tumour diameter was 12.2 mm in men and 11.9 mm in women (Mann–Whitney, $P=0.001$), whereas the tumour thickness had a median of 4.4 and 3.8 mm in men and women, respectively (Mann–Whitney, $P=0.015$). No significant differences were found in age, laterality, initial visual acuity, angle involvement, coronal location, sagittal location, presence of extrascleral tumour extension, histology, and tumour genetic abnormalities (Tables 1–3).

Choroidal melanoma

Of the 3025 choroidal melanomas, 1470 (48.6%) affected women and 1555 (51.4%) occurred in men. The anterior tumour margin extended anterior to ora serrata in 24.1% of women as compared with 19.7% of men (χ^2-test, $P=0.012$). The posterior tumour margin extended to within two disc diameters of the optic disc in 44.6% of women and 50.5% of men (χ^2-test, $P<0.001$). Optic-disc involvement was more extensive in men (Mann–Whitney, $P=0.003$). Tumours in men also tended to have a wider base (Mann–Whitney, $P=0.009$), a greater height (Mann–Whitney, $P=0.005$), and therefore, a more advanced TNM size category (T3 or T4 in 35.1% men *vs* 20.2% women; χ^2-test, $P=0.013$). Perforation of Bruch's membrane with development of a collar-stud tumour shape was more common in men (14.6% in men *vs* 11.4% in women; χ^2-test, $P=0.008$). The prevalence of tumours with epithelioid melanoma cells was higher in men (64.3 *vs* 58.6%; χ^2-test, $P=0.027$; Table 3). There were no significant differences in the prevalence of chromosome 3, 6p, and 8q abnormalities between the two sexes.

Ciliary body melanoma

The 180 ciliary body tumours occurred in 112 (62%) women and 68 (38%) men. Circumferential and antero-posterior extent did not show significant differences between the two sexes. There were also no significant differences in tumour dimensions, histological findings, or genetic results.

Iris melanoma

The 175 iris melanomas were more common in women than in men (ie, 103 *vs* 72, respectively). The only significant difference was in the age at presentation, which was slightly greater in men than women (median, 56.4 *vs* 51.8 years; Mann–Whitney, $P=0.039$). No significant differences were found in tumour dimensions, extent, and histology. The number of tumours examined genetically was too small for statistical analysis.

Discussion

This study found that UMs tended to more posterior in men than in women so that the tumour was more likely to involve the optic disc in men, and tended to show greater involvement of ciliary body and iris in women. Choroidal tumours in men tended to be larger and were more likely to rupture Bruch's membrane, and contain epithelioid cells. Men with iris melanoma tended to present at an older age; otherwise, there were no significant sex differences in iris and ciliary body melanomas, possibly because of smaller sample sizes. Interestingly, no significant differences were found in genetic tumour type.

The main strengths of the study are the large number of patients and the fact that almost all clinical and ultrasonographical examinations were performed by the same surgeon (BED). Another strength is that virtually all the data were collected and computerised prospectively. To our knowledge, no other studies have investigated these factors in such detail and on such a large number of cases. The large number of patients made it possible to perform correlations according to the uveal structure in which the tumour arose, thereby enhancing

Table 1 Patient age, visual acuity, tumour location and size

Variable	*Category*	*All*							*Choroid*							*Ciliary body*							*Iris*						
		Total		*Sex*					*Total*		*Sex*					*Total*		*Sex*					*Total*		*Sex*				
				Female		*Male*					*Female*		*Male*					*Female*		*Male*					*Female*		*Male*		
		Count	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*
Age	=<60 years	1543	45.7	760	45.1	783	46.2	0.694[a]	1346	44.5	640	43.6	706	45.4	0.181[a]	82	45.6	51	45.5	31	45.6	0.270[a]	115	65.7	69	67.0	46	63.9	0.039[a]
	>60 years	1836	54.3	924	54.9	912	53.8	—	1678	55.5	829	56.4	849	54.6	—	98	54.4	61	54.5	37	54.4		60	34.3	34	33.0	26	36.1	—
Eye	Left	1649	48.8	821	48.7	828	48.8	0.942	1494	49.4	723	49.2	771	49.6	0.532	73	40.6	46	41.1	27	39.7	0.856	82	46.9	52	50.5	30	41.7	0.25
	Right	1731	51.2	864	51.3	867	51.2	—	1531	50.6	747	50.8	784	50.4	—	107	59.4	66	58.9	41	60.3		93	53.1	51	49.5	42	58.3	—
Initial vision	6/5–6/12	2207	65.3	1122	66.6	1085	64.0	0.225	1938	64.1	960	65.3	978	62.9	0.3	119	66.1	75	67.0	44	64.7	0.754	150	85.7	87	84.5	63	87.5	0.597
	6/18–6/60	734	21.7	341	20.2	393	23.2	—	681	22.5	309	21.0	372	23.9	—	34	18.9	21	18.8	13	19.1	—	19	10.9	11	10.7	8	11.1	—
	3/60–CF	243	7.2	122	7.2	121	7.1	—	227	7.5	113	7.7	114	7.3	—	14	7.8	7	6.3	7	10.3	—	2	1.1	2	1.9	—	—	—
	HM–NLP	196	5.8	100	5.9	96	5.7	—	179	5.9	88	6.0	91	5.9	—	13	7.2	9	8.0	4	5.9	—	4	2.3	3	2.9	1	1.4	—
Origin	Choroid	3025	89.5	1470	87.2	1555	91.7	<0.001	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Ciliary body	180	5.3	112	6.6	68	4.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Iris	175	5.2	103	6.1	72	4.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Coronal location	Nasal	1260	37.3	635	37.7	625	36.9	0.876	1121	37.1	547	37.3	574	36.9	0.945	78	43.3	52	46.4	26	38.2	0.385	61	34.9	36	35.0	25	34.7	0.634
	Vertical	738	21.8	365	21.7	373	22.0	—	677	22.4	325	22.1	352	22.6	—	34	18.9	22	19.6	12	17.6	—	27	15.4	18	17.5	9	12.5	—
	Temporal	1380	40.9	683	40.6	697	41.1	—	1225	40.5	596	40.6	629	40.5	—	68	37.8	38	33.9	30	44.1	—	87	49.7	49	47.6	38	52.8	—
Sagittal location	Superior	1170	34.6	563	33.4	607	35.8	0.126	1098	36.3	519	35.3	579	37.2	0.335	57	31.7	35	31.3	22	32.4	0.623	15	8.6	9	8.7	6	8.3	0.665
	Horizontal	828	24.5	404	24.0	424	25.0	—	776	25.7	372	25.3	404	26.0	—	30	16.7	21	18.8	9	13.2	—	22	12.6	11	10.7	11	15.3	—
	Inferior	1381	40.9	717	42.6	664	39.2	—	1150	38.0	578	39.3	572	36.8	—	93	51.7	56	50.0	37	54.4	—	138	78.9	83	80.6	55	76.4	—
Basal diameter	<10 mm	906	27.2	478	28.9	428	25.6	0.001[a]	685	22.8	346	23.7	339	21.9	0.009[a]	79	45.7	49	46.2	30	44.8	0.671[a]	142	94.7	83	94.3	59	95.2	0.858[a]
	10–15 mm	1750	52.6	883	53.4	867	51.8	—	1677	55.8	837	57.3	840	54.4	—	65	37.6	41	38.7	24	35.8	—	8	5.3	5	5.7	3	4.8	—
	>15 mm	672	20.2	293	17.7	379	22.6	—	643	21.4	277	19.0	366	23.7	—	29	16.8	16	15.1	13	19.4	—	—	—	—	—	—	—	—
Thickness	=<3 mm	1475	44.1	768	46.3	707	42.0	0.015[a]	1277	42.4	659	45.0	618	39.8	0.005[a]	54	30.9	29	26.9	25	37.3	0.129[a]	144	94.1	80	90.9	64	98.5	0.340[a]
	4–6 mm	912	27.3	443	26.7	469	27.9	—	854	28.3	401	27.4	453	29.2	—	51	29.1	36	33.3	15	22.4	—	7	4.6	6	6.8	1	1.5	—
	>6 mm	956	28.6	449	27.0	507	30.1	—	884	29.3	404	27.6	480	30.9	—	70	40.0	43	39.8	27	40.3	—	2	1.3	2	2.3	—	—	—
TNM size category	T1	1211	36.4	638	38.6	573	34.2	0.006	987	32.9	507	34.7	480	31.1	0.013	78	45.1	47	44.3	31	46.3	0.953	146	97.3	84	95.5	62	100.0	0.235
	T2	1073	32.3	536	32.4	537	32.1	—	1035	34.5	512	35.1	523	33.9	—	34	19.7	20	18.9	14	20.9	—	4	2.7	4	4.5	—	—	—
	T3	743	22.3	352	21.3	391	23.4	—	691	23.0	319	21.9	372	24.1	—	52	30.1	33	31.1	19	28.4	—	—	—	—	—	—	—	—
	T4	300	9.0	127	7.7	173	10.3	—	291	9.7	121	8.3	170	11.0	—	9	5.2	6	5.7	3	4.5	—	—	—	—	—	—	—	—

Abbreviations: CF, counting fingers; HM, hand movements; NLP, no light perception.
[a]Mann–Whitney.

Table 2 Tumour extension antero-posteriorly, circumferentially, into retina and extraocularly

Variable	*Category*	*All*							*Choroid*							*Ciliary body*							*Iris*						
		Total		*Sex*					*Total*		*Sex*					*Total*		*Sex*					*Total*		*Sex*				
				Female		*Male*					*Female*		*Male*					*Female*		*Male*					*Female*		*Male*		
		Count	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*
Anterior margin	Ant. choroid	1019	30.2	467	27.7	552	32.6	<0.001	1019	33.7	467	31.8	552	35.5	0.012	—	—	—	—	—	—	0.784	—	—	—	—	—	—	—
	Post. choroid	1344	39.8	648	38.5	696	41.1	—	1344	44.4	648	44.1	696	44.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Ciliary body	591	17.5	326	19.4	265	15.6	—	552	18.3	301	20.5	251	16.1	—	39	21.7	25	22.3	14	20.6	—	—	—	—	—	—	—	—	—
	Ant. chamber	423	12.5	242	14.4	181	10.7	—	109	3.6	53	3.6	56	3.6	—	141	78.3	87	77.7	54	79.4	—	173	100.0	102	100.0	71	100.0	—
Angle spread	0 h	3025	90.7	1490	89.8	1535	91.5	0.088[a]	2889	96.8	1399	96.8	1490	96.9	0.932[a]	61	34.1	42	37.5	19	28.4	0.212[a]	75	42.9	49	47.6	26	36.1	0.115[a]
	1–4 h	241	7.2	134	8.1	107	6.4	—	81	2.7	40	2.8	41	2.7	—	89	49.7	56	50.0	33	49.3	—	71	40.6	38	36.9	33	45.8	—
	5–8 h	49	1.5	23	1.4	26	1.6	—	10	0.3	4	0.3	6	0.4	—	15	8.4	6	5.4	9	13.4	—	24	13.7	13	12.6	11	15.3	—
	9–12 h	22	0.7	13	0.8	9	0.5	—	3	0.1	2	0.1	1	0.1	—	14	7.8	8	7.1	6	9.0	—	5	2.9	3	2.9	2	2.8	—
Iris spread	0 h	2915	88.5	1426	87.0	1489	90.1	0.004[a]	2856	97.1	1387	97.1	1469	97.0	0.874[a]	59	33.5	39	35.5	20	30.3	0.704[a]	—	—	—	—	—	—	0.677[a]
	1–4 h	347	10.5	198	12.1	149	9.0	—	80	2.7	38	2.7	42	2.8	—	103	58.5	63	57.3	40	60.6	—	164	94.3	97	95.1	67	93.1	—
	5–8 h	19	0.6	9	0.5	10	0.6	—	5	0.2	2	0.1	3	0.2	—	7	4.0	3	2.7	4	6.1	—	7	4.0	4	3.9	3	4.2	—
	9–12 h	11	0.3	7	0.4	4	0.2	—	1	0.0	1	0.1	—	—	—	7	4.0	5	4.5	2	3.0	—	3	1.7	1	1.0	2	2.8	—
Ciliary body spread	0 h	2827	84.7	1368	82.4	1459	86.9	<0.001[a]	2669	89.4	1279	88.5	1390	90.3	0.103[a]	19	10.6	10	8.9	9	13.2	0.300[a]	139	79.9	79	77.5	60	83.3	0.303[a]
	1–4 h	481	14.4	277	16.7	204	12.2	—	299	10.0	159	11.0	140	9.1	—	148	82.2	95	84.8	53	77.9	—	34	19.5	23	22.5	11	15.3	—
	5–8 h	30	0.9	14	0.8	16	1.0	—	17	0.6	8	0.6	9	0.6	—	12	6.7	6	5.4	6	8.8	—	1	0.6	—	—	1	1.4	—
	9–12 h	1	0.0	1	0.1	—	—	—	—	—	—	—	—	—	—	1	0.6	1	0.9	—	—	—	—	—	—	—	—	—	—
Posterior margin	Iris	142	4.2	81	4.8	61	3.6	<0.001	—	—	—	—	—	—	<0.001	—	—	—	—	—	—	0.819	142	81.1	81	78.6	61	84.7	0.312
	Ciliary body	109	3.2	72	4.3	37	2.2	—	—	—	—	—	—	—	—	73	40.6	47	42.0	26	38.2	—	33	18.9	22	21.4	11	15.3	—
	Ant. choroid	386	11.4	224	13.3	162	9.6	—	315	10.4	182	12.4	133	8.6	—	74	41.1	45	40.2	29	42.6	—	—	—	—	—	—	—	—
	Post. choroid	1301	38.5	651	38.6	650	38.3	—	1269	42.0	632	43.0	637	41.0	—	32	17.8	19	17.0	13	19.1	—	—	—	—	—	—	—	—
	≤3mm from D/F	990	29.3	469	27.8	521	30.7	—	989	32.7	468	31.8	521	33.5	—	1	0.6	1	0.9	—	—	—	—	—	—	—	—	—	—
	Involving disc	452	13.4	188	11.2	264	15.6	—	452	14.9	188	12.8	264	17.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Disc spread	0 h	2939	89.9	1492	91.8	1447	88.0	<0.001[a]	2600	88.7	1286	90.6	1314	87.0	0.003[a]	170	100.0	106	100.0	64	100.0	—	170	100.0	100	100.0	70	100.0	—
	1–4 h	155	4.7	63	3.9	92	5.6	—	155	5.3	63	4.4	92	6.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	5–8 h	119	3.6	45	2.8	74	4.5	—	118	4.0	45	3.2	73	4.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	9–12 h	57	1.7	26	1.6	31	1.9	—	57	1.9	26	1.8	31	2.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Collar-stud shape	No	2985	88.3	1517	90.0	1468	86.6	0.002	2631	87.0	1303	88.6	1328	85.4	0.008	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Yes	395	11.7	168	10.0	227	13.4	—	394	13.0	167	11.4	227	14.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Extraocular spread.	No	3176	94.0	1580	93.8	1596	94.2	0.633	2858	94.5	1393	94.8	1465	94.2	0.508	152	84.4	90	80.4	62	91.2	0.052	166	94.9	97	94.2	69	95.8	0.625
	Yes	204	6.0	105	6.2	99	5.8	—	167	5.5	77	5.2	90	5.8	—	28	15.6	22	19.6	6	8.8	—	9	5.1	6	5.8	3	4.2	—

Abbreviation: D/F, disc and/or fovea.
[a]Mann–Whitney.

Table 3 Histological and genetic findings

Variable	*Category*	*All*							*Choroid*							*Ciliary body*							*Iris*						
		Total		*Sex*					*Total*		*Sex*					*Total*		*Sex*					*Total*		*Sex*				
				Female		*Male*					*Female*		*Male*					*Female*		*Male*					*Female*		*Male*		
		Count	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*	*Count*	*Col (%)*	*Count*	*Col (%)*	*Count*	*Col (%)*	*P-value*
Epith. cells	No	607	37.3	297	39.5	310	35.4	0.084	556	38.3	268	41.4	288	35.7	0.027	34	27.4	21	28.0	13	26.5	0.858	17	34.0	8	27.6	9	42.9	0.261
	Yes	1020	62.7	454	60.5	566	64.6	—	897	61.7	379	58.6	518	64.3	—	90	72.6	54	72.0	36	73.5	—	33	66.0	21	72.4	12	57.1	
Closed loops	No	608	52.2	283	54.7	325	50.2	0.12	534	51.3	240	54.2	294	49.2	0.116	52	52.5	29	50.9	23	54.8	0.702	22	84.6	14	82.4	8	88.9	1.000
	Yes	557	47.8	234	45.3	323	49.8	—	506	48.7	203	45.8	303	50.8	—	47	47.5	28	49.1	19	45.2	—	4	15.4	3	17.6	1	11.1	
Mitoses/40 HPF[a]	1	331	26.8	150	27.1	181	26.6	0.638[b]	265	24.3	105	22.4	160	25.6	0.605[b]	31	30.7	22	37.3	9	21.4	0.635[b]	35	83.3	23	85.2	12	80.0	0.657[b]
	2–3	356	28.8	161	29.1	195	28.6	—	315	28.8	141	30.1	174	27.9	—	37	36.6	17	28.8	20	47.6	—	4	9.5	3	11.1	1	6.7	—
	4–7	294	23.8	122	22.0	172	25.3	—	276	25.3	113	24.1	163	26.1	—	18	17.8	9	15.3	9	21.4	—	—	—	—	—	—	—	—
	>7	254	20.6	121	21.8	133	19.5	—	236	21.6	109	23.3	127	20.4	—	15	14.9	11	18.6	4	9.5	—	3	7.1	1	3.7	2	13.3	—
Chromosome 3 loss	Absent	479	48.5	205	47.8	274	49.1	0.681	452	49.0	189	48.1	263	49.7	0.625	23	39.0	14	42.4	9	34.6	0.541	4	66.7	2	66.7	2	66.7	—
	Present	508	51.5	224	52.2	284	50.9	—	470	51.0	204	51.9	266	50.3	—	36	61.0	19	57.6	17	65.4	—	2	33.3	1	33.3	1	33.3	—
Chromosome 6p gain	No 6p gain	195	46.7	87	49.2	108	44.8	0.380	184	45.7	81	47.6	103	44.2	0.493	11	73.3	6	85.7	5	62.5	0.31	—	—	—	—	—	—	—
	6p gain	223	53.3	90	50.8	133	55.2	—	219	54.3	89	52.4	130	55.8	—	4	26.7	1	14.3	3	37.5	—	—	—	—	—	—	—	—
Chromosome 8q gain	No 8q gain	342	39.2	136	36.3	206	41.4	0.121	335	40.4	132	37.6	203	42.5	0.159	7	16.7	4	17.4	3	15.8	—	—	—	—	—	—	—	—
	8q gain	530	60.8	239	63.7	291	58.6	—	494	59.6	219	62.4	275	57.5	—	35	83.3	19	82.6	16	84.2	—	1	100.0	1	100.0	—	—	—

Gender correlations with: (a) baseline features and treatment, (b) tumour features and treatment, and (c) histological and genetical findings.
[a]High-power fields.
[b]Mann–Whitney.

interpretation of the results. For example, women showed more extensive iris involvement, because their tumour tended to be more anterior and not because it was larger.

Our study has several weaknesses. The main weakness is that many tumours were not examined histologically so that some small tumours may have been benign. However, because the diagnosis was based on widely accepted clinical features, and as the same criteria were used in both sexes, the number of misdiagnoses and the chances of bias are likely to be small. With larger numbers of iris and ciliary body tumours, more of the variables may have shown a statistically significant difference between the sexes. Failure to detect genuine sex differences may also have occurred with rare features, such as retinal perforation. Conversely, because of the large number of analyses, it is possible that some of the differences may have been due to chance. Methods of genetic testing changed during the course of this study, but any resulting variations are likely to have affected both sexes equally. In some patients, it was difficult to determine clinically whether the tumour originated in choroid or ciliary body, or in ciliary body or iris, but the reporting of antero-posterior tumour extent should have mitigated this problem.

We are unable to explain why UMs tended to be larger in men than in women. One would have expected men to have smaller tumours than in women, because of the relatively posterior extension, which should have facilitated detection and caused visual disturbances sooner, being closer to fovea; however, this was not the case. We plan to correlate tumour features with mode of presentation. An investigation on cutaneous melanoma suggests that the increased Breslow thickness in men reflects more aggressive tumour growth because their tumours show higher grade of malignancy than melanomas in women.[10] In our study, choroidal melanomas were more likely to show epithelioid cells in men than in women ($P = 0.027$); however, the mitotic count showed no significant difference between sexes. The relatively large size and the higher prevalence of epithelioid cells in men may have occurred because of a longer delay before treatment, or the larger tumour size in men may have been due to more rapid growth of epithelioid melanoma, without a demonstrable increase in the mitotic count.

We are also unable to explain why UMs in men tend to be more posterior than in women. This seems to be a genuine finding, supported by data showing more extensive optic-disc involvement in men and more extensive ciliary body involvement in women. Furthermore, in a study correlating tumour thickness with metastasis, choroidal melanomas were slightly more common in men (51 *vs* 49%), whereas ciliary body and iris melanomas were more common in women (41 *vs* 59% and 48 *vs* 52%, respectively).[15]

A surprising and unexplained finding of the current study was that, although the overall incidence of extraocular melanoma extension was the same in males and females, ciliary body melanomas were perhaps more likely to show extraocular extension in women than in men (19.6 *vs* 8.8%; χ^2-test, $P = 0.052$). This occurred despite the absence of significant differences in circumferential spread and tumour dimensions. These findings are in agreement with those of our previous report (incorporating the same patients as the present study), in which we demonstrated extraocular spread along aqueous drainage channels occurring in 15% of tumours involving ciliary body or angle.[16]

In view of the finding that chromosome 3 loss and chromosome 8q gain were not more common in men than women, one would not expect significances in the metastatic mortality in the long term, after taking any lead time bias into account. This finding is in keeping with a study by Kujala *et al*,[17] which took competing risks into account, reporting no significant difference in survival when the analysis adjusted for death from other causes. We plan to perform our own studies correlating mortality with gender, using different methods for dealing with competing risks.

This study raises several questions. Why is there a tendency for UMs to be more anterior in women than in men? Why are choroidal melanomas larger in men than in women? Why do men with an iris melanoma tend to present at a greater age than women? Are these differences genuine, and if so, do they arise because of gender variation in behaviour or exposure to environmental pathogens? Answers to these questions may provide insights into the cause and behaviour of UVs. In any case, the information provided by this study should be useful in future research investigating the impact of treatment on survival and other outcomes.

Summary

What was known before

- Uveal melanomas are as common in males as in females.

What this study adds

- In males, uveal melanomas tend to be larger, and more posterior than in females. The prevalence of lethal chromosomal abnormalities is the same in both sexes.

Conflict of interest

The authors declare no conflict of interest.

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