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ORIGINAL PAPER

Risk factors, clinical outcomes, and natural history of uveal melanoma: a single-institution analysis

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Abstract

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults. We describe the characteristics of UM patients at a tertiary referral center in the Mid-Southern United States, and explore associations and predictors of outcomes. This is a retrospective cohort study of patients with UM seen at West Cancer Center, from 07/2006 to 08/2017. Clinical characteristics and their relationship to outcomes (time-to-death and metastasis) were explored using Cox regression analysis. We identified 208 patients, 51% males, 97% Caucasians, 80% were symptomatic, with a median follow-up of 2.34 years, IQR (1.01–3.03), of which 19.2% died during follow-up. Metastases were diagnosed in 19% (4 older patients had metastases at diagnosis), 53% of those by surveillance. Without considering metastases as a time-varying covariate, age (HR = 1.06/year, CI 1.0–1.1; $p < 0.001$), headaches (HR = 5.7, CI 1.6–20.5; $p = 0.03$), and tumor stage (T) were significant covariates for time-to-death. Tumor stages T3 versus T1 (HR = 6.4; CI 1.5–27.7; $p = 0.01$) and T4 versus T1 (HR = 5.98; CI 1.3–27.8; $p = 0.02$) were associated with worse outcomes. When considering metastases as a time-varying covariate (HR = 35.8, CI 17–75.2; $p < 0.001$), only age remains in the model (HR = 1.04/year; $p < 0.001$). However, tumor stage ($p < 0.001$), headaches ($p = 0.008$), and age ($p < 0.001$) are associated with time-to-metastasis. One in five patients developed metastasis which was the most influential factor on mortality. Predictors of mortality were metastasis, age, tumor stage, and headache as a reported symptom. Surveillance successfully diagnosed metastatic disease in most patients. Most patients had symptoms preceding their UM diagnosis highlighting an opportunity for earlier recognition of UM.

Keywords Uveal melanoma · Ocular melanoma · Non-cutaneous melanoma · Mid-Southern United States

Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with an average annual age-adjusted incidence of 4.9 cases per million in the United States of America (USA) [1, 2] and 3.5 cases per million in the Mid-South [3]. It arises from the uveal tract, most commonly from the choroid (85–90%) [4], but also from the iris (3–5%) and ciliary body (5–8%) [5]. The median age at diagnosis is 62 years and males have a higher age-adjusted incidence (5.8 per million) than females (4.4 per million) [2].

Significant progress has been made in the diagnosis and local management of UM since the 1990s. Therapy has shifted from enucleation to eye conserving treatment with radiation therapy without compromising survival [6, 7]. Enucleation is usually reserved for large tumors in which radiation would have high ocular morbidity [7]. A 12-year

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follow-up analysis from the Collaborative Ocular Melanoma Study (COMS) could not find a survival advantage of enucleation over brachytherapy [7, 8]. Despite the advances on the diagnosis and local treatment of uveal melanoma, up to 50% of patients develop metastatic disease [9].

Epidemiologic studies have been performed on UM throughout the world [10, 11]. In the USA, epidemiologic studies have used the COMS population and the Surveillance, Epidemiology, and End Results (SEER) database for the most part [6, 8, 12, 13]. Our work adds details about the UM patient population from a single institution in the Mid-South region of the United States to this body of evidence: We describe the characteristics of our patients with UM and its natural history, explore disease associations, and elucidate predictors of outcomes influencing survival.

Materials and methods

Patients

After institutional review board approval, we retrospectively analyzed all patients with UM, regardless of length of follow-up, who were newly diagnosed with uveal melanoma and treated by the medical oncology department at our tertiary referral center [West Cancer Center (WCC), Memphis, TN] from July 1, 2006 to August 31, 2017. All patients with a confirmed clinical or pathological diagnosis of uveal melanoma were included. Clinical and demographic characteristics (age and date of diagnosis, race, gender, state of residence, smoking status, history of choroidal nevi, pertinent past medical history, history of any cancer, melanoma of the skin or skin cancer in the patient, and family history of cancer, symptoms prior to diagnosis, tumor size at diagnosis, area involved, treatment received, age at the time of metastasis, site of metastasis, date of last follow-up, age at death) and outcomes (death and diagnosis/development of metastasis) were obtained by electronic medical record review. If not available in the medical record, date of death was searched within the social security death index (http://www.geneologybank.com/gbnk/ssid/?kbid). Tumor size staging was defined using the American Joint Commission on Cancer (AJCC) 8th edition staging system. All data obtained were treated in accordance with the institution's patient confidentiality rules and regulations, including protection of patients' names.

Institutional surveillance protocol

At WCC, surveillance after UM diagnosis usually includes performing a chest X-ray (CXR), laboratory studies [complete blood count (CBC), basic metabolic panel (BMP), and liver function tests (LFT)], and an abdominal computed tomography (CT) every 6 months for 2 years, and then yearly for 3 more years to complete 5 years. There is no established surveillance modality after 5 years post diagnosis, although this typically continues on a yearly basis up to 10 years post diagnosis.

Statistical analysis

Patients were described with respect to baseline characteristics, follow-up time, and outcome in terms of metastatic disease and/or death. The statistical analysis used R v3.5.0 [14] and the R-packages survival v2.42 [15] and rms v.5.1 [16]. Comparisons with respect to gender and age group were based on Chi-square/Fishers' exact tests and t-tests/Wilcoxon tests for baseline comparisons. A significance level of $p < 0.05$ was used throughout to declare observed differences as statistically significant. Outcomes were defined as time-to-death by any cause with and without diagnosed metastases as time-varying covariate in a Cox regression model, as well as time to diagnosed metastases. Patient time in this analysis was days from initial diagnosis to death or last contact. The metastatic disease outcome was primarily defined as diagnosis of metastatic disease or death (both counting as events), but results were compared to models counting only metastatic disease as an event and death as censoring event. Cox regression models were multivariably adjusted: As a first step, all potentially entertained covariates with $p < 0.20$ in univariable Cox regression models were evaluated for redundancy based on whether one entertained covariate could be "explained" by the others (linear prediction with $R^2 = 0.80$ as cutoff value) [17]. As a second step, potential covariates were selected in a backward-forward variable selection procedure based on minimizing Akaike's information criterion (AIC). In a third step, the model was further pruned by requiring a marginal p value < 0.05. In a final forth step, the identified model was re-estimated based on all patients with possibly missing covariate information being imputed, and results were presented as regression coefficients/hazard ratios (HR) incl. 95% confidence intervals (CI) and associated p values.

Results

At WCC, 208 patients were identified with a median follow-up of 2.34 years with interquartile range (IQR) 1.01–3.03 and maximum follow-up of 10.23 years. The combined follow-up time was of 629.11 years. There were 40 deaths among the patients during the study period, and the unadjusted death rate was 6.36 deaths/100 patient years (roughly translating to about 1 death per 15 patient years). The majority of last recorded visits were for patients with a future follow-up visit scheduled which

had not yet occurred at the time of data extraction (55.3%). Other reasons for last visit include transferred care to a different facility, beginning hospice care, or death. Only 41 patients (19.7%) were truly lost to follow-up. In all cases, in the absence of a death event we censored follow-up time at the date of last contact with our clinic.

Basic characteristics of our patient cohort are described in Table 1. Most patients in this study were Caucasian (96.6%) from Tennessee, Mississippi, and Arkansas (85.1%; not shown). Symptoms were present in 160 patients (80.0%) prior to diagnosis, with change in vision the most common (65.0%). Symptoms were more frequent among males (74.5%) than in females (55.1%) ($p=0.005$), and a trend toward more symptoms was seen in younger patients (< 55 years; 72.8%) as compared to older patients (60.0%, $p=0.070$). Any symptoms at diagnosis with a T1 tumor were reported by 58.5%, and by 75.8, 91.6, and 94.1% with T2, T3, and T4 tumors, respectively ($p<0.001$; not shown). Tobacco and alcohol consumption were present in 45.4% and 39.3% of patients, respectively. Brachytherapy was the most common local treatment (86.8%), but female patients had higher rates of enucleation (18.8%) than male patients (7.7%; $p=0.023$) while having comparable tumor sizes ($p=0.903$).

The tumor most commonly arose from the choroid (92.3%) followed by ciliary body (4.3%), iris (2.88%), and a single unspecified region of the uvea (0.5%). Metastases were diagnosed in 39 patients during the study period (19%; 4 older patients had metastases at diagnosis). Only 11 deaths occurred during the 595.29 follow-up years without diagnosed metastases (raw death rate of 18.48 deaths/1000 patient years), but 29 deaths occurred after diagnosed metastases and during the much shorter combined 33.82 years of follow-up (raw death rate of 857.53 deaths/1000 patient years). The liver was the most common dominant site for distant metastasis (89.7%) followed by the lung (7.7%); other sites of metastasis included the skin, peritoneum, breast, and duodenal mucosa.

Among the 39 patients with confirmed metastatic disease, 4 (10.3%) were diagnosed with metastatic disease at the time they had their first visit to the medical oncologist (typically within 16 weeks post initial UM diagnosis), 21 (53.8%) were diagnosed by means of surveillance methods, and for 12 (30.8%) the diagnosis was prompted by symptoms. Thirty-seven percent of patients with metastases had symptoms at diagnosis. Abdominal discomfort and fatigue were the dominant symptoms in 21% and 8%, respectively. At the time of diagnosis, CT scans showed signs of metastases for all diagnosed patients, while laboratory studies showed evidence for only eight patients (mostly relating to abnormal liver function). The median time from primary UM diagnosis to the diagnosis of metastases was 29.47 months (IQR 17.2; 51), and the median time from the diagnosis of metastases to death was 5.5 months (IQR 2.92; 51.53).

Figure 1 shows Kaplan–Meier curves for time-to-death for the entire group and stratified by tumor category. To determine associations for survival, we looked only at variables available at diagnosis, and identified age (HR per year = 1.058, 95% CI 1.031–1.085; $p<0.001$), headache as a symptom (HR = 5.694, 95% CI 1.579–20.535; $p=0.026$), and tumor stage ($p=0.010$) as being associated with shorter survival times. The increase in HR was not significant in T2 versus T1 disease (HR = 2.881; 95% CI 0.621–13.354), but was notably elevated for T3 versus T1 disease (HR = 6.411; 95% CI 1.483–27.717) and T4 versus T1 (HR = 5.977; 95% CI 1.283–27.840). Other covariates were not significant (see Table 2 for univariable HR ratios of all entertained covariates). When we add diagnosis of metastases as a time-varying covariate (HR = 35.775, 95% CI 17.030–75.164; $p<0.001$), only age remains in the model (HR per year practically unchanged 1.039; $p<0.001$), while tumor stage ($p=0.114$) and headache ($p=0.153$) are no longer included.

Time-to-metastasis was also associated with age (HR = 1.049, 95% CI 1.026–1.071; $p<0.001$), headache (HR = 6.125, 95% CI 2.015–18.619; $p=0.008$) and tumor size ($p<0.001$) with HR T2 versus T1 = 3.777 (95% CI 0.841–16.969), HR T3 versus T1 = 8.048 (95% CI 1.874–34.556), and HR T4 versus T1 = 12.277 (95% CI 2.769–54.441). (No practically appreciable differences result from defining death as a censoring event instead; details not shown.)

Discussion

This study confirms many previously reported findings among patients with uveal melanoma and shows a number of differences that have not been previously reported or explored. These include a higher rate of presentation with symptoms and higher tumor stages than seen in larger databases. Most of the patients in our UM study cohort are not part of the SEER [2, 18, 19] or COMS study populations because they reside in states that do not contribute to these databases (only 9.6% and 38.9% lived in states that do contribute to the COMS and SEER population database, respectively) [6, 8, 12]. Additionally, the population we have studied involves several states with some of the lowest median family income in the USA (most patients are from Tennessee, Mississippi, and Arkansas). This finding may have influenced the higher prevalence of symptomatic patients and higher tumor stages in our study compared to other studies [9, 11, 18, 20, 21].

Four out of five patients experienced symptoms at the time of diagnosis, and one out of five had or developed metastases, with the liver being the most common site.

Table 1 Baseline characteristics of the newly diagnosed patients with uveal melanoma seen by medical oncology at West Cancer Center between July/2006 and August/2017 (by gender)

	All ($N = 208$)	Female ($N = 102$)	Male ($N = 106$)	p value
Age	57.27 (15.55)	56.89 (15.31)	57.64 (15.84)	0.729
Race				0.446
Caucasian	201 (96.63)	100 (98.04)	101 (95.28)	
Other than Caucasian	7 (3.37)	2 (1.96)	5 (4.72)	
Eye				0.141
Right eye	103 (50.74)	45 (45.00)	58 (56.31)	
Left eye	100 (49.26)	55 (55.00)	45 (43.69)	
Area of tumor				0.261
Choroid	192 (92.31)	92 (90.20)	100 (94.34)	
Ciliary body	9 (4.33)	5 (4.90)	4 (3.77)	
Uvea (unspecified)	1 (0.48)	0 (0.00)	1 (0.94)	
Iris	6 (2.88)	5 (4.90)	1 (0.94)	
T-stage				0.903
T1	43 (20.67)	20 (19.61)	23 (21.70)	
T2	61 (29.33)	33 (32.35)	28 (26.42)	
T3	63 (30.29)	29 (28.43)	34 (32.08)	
T4	34 (16.35)	17 (16.67)	17 (16.04)	
Not recorded	7 (3.37)	3 (2.94)	4 (3.77)	
First treatment (local)				0.023
Brachytherapy	178 (86.83)	82 (81.19)	96 (92.31)	
Enucleation	27 (13.17)	19 (18.81)	8 (7.69)	
History of cancer not including skin cancer (SCC/BCC)				0.208
No	168 (81.95)	80 (78.43)	88 (85.44)	
Yes	37 (18.05)	22 (21.57)	15 (14.56)	
History of skin melanoma				1.000
No history of skin melan recorded	200 (96.15)	98 (96.08)	102 (96.23)	
History of skin melan recorded	8 (3.85)	4 (3.92)	4 (3.77)	
History of skin cancer (SCC/BCC)				0.253
No history of skin cancer (SCC/BCC)	195 (93.75)	98 (96.08)	97 (91.51)	
History of skin cancer (SCC/BCC)	13 (6.25)	4 (3.92)	9 (8.49)	
History of choroidal nevus				0.462
No history of choroidal nevus	190 (91.35)	95 (93.14)	95 (89.62)	
History of choroidal nevus	18 (8.65)	7 (6.86)	11 (10.38)	
Family history of skin melanoma				1.000
No skin melanoma in family recorded	191 (91.83)	94 (92.16)	97 (91.51)	
Skin melanoma in family recorded	17 (8.17)	8 (7.84)	9 (8.49)	
Family history of ocular melanoma				1.000
No ocular melanoma in family recorded	205 (98.56)	101 (99.02)	104 (98.11)	
Ocular melanoma in family recorded	3 (1.44)	1 (0.98)	2 (1.89)	
Family history of skin cancer				0.569
No skin cancer in family recorded	195 (93.75)	97 (95.10)	98 (92.45)	
Skin cancer in family recorded	13 (6.25)	5 (4.90)	8 (7.55)	
Tobacco				0.178
No tobacco use	113 (54.59)	61 (59.80)	52 (49.52)	
Tobacco use	94 (45.41)	41 (40.20)	53 (50.48)	
Alcohol				0.279
No	125 (60.68)	62 (60.78)	63 (60.58)	
Social	56 (27.18)	31 (30.39)	25 (24.04)	
Abuse (current or history)	25 (12.14)	9 (8.82)	16 (15.38)	
Any symptoms				0.480

Table 1 (continued)

	All ($N = 208$)	Female ($N = 102$)	Male ($N = 106$)	p value
Without symptoms	40 (20.00)	22 (22.45)	18 (17.65)	
With symptoms	160 (80.00)	76 (77.55)	84 (82.35)	
Vision change				0.005
No vision change	70 (35.00)	44 (44.90)	26 (25.49)	
Vision change	130 (65.00)	54 (55.10)	76 (74.51)	
Erythema				0.324
No erythema	191 (95.50)	92 (93.88)	99 (97.06)	
Erythema	9 (4.50)	6 (6.12)	3 (2.94)	

Shown are mean (std. dev.) and count (%), respectively, depending on whether the variable is continuous or discrete

T tumor, *SCC* squamous cell carcinoma, *BCC* basal cell carcinoma

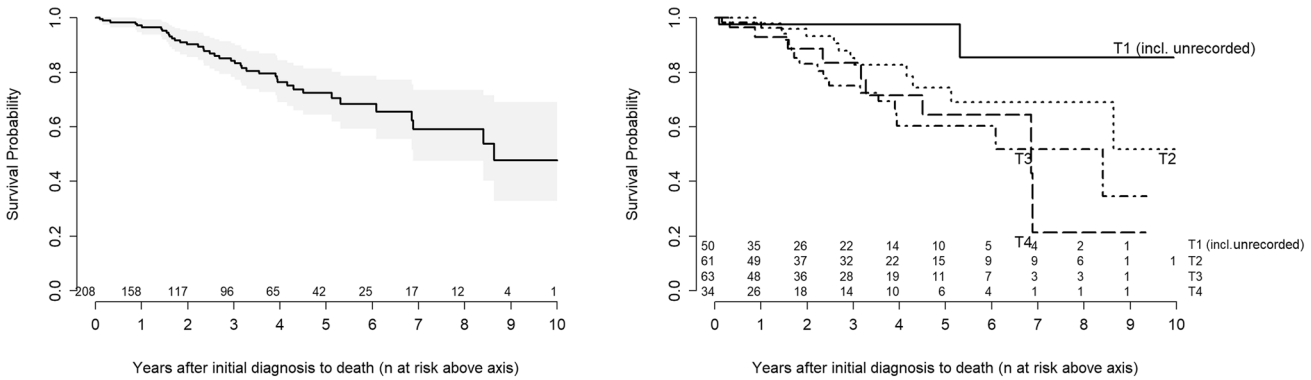

Fig. 1 Kaplan–Meier curve (time-to-death) for all 208 patients with 95% confidence interval (left panel) and stratified by tumor size (right panel; log-rank test for equality of survival experience $p = 0.010$). The n at risk are displayed above the x-axis

Interestingly, younger patients had a higher frequency of symptoms prior to UM diagnosis than older patients; this is likely related to older patients having an established relationship with an ophthalmologist for the ongoing care of age- or comorbidity-related conditions and were diagnosed during scheduled office visits. At time of UM diagnosis, higher age, higher tumor stage, and presence of headache were statistically associated with shorter time-to-death for any cause as well as the subsequent development of metastases. When diagnosis of metastases is included as a time-varying covariate (highly significant), neither tumor category nor headache is statistically significant any longer; it is for this reason that "metastases" satisfy the classical definition for being a *mediator* [22]. Metastasis was diagnosed by surveillance in most of the patients.

This study provides a comprehensive description and analysis of the patient population with uveal melanoma managed by West Cancer Center in Memphis, TN. This observational data set is relatively small (208 patients with 40 death events), and was collected for clinical purposes. A strength of the study is that symptoms are as reported by patients during interactions in a clinical setting, rather than extrapolated from a larger database and are consequently of direct interest for clinical practice purposes. On the other hand, some data were missing regarding possible risk factors. It is important to note that our cohort could have been subject to referral bias as we are only considering patients treated at our tertiary referral center, while other patients with UM in this area may have been referred to other facilities. Also, some patients did not have a complete tumor staging (including tumor extension). As most patients were treated with brachytherapy, molecular studies were not available as gross tissue was not available. Our study may also have underestimated the true metastatic rate with lack of consistent universal surveillance. However, this potential underestimate did not weaken the association between metastasis and death in uveal melanoma.

As seen in previous studies, the most common presenting symptom was change in vision, followed by photopsia and floaters [9, 11]. Notably, UM associated death has been described as more frequent in symptomatic patients in the first year after diagnosis (88% compared to 69%), while no difference was seen by the second year [23]. Similar to other studies, larger tumor size and older age at diagnosis

Table 2 Uveal melanoma cohort from the West Cancer Center between July 1 2006 and August 31 2017

	HR	95% CI	*p* value
Age	1.057	(1.031–1.085)	< 0.001
Gender			0.415
Female	Reference		
Male	1.297	(0.694–2.422)	0.415
Race			0.387
Caucasian	Reference		
Other than Caucasian	0.416	(0.057–3.038)	0.387
Eye			0.141
Right eye	Reference		
Left eye	0.615	(0.323–1.174)	0.141
Area of tumor			0.130
Choroid	Reference		
Other than choroid	1.965	(0.820–4.710)	0.130
Tumor category			0.006
T1 (incl. unrecorded)	Reference		
T2	3.524	(0.781–15.907)	0.101
T3	6.865	(1.591–29.616)	0.010
T4	6.587	(1.422–30.508)	0.016
First treatment (local)			0.688
Brachytherapy	Reference		
Enucleation	1.237	(0.438–3.493)	0.688
History of cancer not including skin cancer (SCC/BCC)			0.074
No	Reference		
Yes	1.922	(0.938–3.941)	0.074
History of melanoma of the skin			0.834
No history of Melanoma of the skin recorded	Reference		
History of Melanoma of the skin recorded	0.809	(0.111–5.909)	0.834
History of skin cancer (SCC/BCC)			0.738
No history of Skin Cancer (SCC/BCC)	Reference		
History of Skin Cancer (SCC/BCC)	1.193	(0.424–3.355)	0.738
History of choroidal nevus			0.556
No history of choroidal nevus	Reference		
History of choroidal nevus	0.652	(0.157–2.707)	0.556
Family hx. of skin melanoma			0.856
No skin melanoma in family recorded	Reference		
Skin melanoma in family recorded	1.116	(0.343–3.629)	0.856
Family hx. of ocular melanoma			0.557
No ocular melanoma in family recorded	Reference		
Ocular melanoma in Family recorded	1.815	(0.248–13.288)	0.557
Family hx. of skin cancer			0.135
No skin cancer in family recorded	Reference		
Skin cancer in family recorded	1.944	(0.813–4.648)	0.135
Tobacco			0.725
No tobacco use	Reference		
Tobacco use	0.891	(0.470–1.692)	0.725
Alcohol			0.671
No	Reference		
Social	0.704	(0.318–1.557)	0.386
Abuse (current or history)	0.934	(0.384–2.276)	0.881
Any symptoms			0.887
Without symptoms	Reference		

Table 2 (continued)

	HR	95% CI	*p* value
With symptoms	0.942	(0.413–2.146)	0.887
Vision change			0.953
No vision change	Reference		
Vision change	0.980	(0.499–1.924)	0.953
Erythema			0.201
No erythema	Reference		
Erythema	2.167	(0.663–7.081)	0.201
Scotoma			0.450
No scotoma	Reference		
Scotoma	1.438	(0.560–3.693)	0.450
Headache			0.035
No headache	Reference		
Headache	3.607	(1.096–11.868)	0.035
Floaters			0.653
No floaters	Reference		
Floaters	1.311	(0.403–4.266)	0.653
Photopsia			0.410
No photopsia	Reference		
Photopsia	0.609	(0.187–1.983)	0.410

Hazard ratios based on univariable Cox regression (time-to-death)

Hx history, *HR* hazard ratio, *CI* confidence interval

were significant covariates for mortality [20] and metastasis development [8, 20, 24, 25]. The fact that we replicate these established risk factors in our well-documented relatively small cohort further documents the strength and consistency of these factors, including the formal confirmation of metastasis development as a mediator in the tumor size–death pathway on statistical grounds. Kaliki et al. described the incidence of tumor-related metastasis at 5 years post diagnosis of 11% in patients aged ≤ 20 years, 14% in 21–60 years and 34% in > 60 years old [24]. Similar to other studies, no difference in overall survival was observed between genders [19].

In the United Kingdom, a study revealed that the referral process to the Liverpool Ocular Oncology Center was initiated by an optometrist in 68%, family doctor in 18%, or ophthalmologist in 14% of the patients. Many patients experienced long delays in treatment because their tumor was initially missed or misdiagnosed; they tended to have more advanced tumors and were more likely to require enucleation [11]. In a study performed in the Mid-Southern states, Shildkrot et al. observed an increased frequency of UM diagnosis associated with higher area-based socioeconomic measures [3]. Another study suggested that disparity in access to eye care could be based on insurance status; in that study, the odds of receiving an appointment with an eye care provider (optometrist or ophthalmologist) was 60% lower for a patient with Medicaid than a patient with Blue Cross Blue Shield insurance [26]. This may reflect the higher likelihood of patients with higher income to receive an ocular examination, and thus a higher diagnosis rate.

After local treatment has been achieved, no consensus on the best surveillance modality for detection of metastatic disease in patients with UM has been established [27]. Although LFTs are economical and easy to perform, imaging modalities including abdominal CT and magnetic resonance imaging (MRI) have greater predictive value for metastasis detection [9]. Consideration for surveillance based on routine imaging (CT or MRI) on an every 3- to 6-month interval for patients at higher risk of recurrence, and every 6- to 12-month interval for patients at lower risk for recurrence is thought to be reasonable [9, 27].

In this study, median time from UM diagnosis to metastasis diagnosis was 2.46 years, comparable to the study from Kim et al. [23] who reported medians of 2.62 years and 3.36 years in their groups of metastasis diagnosed by surveillance and metastasis diagnosed after development of symptoms, respectively; while shorter than the study from Lane et al. [28] with 3.45 years (IQR 2–5.56). The surveillance protocol used by Kim et al. [23] involved LFTs annually with CT imaging if abnormalities on LFTs were found, and the surveillance protocol used by Lane et al. [28] was not described. The median time from metastasis diagnosis to death was 5.5 months (IQR 2.92; 51.53) in our study, and this is similar to the studies from Kim et al. [23] with a median of 6.1 months in the surveillance group and 2.7 months in the symptomatic group, and Lane et al. [28]

with 3.0 months (IQR 1.64–10.07), pointing out there is likely no lead-time bias on survival after metastasis diagnosis in this study and that there is still lack of effective treatment options for patients with metastatic UM. Routine imaging surveillance detects metastases before the onset of symptoms, enhancing any opportunities for early treatment of metastatic disease including complete resection of liver metastasis and early referral to specialized centers with ongoing clinical trials [27, 29, 30]. It is important to discuss surveillance alternatives with every patient diagnosed with UM while also pointing out the lack of proven treatment options for metastatic disease so they can make an informed decision on surveillance and have a prompt referral to specialized centers with ongoing clinical trials to the patients interested in this option.

It is important to highlight the fact that metastatic development was the most influential factor predicting mortality in our study. Approximately, 16% of our cohort developed metastatic disease during the follow-up period and most of them died during the year following the diagnosis of metastasis, reflecting the progressive nature of the disease and lack of effective therapies. In a cumulative incidence analysis performed in a study in Finland, 31% of their patients died of uveal melanoma by 5 years of diagnosis, 45% by 15 years, 49% by 25 years, and 52% by 35 years [13]. (Only 25% of our patients have been followed longer than 4.6 years and we therefore refrain from long-term assessments due to small numbers in our study.) In the COMS trial, the 5- and 10-year cumulative metastasis rates were 25% and 34%, respectively; 80% died within 1 year of diagnosis of metastasis and 92% within 2 years. Their median time-to-death was of less than 6 months [12]. The optimal duration, method, and frequency of surveillance remains controversial,[27, 31, 32] although with this information, it may be reasonable to extend imaging surveillance of patients with UM for at least 15 years, and it would be optimal to refer patients with newly diagnosed metastatic disease to get involved in clinical trials for the management of metastatic UM.

The strong association of tumor stage with the development of metastatic disease, and this with time-to-death, suggests that it is necessary to continue to educate our population in order to perform periodic ophthalmologic screening in at-risk individuals and thus increase the likelihood of UM diagnosis at earlier stages. Complete ophthalmologic exam recommendations vary depending on individual risk factors, comorbidities, and family history. In the general population, it should start in the age range of 20–30 years with a frequency of every 5–10 years in patients younger than 40 years [33, 34]. Primary care providers should be aware of the necessity for early referral and counsel on periodical ocular exams. The necessity for referral by several insurance companies often poses a delay in the proper diagnosis of UM. Unfortunately, these delays are associated with advanced tumor stages and ultimately influence metastasis development and survival. Guidelines are required for medical oncologists and insurance companies in order to provide an adequate surveillance modality not affected by insurance policies.

Conclusions

This analysis was one of the first studies on this rare cancer performed with data gathered from a single institution. At the West Cancer Center, approximately one in five patients with uveal melanoma developed metastasis, which was the most influential factor on mortality. Surveillance successfully diagnosed asymptomatic metastatic disease in most of our patients. Predictors of mortality (without considering metastasis development) included age, tumor size, and presenting with headaches at diagnosis. Most patients had preceding symptoms prior to primary diagnosis highlighting an opportunity for earlier recognition in primary care and primary ophthalmologic specialties.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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