Gender Differences in Clinical Presentation and Prognosis of Uveal Melanoma

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Purpose. We examined the clinical differences in manifestation and prognosis of uveal melanoma (UM) between men and women.

Methods. We evaluated 723 UM patients (325 males) who were treated between 1988 and 2010 at a national referral center. Men and women were compared regarding differences in annual distribution, age at diagnosis, size and intraocular location of the tumor, symptoms leading to diagnosis, recurrence, development of metastases, and mortality. Statistical analysis included ANOVA, Pearson correlations, and competing risks for melanoma-related mortality.

Results. Significant gender differences were not found for annual distribution, diagnosis age, tumor size, or recurrence rate. Tumors were located more frequently posterior to the equator in men than in women. However, men were less likely than women to complain of symptoms before the diagnosis (77.10% vs. 84.65%). Men suffered more metastases. In the subgroup of patients who had metastases, the time until development of metastases was shorter in men (metastases 1 and 5 years after diagnosis of UM: 26% vs. 12.96% and 84% vs. 50%, respectively). The cumulative incidence for melanoma-related mortality was higher for men, with an almost two-fold excess of male melanoma-related mortality in the first 10 years after the diagnosis of UM.

Conclusions. Men have earlier and more frequent metastases in the first decade after the diagnosis of UM, a fact that may have significant implications in planning clinical trials to test adjuvant therapies to prevent metastasis. (*Invest Ophthalmol Vis Sci.* 2013;54:652–656) DOI:10.1167/iovs.12-10365

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults. A thorough study based on the American Surveillance, Epidemiology and End Results (SEER) cancer registry, showed that the mean age-adjusted incidence of UM in the United States was 5.1 per million, with significantly more men affected (men 5.8, women 4.4).[1] In a previous study Singh et al. presented a summary of studies from all over the world that showed variation in incidence rates among different countries, although generally the incidence rate in women was lower than in men.[2]

The underlying causes of UM are still unknown despite extensive research into the etiology of the disease during the last decades. The disease seems to be multifactorial. Race[3] and genetic predisposition[4] have been suggested as possible risk factors.

The tumor is usually diagnosed due to complaints of disturbances in visual fields, blurred vision, and sometimes due to an episcleral pigmented lesion. However, the tumor can occasionally be found on a routine eye examination. The age at diagnosis, intraocular localization of the tumor, size of the tumor, and existence of metastasis are important clinical prognostic factors of the disease, and can be augmented by histopathologic, cytogenetic, and molecular characteristics.[5,6] According to the Collaborative Ocular Melanoma Study (COMS), even if the treatment was considered a success, 5- and 10-year cumulative metastasis rates were 25% and 34%, respectively.[7] The primary site for UM metastasizes is the liver (89%).[7] The prognosis after detection of metastatic disease was poor. The death rate following the report of metastasis was 80% by one year, and 92% by two years.[7]

Gender medicine is a rather new, developing area that focuses on the impact of gender on human physiology, clinical features, and prognosis of diseases. Few articles about the role of gender in cutaneous malignant melanoma have been published.[8,9] In cutaneous malignant melanoma, male gender was associated with a greater incidence of unfavorable primary tumor characteristics without an increased risk for nodal metastasis.[8] Nonetheless, gender was an independent factor affecting survival, and the prognosis was worse for men.[9] Some epidemiologic studies demonstrated significant gender-based differences in ocular conditions, such as idiopathic full-thickness macular hole[10,11] and age-related macular degeneration (AMD).[12]

Data on gender differences among UM patients have been analyzed partially in several studies, but have not been evaluated for all study parameters. To our knowledge, this is the first study aimed at searching for gender differences in UM patients from the first visit through the treatment to the survival data. Damato and Coupland performed a study that compared the intraocular localization, size, and histopathologic and genetic differences between men and women, but did not assess treatment and prognosis.[13] Therefore, we found that a complete analysis on differences between men and women is necessary.

Methods

Patients

A cohort of patients who were diagnosed with UM, and treated at a national referral center (Hadassah-Hebrew University Medical Center, Jerusalem, Israel) between 1988 and 2010, were included in this retrospective analysis. During the study period no other ocular oncology services existed in the country.

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The following parameters were documented: patient demographic information (gender and age at diagnosis), previous/concurrent malignancies, symptoms and complaints leading to the diagnosis of UM, clinical findings (including intra-ocular localization, tumor largest basal diameter [LBD], and tumor height as measured by ultrasound), treatment, histopathologic findings for the enucleated cases, and biannual follow-up data (including recurrences, appearance of metastases, additional treatments, and survival data). The cause of death was recorded in the patients' charts at the time of death. Metastatic death was noted only for biopsy-proved metastases.

Tumor Classification

The intraocular localization of the tumors was noted according to the involved areas. The retinal area was divided into the macular area within the central posterior pole and the peripheral fundus. The peripheral retina was divided further into mid periphery (posterior to the equator) and far periphery (anterior to the equator) retina, with their junction at the equator of the globe.

Tumors were categorized into subgroups according to the LBD and apical height (H) following the COMS classification: If LBD >16 mm and/or H >10 mm, then the tumor was classified as a large tumor; if 10 $\leq$ LBD < 16 mm and 2.5 mm < H < 10, then the tumor was classified as a medium tumor; other cases were classified as small tumors. Additionally, we used the new American Joint Committee on Cancer (AJCC) 7 tumor, nodes, and metastasis (TNM) classification of tumor size (T parameter) to stage the 4 sizes of tumors.[14]

Statistical Analysis

Comparisons between the genders were performed by analyzing means with Student's *t*-test and Pearson correlations. Contiguous parameters were grouped into categories. Survival function was estimated using the Kaplan-Meier method and log-rank tests.

Competing risks for melanoma-related mortality as well as the semiparametric proportional hazard model were calculated via Gray's K-sample tests.[15]

The overall significance level was set to an alpha of 0.05. Statistical analyses were performed using JMP Statistical Discovery Software 7.0 (SAS Institute, Cary, NC) and R, version 2.13.0 (freely available online at http://www.r-project.org, provided by The R Foundation for Statistical Computing, Vienna, Austria).

Results

Uveal melanoma was diagnosed in 723 patients: 325 men (44.95%) and 398 women (55.04%). The mean annual distribution was 43.3% men and 56.7% women (paired *t*-test, $P = 0.001$). The mean age at diagnosis for male patients was 60.96 years (95% confidence interval [CI] 58.66–63.27), and the mean age at diagnosis for female patients was 60.16 years (95% CI 58.15–62.18). No significant gender difference in diagnosis age was observed (*t*-test, $P = 0.607$).

Tumor Size and Classification

There were no statistically significant differences in tumor size between male and female patients (Table 1).

Intraocular Tumor Location

Tumors were located most often in the choroid (in 86.15% of male and 82.66% of female patients). There was a similar distribution between the genders of tumors located in the iris and ciliary body (CB, Table 1). Regarding tumors located in the choroid, male patients tended to have a significantly higher rate of tumors detected posterior to the equator (42.28% vs. 33.99%, Pearson χ^2, $P = 0.0294$). Moreover, tumors were located more frequently in the posterior pole in men compared with women (17.79% vs. 10.96%, Pearson χ^2, $P = 0.0123$).

Reason for Referral

Most patients of both genders were symptomatic at diagnosis (the remainder were diagnosed during routine eye examination). However, despite the more posterior tumor location, men were less likely to complain about symptoms before the diagnosis than women (77.10% vs. 84.65%, Pearson χ^2, $P = 0.0402$). The most frequent complaints of both genders were disturbances in visual field, decreasing visual acuity, and blurred vision. Rare complaints were photopsia, redness, pain, and hemorrhage. No significant gender difference in the type of complaints before the diagnosis was observed (likelihood ratio $P = 0.436$).

Treatment

Brachytherapy via a Ruthenium 106 plaque was the most common treatment for both genders, and was used for 79.04% of the women and 75.49% of the men. Eyes with tumors that were too large for brachytherapy were enucleated at the same rate for both genders: 17.56% for women and 20.92% for men. Overall, there was no statistically significant difference in the treatment modalities (likelihood ratio, $P = 0.579$, Table 2).

Tumor Recurrence

Of the 723 patients, 42 (5.81%) had recurrence: 18 male (5.54%) and 24 female (6.03%) patients. No significant gender difference in recurrence was observed in this analysis (Pearson χ^2, $P = 0.778$).

Metastatic Disease and Survival

Of the 723 patients, 89 (12.31%) had metastases in the study period: 49 (15.08%) male and 40 (10.05%) female patients (Pearson χ^2, $P = 0.040$).

Among those who had metastases during the first five years after diagnosis of UM, men suffered metastases at an almost two-fold rate compared with women, with 26% of the men versus only 13% of the women having metastases within one year, and 84% and 50%, respectively, having metastases within five years from UM diagnosis (log-rank $P = 0.007$, Table 3, Fig. 1). Moreover, the cumulative incidence for melanoma-related mortality was significantly higher for men, with an almost two-fold excess of male melanoma-related mortality in the first 10 years after diagnosis of UM (Gray's K-sample test $P = 0.018$, Table 3, Fig. 2 top). This gender difference favoring the survival of female patients also was apparent in the length of survival time after the diagnosis of metastases with a mean $\pm$ SE survival of 20.1 $\pm$ 4.5 months for men and 36.8 $\pm$ 9.2 months for women (log-rank $P = 0.134$). Finally, the cumulative incidence for nonmelanoma-related deaths was higher for women (Gray's K-sample test $P = 0.096$, Fig. 2 bottom).

A Multivariable Regression Analysis for Melanoma-Related Mortality

A regression model for competing risks was constructed to analyze variables that may be predictive of melanoma-related mortality. The variables that showed a correlation with prognosis in the univariate analysis included age, gender, intraocular tumor location, and tumor size (height and LBD, or TNM T status). For male patients, intraocular tumor location at CB and tumor size were independently predictive of increased risk of melanoma-related mortality, whereas age was not

Table 1. Tumor Size and Intraocular Tumors' Location

	Men	Women	*P* Value*
Height, mm, mean ± SD	6.03 ± 3.41	5.60 ± 3.23	0.207
Small	11.03%	11.40%	
Medium	72.76%	77.21%	
Large	16.21%	11.40%	
LBD, mm, mean ± SD	11.57 ± 4.33	11.04 ± 3.86	0.241
Small	35.90%	41.18%	
Medium	50.55%	48.92%	
Large	13.55%	9.91%	
LBD + H group			
Small	9.68%	9.82%	0.332
Medium	67.03%	71.78%	
Large	23.30%	18.40%	
TNM (AJCC7)			
T1	28.10%	32.50%	0.145
T2	38.69%	35.63%	
T3	24.09%	26.88%	
T4	9.12%	5.00%	
Intraocular location			
Iris	5.37%	8.43%	0.124
CB	16.78%	19.94%	0.298
Choroid			
Anterior to equator	44.30%	44.94%	0.868
Equator	37.58%	39.04%	0.701
Posterior to equator	42.28%	33.99%	0.029
Posterior pole	17.79%	10.96%	0.012
Juxtapapillary	8.72%	11.80%	0.197

* Pearson χ^2.

associated with melanoma-related mortality in this model (Table 4).

Discussion

Uveal melanoma, the most common primary intraocular tumor in adults, has been studied intensely in the last decades. However, little attention has been dedicated to finding gender differences in uveal melanoma. This is in contrast with other tumors, such as cutaneous melanoma, where gender differences in tumor thickness and survival have been found.[8,9]

Table 2. Treatment Types

	Men	Women
Biopsy		
% Column	0.33	0.00
% Row	100.00	0.00
Brachytherapy		
% Column	75.49	79.04
% Row	45.29	54.71
Enucleation		
% Column	20.92	17.56
% Row	50.79	49.21
Local resection		
% Column	1.96	2.27
% Row	42.86	57.14
Proton beam irradiation		
% Column	1.31	1.13
% Row	50.00	50.00

Table 3. Metastases and Survival

	Men, %	Women, %	*P* Value
Metastases cumulative incidence*			
1 y	26.0	13.0	0.007
2 y	44.0	27.8	
3 y	68.0	33.3	
4 y	80.0	44.4	
5 y	84.0	48.2	
Cumulative incidence of melanoma-related mortality†			
5 y	9.7	4.7	0.018
10 y	14.8	8.2	
15 y	17.3	12.3	
Survival after diagnosis of metastases‡			
1 y	54.0	65.2	0.134
2 y	26.0	38.0	
3 y	14.0	30.8	

* The cumulative incidence of metastases developing after the diagnosis of UM among those who had metastases (log-rank).

† The cumulative incidence of melanoma-related mortality among all patients (Gray's K-sample test).

‡ The survival rate after the diagnosis of metastases for the metastatic patients (log-rank).

Gender differences in characteristics of UM regarding the incidence of the disease, melanoma related mortality, and non-neoplastic related mortality have been only mentioned in the past.[16,17] The Hadassah-Hebrew University Medical Center Ocular Oncology Service has been the Israeli national referral center for over two decades. Almost all the UM patients in Israel have been diagnosed and treated at our center, and are followed biannually for life. In contrast with the SEER data on UM in the United States,[2] we had slightly more female than male patients in our study and a lower annual incidence of UM in male compared to female patients.

Tumor size has a great influence on the choice of treatment, development of metastases and the prognosis of the patients.[7] In our study men and women had tumors of comparable size.

Another important prognostic factor that was assessed for all the patients and compared between genders in this study was the intraocular tumor's location.[18] Damato and Coupland described the differential incidence and intraocular localization of UM between genders. They found that men had larger and more posterior tumors. In another study, Damato described symptoms to be correlated with male gender.[16] We found that men tended to have a higher rate of tumors that were diagnosed posterior to the equator. It has been shown that tumors posterior to the equator produce symptoms earlier.[19] Surprisingly, we found that men tended to complain less about symptoms before diagnosis. The tumor in male patients was diagnosed more often during a routine eye examination, while in female patients it was diagnosed more often because of complaints about disturbances in visual field, although the tumors of both genders were of comparable size. We assume that the differences in reason of referral result from personality and social features that were not within our scientific scope. We were unable to explain why UMs were not larger in male compared to female patients despite the later diagnosis in men.

One of the most important goals of our study was to determine whether gender has a role in the prognosis of uveal melanoma. Our study showed a distinct disadvantage for male patients. We found that men are at a higher risk for metastases. Moreover, we found that metastases appeared earlier in male than in female patients. We also found that men had a worse survival rate from the time of diagnosis of metastases than

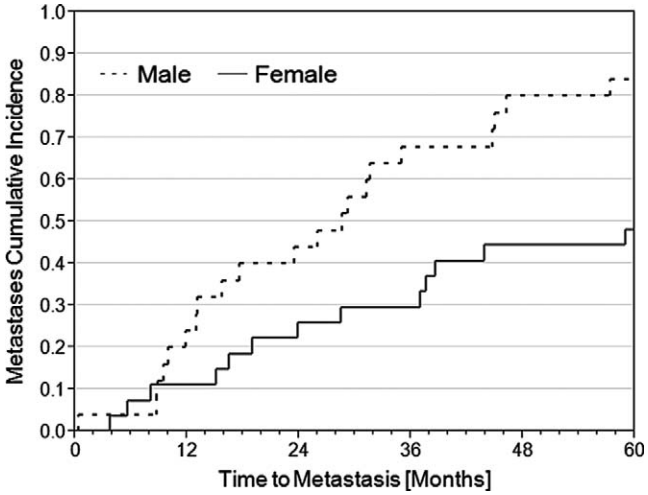

Figure 1. The 5-year cumulative incidence of metastases from the time of diagnosis of UM. The incidence rate refers to the subgroup of patients who had metastases and not to all the patients in the study.

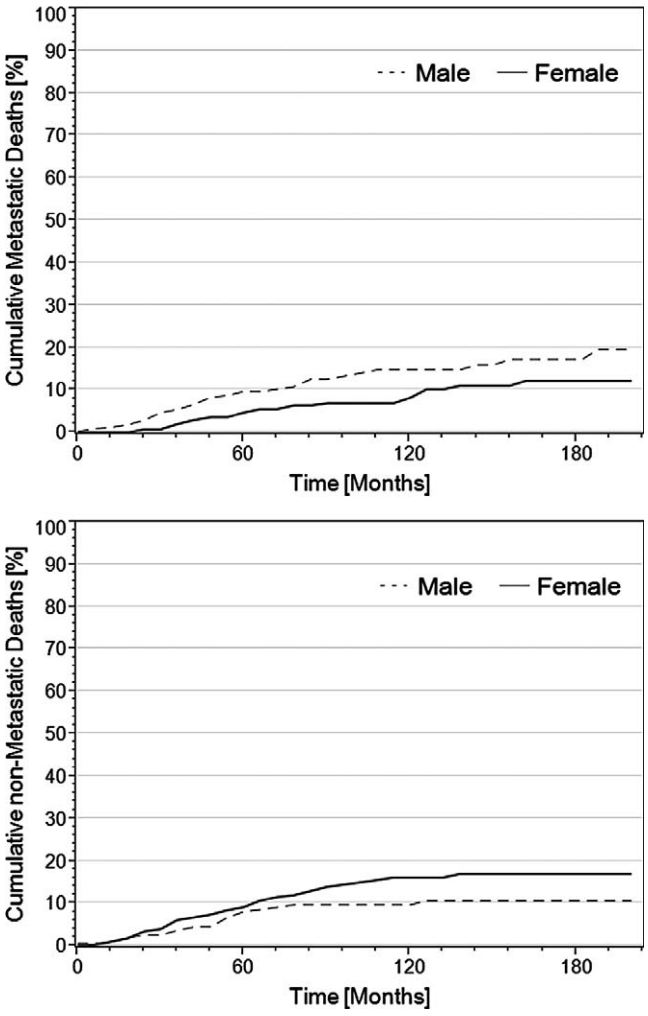

Figure 2. Cumulative incidence of melanoma-related mortality and melanoma-unrelated mortality.

Table 4. A Multivariable Regression Analysis of Melanoma-Related Mortality

Variant	RR	95% CI	*P* Value*
Age	0.99	0.98–1.01	0.760
Gender			
Men	1.66	0.99–2.77	0.051
Women	0.60	0.36–1	0.051
Tumor size	1.61	1.02–2.55	0.054
Intraocular tumor location	1.93	1.09–3.43	0.013

RR, relative risk.
* Gray's K-sample test.

women. One would expect this to lead to a worse overall survival in comparison to women; however, this was not the case, because the cumulative incidence of nonmelanoma-related deaths was higher in women (albeit not statistically significant).

Our study focused on the effect of gender on UM patients. A univariate analysis of competing risks found gender to be important for the rate at which metastases appear and their apparent aggressiveness, which led to a shorter survival from the day of diagnosis of metastases in men. Similar to our findings, Rietschel et al. found that female gender correlated independently with prolonged survival in UM metastatic patients.[20] In a multivariable regression analysis, male gender was associated with significantly higher risk of melanoma-related mortality than female gender. Kujala et al. also used the cumulative incidence method,[17] while Bergman et al. used a similar method that deals with competing risks (the relative survival method).[10] However, they did not find significant differences between the genders in melanoma-related mortality.[15] This may lead to the assumption that the ethnic group of the patient also has a role in the prognosis of the disease. The COMS compared overall survival and did not find a difference between men and women.[21] In our study we delved deeper into the data and found that, although there may not be a difference in overall survival, breaking up the metastatic survival (survival past the diagnosis of metastasis) into melanoma-related mortality and melanoma-unrelated mortality showed a difference between genders in the first decade (Fig. 2).

Several explanations can be proposed regarding the differences in prognosis between the genders, but the most likely one would be a hormonal mechanism. The direct effect of estrogen and progesterone on UM has been tested by looking for estrogen and progesterone receptors on primary and metastatic UM tissues.[22] It has been found that oral contraceptives or postmenopausal estrogens have no role in the etiology of uveal melanoma.[22] Controversy exists regarding the role of gravidity in the etiology of the disease. Some studies found that it increases the risk of UM,[23] while others claim that pregnancies actually decrease the risk.[22] It also was found that women's hormonal environment has no appreciable influence on the risk of metastases in younger women with uveal melanoma.[24] Estrogen receptors were not found in primary UM or in normal choroidal tissue, suggesting that estrogen receptor activity may not be involved in the presentation or growth of primary uveal melanomas.[24] We are not familiar with a study of testosterone levels in UM. One may conclude that testosterone receptors may exist on the tumors and result in a worse prognosis for men, or that estrogen indirectly influences tissue via the regulation of other factors that directly affect the melanoma.

One such indirect effect could be a female hormone–derived inhibitory action of the liver on the growth on micrometastases within it. However, further study into the

mechanism of growth of the micrometastases and the interaction with their surrounding liver is needed.

The initial site of metastasis in all of our patients but one was the liver, so this factor had no effect of the survival. In a previous study on the UM metastases we discussed the number of lesions in the liver and their treatment.[25] In that study, we did not find a difference between men and women when comparing the number of metastases and their treatment. Therefore, we did not repeat that evaluation here.

In summary, our retrospective study found gender differences in clinical behavior, the location of the tumor and reason of referral, and in prognosis. The results of our study suggested that the prognosis of UM in male patients is worse than in female patients. Male patients have more metastases than female patients, and the time from the diagnosis of UM until development of metastases was shorter. Male overall mortality rate from UM was higher than female mortality rate. Future studies are needed to clarify whether some biologic factors are responsible for these differences.

References

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118: 1881–1885.
2. Singh AD, Topham A. Incidence of uveal melanoma in the United States: 1973-1997. *Ophthalmology*. 2003;110:956–961.
3. Hu DN, Yu GP, McCormick SA, Schneider S, Finger PT. Population-based incidence of uveal melanoma in various races and ethnic groups. *Am J Ophthalmol*. 2005;140:612–617.
4. COMS Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. *Arch Ophthalmol*. 2006;124:1684–1693.
5. Augsburger JJ, Gamel JW. Clinical prognostic factors in patients with posterior uveal malignant melanoma. *Cancer*. 1990;66: 1596–1600.
6. Onken MD, Lin AY, Worley LA, Folberg R, Harbour JW. Association between microarray gene expression signature and extravascular matrix patterns in primary uveal melanomas. *Am J Ophthalmol*. 2005;140:748–749.
7. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol*. 2005;123:1639–1643.
8. Scoggins CR, Ross MI, Reintgen DS, et al. Gender-related differences in outcome for melanoma patients. *Ann Surg*. 2006;243:693–698.
9. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19:3622–3634.
10. Bergman L, Seregard S, Nilsson B, Lundell G, Ringborg U, Ragnarsson-Olding B. Uveal melanoma survival in Sweden from 1960 to 1998. *Invest Ophthalmol Vis Sci*. 2003;44:3282–3287.
11. Chung SE, Kim SW, Chung HW, Kang SW. Estrogen antagonist and development of macular hole. *Korean J Ophthalmol*. 2010;24:306–309.
12. Klein BE, Klein R, Jensen SC, Ritter LL. Are sex hormones associated with age-related maculopathy in women? The Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 1994;92: 289–297.
13. Damato BE, Coupland SE. Differences in uveal melanomas between men and women from the British Isles. *Eye (London)*. 2011;26:292–299.
14. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17:1471–1474.
15. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res*. 2007;13: 559–565.
16. Damato B. Detection of uveal melanoma by optometrists in the United Kingdom. *Ophthalmic Physiol Opt*. 2001;21:268–271.
17. Kujala E, Makitie T, Kivela T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*. 2003;44:4651–4659.
18. Shildkrot Y, Wilson MW. Update on posterior uveal melanoma: treatment of the eye and emerging strategies in the prognosis and treatment of metastatic disease. *Curr Opin Ophthalmol*. 2009;20:504–510.
19. Li W, Judge H, Gragoudas ES, Seddon JM, Egan KM. Patterns of tumor initiation in choroidal melanoma. *Cancer Res*. 2000;60: 3757–3760.
20. Rietschel P, Panageas KS, Hanlon C, Patel A, Abramson DH, Chapman PB. Variates of survival in metastatic uveal melanoma. *J Clin Oncol*. 2005;23:8076–8080.
21. Hawkins BS. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. *Am J Ophthalmol*. 2004;138:936–951.
22. Holly EA, Aston DA, Ahn DK, Kristiansen JJ, Char DH. Uveal melanoma, hormonal and reproductive factors in women. *Cancer Res*. 1991;51:1370–1372.
23. Hartge P, Tucker MA, Shields JA, Augsburger J, Hoover RN, Fraumeni JF Jr. Case-control study of female hormones and eye melanoma. *Cancer Res*. 1989;49:4622–4625.
24. Makitie T, Tarkkanen A, Kivela T. Comparative immunohistochemical oestrogen receptor analysis in primary and metastatic uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*. 1998; 236:415–419.
25. Frenkel S, Nir I, Hendler K, et al. Long-term survival of uveal melanoma patients after surgery for liver metastases. *Br J Ophthalmol*. 2009;93:1042–1046.