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ORIGINAL RESEARCH

Trends in incidence, survival, and management of uveal melanoma: a population-based study of 7,516 patients from the Surveillance, Epidemiology, and End Results database (1973–2012)

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Introduction: Uveal melanoma (UM) is the most common primary intraocular malignancy, despite comprising <5% of all melanomas. To date, relatively few case series of UM have been published. Moreover, the factors influencing survival remain largely unknown. This study sought to analyze the impact of demographics, histology, clinical presentation, and treatments on the clinical outcomes of UM in a large modern nationwide patient cohort.

Methods: Demographics and clinical data were abstracted on 277,120 histologically confirmed melanoma patients from the Surveillance, Epidemiology, and End Results database between 1973 and 2012.

Results: A total of 7,516 cases of UM represented 3.2% of all recorded cases of melanoma. The mean age-adjusted incidence was 5.1 per million (95% CI 4.2–6.1) and was higher in males (5.9, CI =4.4–7.6) compared to females (4.5, CI =3.3–5.8), $P<0.001$. UM occurred most commonly in the sixth decade of life (61.4±15) and among Caucasians (94.7%). A total of 52.3% of cases were reported in the Western US (35.7% in California). The initial diagnoses in 65.2% of cases were by histopathology, followed by clinical diagnosis (18.8%) and radiographic imaging (16.0%). The percentage of UM cases managed by surgery alone decreased by 69.4% between the 1973–1977 and 2006–2012 time periods, concomitant with a 62% increase in primary radiotherapy, $P<0.001$. The UM mean overall and cancer-specific 5-year relative survival rates were 79.8%±5.8% and 76%±5.3%, respectively. The mean 5-year cancer-specific survival rate (76%) remained stable during the study period between 1973 and 2012. The mean survival for patients treated with primary radiotherapy was significantly improved compared to those treated with surgery alone (15.4±0.4 vs 13.6±0.3, $P<0.001$). Multivariate analysis identified male sex (odds ratio [OR] 1.1, CI =1.0–1.3), age >50 years (OR 4.0, CI =3.4–4.6), distant metastases (OR 8.6, CI =4.7–15), and primary surgical treatment (OR 2.6, CI =2.0–3.3) as independently associated with increased mortality, $P<0.005$. Conversely, patients identified as Hispanic (OR 0.6, CI =0.5–0.8) and patients receiving radiation treatment (OR 0.5, CI =0.4–0.7) were independently associated with reduced mortality, $P<0.005$.

Conclusion: UM remains a rare form of melanoma that occurs primarily in Caucasian patients older than 50 years. More than two-thirds of UM patients are curatively treated with primary radiotherapy as opposed to surgery, which has resulted in a significant improvement in both overall survival and cancer-specific survival. Despite this shift in management strategy, the mean 5-year cancer-specific survival rate remained relatively unchanged during the study period. Male sex, older age, distant disease, and primary surgical therapy rather than radiotherapy are associated with an increased risk of mortality.

Keywords: uveal melanoma, ocular melanoma, SEER

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Introduction

Ocular melanoma is the second most common form of melanoma after cutaneous melanoma and accounts for 3.7% of all melanoma cases.[1,2] The incidence rate of ocular melanoma is 0.7/100,000 people among Caucasians.[3] Uveal melanoma (UM) accounts for the majority (85%) of all ocular melanoma cases and represents the most common primary intraocular malignancy among adults.[4–9] The incidence of UM in the US is 4.9 per million and has remained stable over the last three decades. Historically, UM has been treated with enucleation, radiation alone, or surgery combined with radiation.[4] Regardless of the management strategy, up to 30% of affected patients develop metastases to the liver, lung, bone, or skin within 10 years of successful local control of the primary neoplasm, with liver involved in approximately two-thirds of cases.[10–12] Although radiotherapy has replaced surgical therapy as the primary means of treating most UM patients, the overall impact that this change in primary treatment has had on overall survival is poorly studied.[4,13]

Current data detailing survival trends among UM patients are primarily based on limited population-based studies involving small groups of patients from high-volume melanoma centers.[11,14] The demographic, pathologic, and clinical factors specifically influencing clinical outcomes in UM patients are not well understood. The current study examines a large cohort of UM patients from the Surveillance, Epidemiology, and End Result (SEER) database[15,16] in an effort to identify demographic, clinical, and treatment strategies that may impact the changes of clinical outcomes in a modern cohort of primary UM patients.

Methods

Data for the current study were extracted from the SEER database provided by the National Cancer Institute between 1973 and 2012. SEER Stat software Version 8.0.4 was utilized to extract data from 18 SEER registries (Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah). A total of 277,120 patients with confirmed melanoma were identified and their data were exported to IBM SPSS v20.2. A total of 7,516 patients with a primary diagnosis of UM were identified to form the final study cohort, using the SEER International Classification of Disease for Oncology (ICD-O-3) codes C69.3 (choroid) and C69.4 (ciliary body and iris). Demographic and clinical data extracted included age, sex, ethnicity, geographic location, prior malignancy status, tumor stage, laterality, and type of treatment received (surgery, radiation, both, or unknown/no treatment). Patients with in situ cancers were excluded from the final study cohort. Endpoints examined included overall survival, mortality, and 1-, 2-, and 5-year cancer-specific survival. Categorical variables were compared using the chi-square test, and continuous variables were compared using Student's *t*-test and analysis of variance. Multivariate analysis using the "backward Wald" method was performed to calculate odds ratios (ORs) and determine independent factors affecting survival. Missing and unknown data were excluded from the multivariate analysis. Statistical significance was accepted at the level of $P<0.05$.

The study was approved by the Saint Barnabas Medical Center Ethics Board. The study is a retrospective study utilizing data from the SEER database; no specific patient identifiable information was utilized, and no patient consent was required by the ethics board.

Results

Demographic data

A total of 7,516 cases of UM were reported in the SEER database over the 40-year study period (1973 to 2012), representing 3.2% of all melanoma cases. A total of 5,955 UM patients (78.4%) were older than 50 years, with a mean age at diagnosis of 61.4±15 years (Table 1). Specifically,

Table 1 Demographic profiles of 7,516 uveal melanoma patients from the SEER database, 1973–2012

Variable	Frequency	%
Sex		
Male	3,933	52.3
Female	3,583	47.7
Age (years, mean =61.4±15 years; median =62 years)		
<50	1,561	20.8
50–79	5,144	68.4
≥80	811	10.8
Ethnicity[a]		
Caucasian	7,000	94.7
Hispanic	287	3.9
African American	40	0.5
Asian/Pacific Islander	51	0.7
Native American	16	0.2
Prior malignancy		
Present	981	13.1
Absent	6,535	86.9
Geography		
Midwest	1,473	19.6
Northeast	1,074	14.3
South	1,033	13.8
West	3,936	52.3

Note: [a]Data presented for patients with available information only.
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

5,144 patients (68.4%) were 50–79 years old, while 811 patients (10.8%) were >80 years old and 1,561 patients (20.8%) were <50 years old, $P<0.001$. There were 3,933 male patients (52.3%) and 3,583 female patients (47.7%), with a male-to-female ratio of 1.1:1, $P<0.001$. The incidence of UM was 5.1 per million (95% CI, 4.2–6.1), which was significantly higher among males (5.9, CI =4.4–7.6) compared to females (4.5, CI =3.3–5.8), $P<0.001$.

The majority of UM cases (94.7%; N=7,000) occurred among Caucasians, followed by Hispanic patients (3.9%; N=287) and African Americans (0.5%; N=40), $P<0.001$. Less than 1% of patients were of Asian, Pacific Islander, or Native American descent.

Geographically, 52.3% (N=3,936) of cases have been reported in the Western US (35.7% of cases in California alone), followed by the Midwest (19.6%; N=1,473), Northeast (14.3%; N=1,074), and South (13.8%; N=1,033), $P<0.001$. A total of 13.1% (N=981) of patients had a history of prior malignancy.

Tumor characteristics

The majority of UM (83.5%; N=6,279) arose from the choroid followed by the ciliary body (16.5%; N=1,237), $P<0.001$. A total of 90.9% (N=6,126) of UM cancer were localized at presentation, 7.5% (N=506) had regional disease, and 1.6% (N=109) had distant metastasis, $P<0.001$. Right and left eyes were equally affected (50.5% right eye and 49.4% left eye) (Table 2). Only two patients had bilateral UM. A total of 65.2% of UM cases were diagnosed by histopathological reporting, followed by clinical diagnosis (18.8%) and radiographic imaging (16.0%). A total of 13.1% (N=981) had a history of prior malignancy.

Table 2 Tumor characteristics of 7,516 uveal melanoma patients from the SEER database, 1973–2012

Variable	Frequency	%
Laterality[a]		
Right	3,759	50.5
Left	3,679	49.4
Bilateral	2	<0.1
Stage[a]		
Localized	6,126	90.9
Regional	506	7.5
Distant	109	1.6
Diagnostic confirmation[a]		
Histopathology	4,845	65.2
Clinical diagnosis	1,400	18.8
Radiography	1,191	16.0

Note: [a]Data presented for patients with available information only.
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

Table 3 Treatment and survival outcomes profiles of 7,516 uveal melanoma patients from the SEER database, 1973–2012

Variable	Frequency	%
Treatment		
Surgery only	3,218	42.8
Radiation only	3,232	43.0
Both	527	7.0
Neither	539	7.2
Cancer-specific relative survival		
1 year	–	97.1
2 years	–	90.5
5 years	–	76.0
Overall survival in years (expressed as mean ± SD)	14.6±0.2	
Mortality	3,466	46.1
Cancer-specific mortality	1,870	24.9

Abbreviations: SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

Treatment

A majority of UM patients were treated initially with either surgery alone (42.8%; N=3,218) or radiation alone (43.0%; N=3,232) (Table 3). A total of 7.0% (N=527) received both surgery and radiotherapy, while 7.2% (N=539) had no treatment. UM cases managed surgically decreased by 69.4%, from a high of 93.4% of cases between 1973 and 1977 period to only 25% of cases between 2006 and 2012, $P<0.001$. Simultaneously, there was a 62% increase in the use of primary radiotherapy (1.1% in the 1973–1977 period increasing to 63.1% in the 2006–2012 period), $P<0.001$. No change was observed in the number of patients treated with concurrent therapies or with no treatment (Figure 1). The mean survival for patients treated with primary radiotherapy was significantly improved compared to those treated with surgery alone (15.4±0.4 years vs 13.6±0.3 years, $P<0.001$).

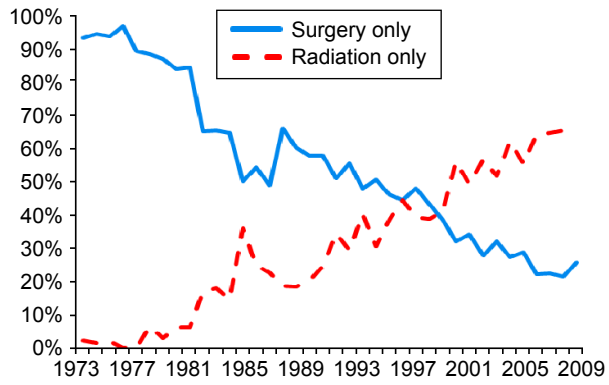

Figure 1 Temporal changes in the primary management of 7,516 uveal melanoma patients from the SEER database, 1973–2012.
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

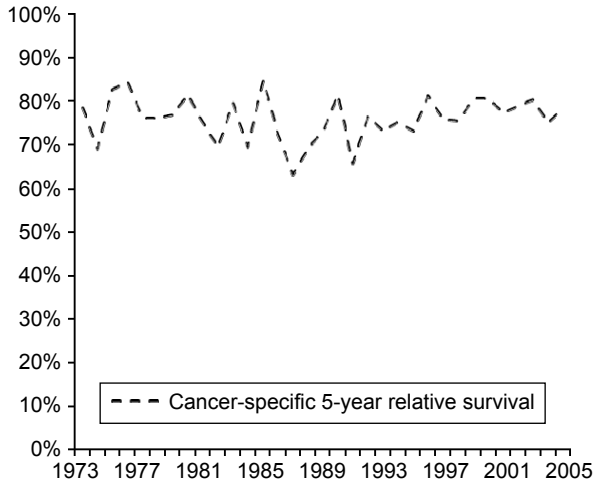

Figure 2 Cancer-specific 5-year survival among 7,516 uveal melanoma patients from the SEER database, 1973–2012.
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

Outcomes

The mean 5-year cancer-specific survival rate (76%) remained stable during the study period between 1973 and 2012 (Figure 2). Overall mortality and cancer-specific mortality were 46% and 24.9%, respectively, for the entire cohort. The UM mean overall and cancer-specific 5-year relative survival rates were 79.8%±5.8% and 76%±5.3%, respectively, $P<0.001$. The mean overall survival was 14.6±0.2 years, $P<0.001$. UM patients undergoing radiation therapy experienced significant survival benefit (mean survival 15.5±0.4 years), compared to those treated with primary surgical therapy (13.6±0.3 years), $P<0.001$. Patients receiving combination surgery and radiotherapy had a mean survival of 11.5±0.7 years, while patients receiving no therapy had the lowest survival of 6.2±1.7 years, $P<0.001$. There were no significant survival differences between different sex, ethnicities, and geographic locations.

Univariate and Multivariate Analyses

Univariate and multivariate analyses identified male sex (OR 1.1, CI =1.0–1.3), age >50 years (OR 4.0, CI =3.4–4.6), distant metastases (OR 8.6, CI =4.7–15), and surgical treatment only (OR 2.6, CI =2.0–3.3) as independently associated with increased mortality, $P<0.005$. Conversely, Hispanic ethnicity (OR 0.6, CI =0.5–0.8) and radiation treatment (OR 0.5, CI =0.4–0.7) were independently associated with reduced mortality, $P<0.005$.

Discussion

UM, arising in the uveal tract comprising the iris, ciliary body, and choroid, is the most common primary intraocular malignant tumor in adults.[1–3] The incidence of UM was 5.1 per million, which is consistent with a SEER study by Singh et al[17] who reported age-adjusted incidence rates of 5.0 and 5.1 per million in a large cohort of UM patients between 1973–1997 and 1997–2008. A Norwegian study by Mork reported a UM incidence of nine cases per million between 1953 and 1960, with other large European studies reporting UM incidence rates ranging from 5.7 to 7.1 cases per million.[18–22]

UM patients typically present with blurred vision, visual field defects, photopsia, or metamorphopsia, but up to 30% of patients may be asymptomatic.[6–11,14,23–25] Historically, UM was diagnosed histologically or cytologically following a surgical excision of the tumor. Histopathologically, UM is composed of either spindle or epithelioid cells. Spindle cell tumors are associated with a better prognosis than those that contain epithelioid cells in any proportion.[26,27] Recent advancements in optical and radiologic diagnostic modalities have resulted in the ability to detect UM earlier, enabling prompt initiation of treatment. Modern diagnostic tools such as A and B ultrasonography, fluorescein angiography, and optical coherence tomography now make it possible to avoid biopsy in nearly all cases.[10,24] Today, diagnosis is accurately established with clinical examination alone in >99% of cases.[24]

UM is more prevalent among Caucasian males older than 50 years, which is consistent with previously published data.[1–5,17,28–31] Caucasian males in their sixth decade of life are most likely to benefit from fundoscopic screening for UM during regular health visits, with the option for further workup in patients with visual symptoms.

More than 50% of cases in the current study occurred in the Western US with a majority of cases in California alone. This seems to suggest a possible association between ultraviolet ray exposure from sunlight and the development of UM. However, in contrast with cutaneous melanoma, epidemiologic studies have failed to demonstrate an association between degree of sun exposure and UM incidence.[32–35] More recent studies have suggested that blue light exposure may be a possible risk factor for UM; however, more studies are needed to draw definitive conclusions.[36–38] Despite the results identified in the current time, there is no clear correlation between geographic region or sunlight exposure and UM, and no evidence-based recommendations for sun protection can be made at this time. Whether specific sex or ethnic populations are at increased susceptibility could not be assessed but is worthy of additional investigation.

In the current study, 13.1% of UM patients had a history of prior malignancy especially cutaneous melanoma. This

finding is consistent with the Collaborative Ocular Melanoma Study findings that 5% of individuals with UM had a history of malignancy.[39] Bergman et al[40] analyzed the records of 2,995 UM patients from the Swedish Cancer Registry over a 38-year period, determined that the most common prior malignancy in UM patients was cutaneous melanoma (~20%), and calculated the lifetime risk of a UM patient developing a subsequent malignancy to be 13%. Some studies have shown that the incidence of prior primary malignancies was increased in UM patients, mainly cutaneous melanoma and breast and colon cancers, while others have shown no increase in prior malignancies in UM patients compared with controls.[17,39,41–44] These results, though inconsistent, suggest that there may be an association between UM and cutaneous melanoma and breast or colon cancer. The implication, though unproven, is that it may be beneficial to periodically monitor UM patients for the development of specific subsequent malignancies, particularly cutaneous melanoma to allow for early detection, intervention, and treatment.

Despite a stable UM incidence over time, a significant temporal change in UM treatment approaches has occurred over the last 40 years (Figure 1). The current study observed a 69.4% decrease in surgery or enucleation as primary treatment with a corresponding 62% increase in the use of eye-preserving primary radiotherapy. Brachytherapy using iodine-125 or ruthenium-106 was introduced as an alternative to enucleation for UM management in the late 1980s and has gradually become first-line treatment.[31,40,45–47] Vicente et al[47] conducted a prospective study involving 500 UM patients receiving episcleral brachytherapy and reported that a majority of tumors were diagnosed at early to medium stages, allowing for the use of conservative treatment such as brachytherapy. The Collaborative Ocular Melanoma Study centers reported a trend toward diagnosing small UMs with advances in diagnostic modalities, resulting in an overall shift toward eye-sparing and vision-sparing treatment of smaller tumors since the early 1990s.[48]

In addition to the esthetic benefit associated with avoiding enucleation and preserving vision in up to 43% of patients undergoing primary radiotherapy for UM, there is a significant survival advantage in patients receiving radiotherapy compared to surgical treatment (15.4±0.4 years vs 13.6±0.3 years, $P<0.001$). Similarly, the COM study demonstrated improved survival rates for iodine-125 brachytherapy compared to enucleation for medium sized melanomas, with comparable 5-year all-cause mortality (19% vs 18%) and 5-year tumor-related mortality (11% vs 9%).[45] In a retrospective analysis of 47 consecutive UM patients over a 10-year period, Semenova and Finger[49] concluded that the rate of local control with palladium-103 brachytherapy was 91% at a median of 47 months, with an eye retention rate of 89%. Given the slow adoption of radiotherapy for UM over the study period, it is difficult to assess whether the improved survival with radiotherapy is due to a true survival advantage conferred by radiation itself or a result of earlier detection of UM with improved diagnostic modalities permitting earlier treatment of patients with localized disease. Despite this, radiotherapy is now utilized in >90% of UM patients and is associated with a significantly decreased mortality (OR 0.5). Furthermore, despite advances in the diagnosis and treatment of the primary tumor, the mean 5-year cancer-specific survival remained relatively unchanged during the study period between 1973 and 2012 (76%).

More recently, the use of external beam radiation (EBRT), including Gamma Knife radiosurgery and proton beam radiotherapy has been increasingly investigated, with variable success.[50] Abrams et al[50] conducted a retrospective SEER study involving 1,004 UM patients (380 treated with EBRT and 624 treated with brachytherapy) and reported no difference in 5-year overall survival (83.3% vs 82.5%, $P=0.69$) and 5-year cause-specific survival (88.3% vs 88.3%, $P=0.92$) between EBRT and brachytherapy. On multivariate analysis, however, the treatment of lower T-stage tumors favored brachytherapy, whereas higher T-stage tumors favored EBRT.[50] This is likely attributable to the difficulty in delivering prescriptive dose to advanced stage tumors.[50] In a Cox proportion hazards regression analysis, Andreoli et al[51] identified that tumor histology, stage, and age at diagnosis were associated with disease-specific survival.

The optimal management of UM continues to evolve. Novel therapies like transpupillary thermotherapy were introduced as a means of managing small tumors conservatively without surgery or radiation.[51–55] In addition, targeted therapies such as histone deacetylase inhibitors and ipilimumab, as well as genetic counseling to identify *BAP1* mutations for patients at high risk for developing UM, are currently under investigation.[56] Finally, there are several ongoing adjuvant treatment trials for high-risk UM patients with poor prognosis or existing metastatic disease.[57] Moser et al[58] conducted a study involving 746 patients and reported that patients treated with ipilimumab had a median survival time of 28 months compared to 13 months in patients treated with local therapy ($P=0.07$). Patients treated with bevacizumab had a slightly prolonged survival compared to those not receiving the drug (25 months vs 12 months, $P=0.09$).[58] These alternative modalities have been used with varying

degrees of success; however, it remains to be seen how these therapies will unfold in the future management of UM. More research and interest from the clinicians must take place in order to provide the best possible care as well as to improve the prognosis for UM.

There are several limitations of this study, which should be taken into account. First, the SEER database did not accurately code for important clinical factors, such as socioeconomic status, tumor depth, and size, which have an influence on survival. Second, information on diagnostic imaging and follow-up was lacking. Data on surgical and radiation therapy were available in the SEER database; however, information on surgical margins and chemotherapy received was not, which limited the ability of this study to evaluate the impact of adjuvant or neoadjuvant therapy. There may also be an element of selection bias, since SEER registries are more likely to sample from urban than from rural areas. Despite these limitations, the SEER database has data obtained from 26% of the US population, and these findings can be generalized to the overall population.

Conclusion

UM is an uncommon form of melanoma that occurs primarily in Caucasian male patients older than 50 years in the Western US. The primary treatment has shifted from surgical therapy to radiotherapy, with more than two-thirds of all patients currently treated with primary radiotherapy. In addition to the obvious esthetic benefits of avoiding enucleation as well as vision preservation in almost half the patients, primary radiotherapy has been associated with significantly prolonged survival. Despite improvements in diagnosis and treatment of the primary tumor, the mean 5-year cancer-specific survival has remained relatively stable during the study period between 1973 and 2012. Additional studies investigating the role of enhanced diagnostic modalities and targeted therapies for UM treatment are required to optimize treatment for these patients.

Disclosure

The authors report no conflicts of interest in this work.

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