Sex Disparity in Survival of Patients With Uveal Melanoma: Better Survival Rates in Women Than in Men in South Korea

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Purpose. The purpose of this study was to determine the survival rate of patients with uveal melanoma and sex disparity in this rate in South Korea.

Methods. We extracted incident uveal melanoma patients using the Korea Central Cancer Registry (KCCR) database, which covered the entire population from 1999 to 2012 in South Korea. We estimated all-cause survival probabilities and cancer-specific survival probabilities of patients with uveal melanoma and compared these probabilities between subgroups (sex, tumor site, age at diagnosis, etc.) using Kaplan-Meier methods and log-rank tests. We fitted the Cox-proportional hazards models for all-cause death and cancer death to determine sex disparities in survival.

Results. A total of 344 uveal melanoma patients (175 women, 51%) were ascertained. They comprised 283 patients with choroidal melanoma (82%) and 61 patients with ciliary body/iris melanoma (18%). The observed 5-year survival probability from all-cause death was 75% (95% confidence interval [CI]: 69%–79%); women with uveal melanoma showed higher survival probability (83% [95% CI: 76%–89%]) compared with men (66% [95% CI: 58%–73%], P < 0.01). After adjusting for age, year of diagnosis, tumor sites, and diagnostic verification method, the hazards for all-cause death and cancer death in women with uveal melanoma were lower than those in men (hazards ratio for cancer death = 0.50 [95% CI: 0.30–0.81]; hazards ratio for all-cause death = 0.39 [95% CI: 0.25–0.61]).

Conclusions. Women with uveal melanoma have better survival probabilities relative to men with uveal melanoma. Our findings show a comprehensive picture of survival probability in uveal melanoma cancer patients in Korea, which requires further investigation of mechanism of the sex disparity in uveal melanoma.

Keywords: uveal melanoma, survival, cancer registry, sex disparity, Korea
Sex Disparity in Uveal Melanoma Survival

MATERIALS AND METHODS

Data Sources

We obtained the 1999 to 2012 uveal melanoma data from the KCCR database. In 1999, the KCCR began to collect nationwide cancer incidence data by covering the entire Korean population under a population-based regional cancer registry program.\textsuperscript{2,25} Detailed descriptions of the KCCR database have been published.\textsuperscript{2,25,25} Briefly, for each cancer patient, the database includes information such as age, sex, region, birthdate, histologic type, date of diagnosis, and primary cancer site. Information regarding vital status and cause of death are obtained from the death registry of Statistics Korea and linked to the KCCR database.\textsuperscript{25} The institutional review board of the National Cancer Center approved the research protocol of present study (Institutional Review Board no. NCC2014-0156, Goyang, Korea), and the study was conducted in accordance with the Declaration of Helsinki.

Definition and Classification of Uveal Melanoma

We defined uveal melanoma as sites C69.2, C69.3, and C69.4 and morphology as 8720–8790 according to the International Classification of Diseases for Oncology, 3rd edition.\textsuperscript{25} We then classified uveal melanoma types as choroidal melanoma (C69.2, C69.3) and ciliary body/iris melanoma (C69.4) by tumor sites. Retinal melanoma was considered a choroidal melanoma.\textsuperscript{2,5,10} Most cases (91.6%) were first and only primary cancer, and only 8.4% of cases (29 cases) had multiple primary cancer. If patients have multiple primary cancers, the first primary cancer diagnosed was selected to estimate the survival probability of patients with cancer.

Statistical Analysis

We determined the distribution of the demographic characteristics (i.e., sex, age at diagnosis [patients diagnosed before 54 years and after 55 years of age], tumor sites [i.e., choroidal melanoma and ciliary body/iris melanoma], year at diagnosis [1999–2005 and 2006–2012], and diagnostic verification methods of uveal melanoma patients identified during the 14-year study period from 1999 to 2012). Differences in the distributions of categorical variables were assessed using \( \chi^2 \) tests, and mean difference (±SD) of age was tested by independent \( t \)-test. The survival duration for each uveal melanoma patient was determined as the time from the date of initial uveal melanoma diagnosis to the date of death or end of follow-up (December 31, 2015). The KCCR is also linked to database of the Ministry of the Interior to identify the follow-up loss (e.g., immigration). In our study, there was no loss to follow-up. We estimated the probability of survival from all-causes death and cancer death using the Kaplan-Meier method, according to age at diagnosis, tumor sites, year at diagnosis, and diagnostic verification methods, stratified by sex. Subgroup analysis was performed with the purpose of exploratory assessment. Sex disparities in the survival probability from all-cause death and cancer death of patients with uveal melanoma were addressed and tested using log-rank tests. The life table method was used to estimate 5-year survival and 95% confidence intervals (CIs). In addition, we performed the Cox-proportional hazards model for all-cause deaths and cancer deaths to determine the difference of the survival probability from all-cause death and cancer death between men with uveal melanoma and women with uveal melanoma. There is a limitation to identify uveal melanoma death from causes of death information, because the cause of death data was recorded and classified using only ICD-10 code, which contains only tumor site information and does not contain morphologic information. Therefore, melanoma and eye cancer were treated as the main cause of death for patients diagnosed with uveal melanoma. Of patients with uveal melanoma, the total number of deaths was 90. Of these, 78 patients died from cancer, and 12 died from noncancer deaths. Of these 78 cancer deaths, 8 cases who also had secondary cancers and died of diagnosed secondary cancer other than eye cancer or melanoma, were excluded from cancer death, because we wanted to capture primary cancers with uveal melanoma-related cancer death. Then, we considered the death for remaining 70 cases from other tumor as metastasis that primary tumors were originated from uveal melanoma, because there was no case with multiple primary tumors which died from cancer except for the two cases with unspecified or ill-defined tumor (ICD-10 code C80, C97).\textsuperscript{26} In short, we treated these 70 patients who died from cancer death as uveal melanoma-related cancer death. The Cox-proportional hazards model was performed to measure the hazard ratios (HRs) for all-cause death and cancer death as events of interest after adjusting for covariates (age, year of diagnosis, tumor site, and diagnostic verification method). We used the backward elimination procedure to fit the best parsimonious model. We checked for the proportional assumptions using martingale residuals and Schoenfeld residuals, and the proportional hazard assumptions were satisfied. \( P < 0.05 \) was considered statistically significant, and Bonferroni correction was applied to the subgroup analysis. We used Stata 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.3 (SAS Institute, Cary, NC, USA) software for statistical analyses.

RESULTS

We included a total of 344 patients (175 women; 51%) with uveal melanoma in the analyses. The mean follow-up period was 5.4 years, and it ranged from 2.5 months to 14.8 years. Median follow-up times for those who diagnosed in 1999 to 2005 is 9 years and 3.6 years for the recently diagnosed patients in 2006 to 2012. Most of recently diagnosed patients are alive as of December 31, 2013. Table 1 provides the demographic and tumor characteristics of the study population. The mean age (±SD) of women (53.7 ± 15.9 years) is older than men (50.3 ± 15.4 years, \( P = 0.049 \)). However, there were no significant differences in year of diagnosis and diagnostic verification method between men and women. There were 283 patients with choroidal melanoma (82%) and 61 patients with ciliary body/iris melanoma (18%); this was not different between sexes (men: choroidal: 85%, ciliary body/iris melanoma: 17% versus women: choroidal: 82%, ciliary body/iris melanoma: 18%; \( P = 0.78 \)).

The 5-year survival probability from all-cause death of patients with uveal melanoma was 75% (95% CI, 69%–79%). The 5-year survival probability from all-cause death of women (83% [95% CI, 76%–88%]) was significantly higher than that of men (66% [95% CI, 58%–73%]; \( P < 0.0001 \); Fig. A). Sex disparity for 5-year survival probability from all-cause death was observed in patients with choroidal melanoma (men: 67% [95% CI, 57%–75%], women: 83% [95% CI, 74%–89%]; \( P = 0.001 \)). Although there was no significant differences in 5-year survival probability at the significance level of 0.025 (\( P = 0.06 \)), women with ciliary body/iris melanoma (86% [95% CI, 66%–94%]) had higher 5-year survival probability from all-cause death than men with ciliary body/iris melanoma (62% [95% CI, 41%–78%]; Fig. B, C).

According to the age at diagnosis, women had higher 5-year survival probability from all-cause death than men for both subgroups aged 0 to 54 years at diagnosis (men: 73% [95% CI,
Diagnostic verification

Year at diagnosis

Tumor site

1999 to 2005 (melanoma (59% [95% CI, 46%–69%]) for patients diagnosed in melanoma (80% [95% CI, 67%–88%]) showed higher 5-year CI, 73%–86%) for patients diagnosed in 2006 to 2012.

60%–76%) for patients diagnosed in 1999 to 2005 to 80% (95% CI, 62%–81%

‡ Bonferroni correction was applied and the level of significance was set as P < 0.025.

The HRs and 95% CIs for all-cause death and cancer death are shown in Table 3 and Table 4, respectively. In the unadjusted Cox proportional hazards model, the HRs and 95% CIs of women for all-cause death and cancer death were 0.44 (95% CI, 0.29–0.68) and 0.52 (95% CI, 0.43–0.85), respectively. In the fully adjusted Cox proportional hazards model, the HRs and 95% CIs of women for all-cause death and cancer death were 0.40 (95% CI, 0.25–0.62) and 0.49 (95% CI, 0.30–0.81), respectively, after adjusting for age, year of diagnosis, tumor sites, and diagnostic verification method. In the Cox proportional hazards model fitted by using the backward elimination procedure, the HRs and 95% CIs of women for all-cause death and cancer death were 0.39 (95% CI, 0.25–0.61) and 0.50 (95% CI, 0.30–0.81), respectively, after adjusting for age and diagnostic verification method.

**DISCUSSION**

We characterized survival probability from all-cause death and cancer death of patients with uveal melanoma in Korea using population-based cancer registry data. The results illustrated sex disparities in survival probability of patients with uveal melanoma—women with uveal melanoma had better survival probability than men with uveal melanoma—in Korea. As uveal melanoma is quite rare in Asian populations compared with Anglo-European populations, a representative national registry with a large number of the population at risk and sufficient follow-up periods is needed to reliably estimate survival rates in an Asian population. South Korea is one of the populous countries worldwide (approximately 50 million people), and the Korean national cancer registry, the KCCR, has covered the entire Korean population since 1999.

Therefore, we were able to calculate detailed estimates of survival probability from all-cause death and cancer death of patients with uveal melanoma in the Korean population, despite a low incidence rate of uveal melanoma in Korea.
The estimated 5-year survival probability from all-cause death was 75% in Korea; unlike the incidence estimates, survival probabilities were similar to those of recent studies across populations and regions, especially considering that our estimates were observed survival probabilities.10,12–14 Interestingly, women with uveal melanoma in Korea had better 5-year survival probability than did men over the study period, whereas characteristics of uveal melanoma patients (e.g., tumor site, year at diagnosis, diagnostic verification method) were not different between sexes. The better survival probabilities for women with uveal melanoma, compared with men, were found consistently in the results of the Cox-proportional hazards model for all-cause death and cancer death. In addition, sex, age, and diagnostic verification method were the major factors for survival of patients with uveal melanoma, regardless of which model was selected. The sex disparity in survival was also consistently for the younger people <55 years old with uveal melanoma or patients with microscopically diagnosed uveal melanoma. Several studies in Anglo-European populations have also reported sex disparity—women with uveal melanoma have greater longevity—in uveal melanoma survival.12,14,15,17 Historically, studies have explained the greater women’s longevity in two ways: biological differences and health behavior discrepancies between men and women. Previous studies showed sex differences in tumor characteristics (thickness, diameter, and location), behavior of metastasis, and hormonal mechanism: men tend to have thicker, larger, and posteriorly located tumors and experience early and more aggressive metastasis compared with women.15,16,27–29 In addition, Damato et al. also reported that iris melanoma is more commonly observed in women than in men.16,30 However, unfortunately, we were not able to distinguish between iris melanoma and ciliary body melanoma in our cancer registry database (KCCR). These biological differences between men and women might result in the longer survival duration among women with uveal melanoma. On the other hand, Zloto et al. reported that men were less likely to complain of symptoms before uveal melanoma diagnosis than women,29 which might lead to a delayed diagnosis in men and result in survival differences. Similarly, Virgili et al. suggested that a delayed diagnosis could cause lower survival in men in population-based cancer registry studies.12

Interestingly, our results showed that the change in 5-year survival probability from all-cause death from 1999–2005 to 2006–2012 was different between men and women. In men with uveal melanoma, 5-year survival probability from all-cause death improved substantially from 1999–2005 to 2006–2012, whereas women with uveal melanoma experienced only a minor improvement in 5-year survival probability from all-cause death in the same period. However, there was no significant improvement in 5-year survival probability from cancer death both for men and women from 1999–2005 to 2006–2012 (Supplementary Table S1). In Anglo-European populations, an improvement of survival probability among patients with uveal melanoma was not observed in recent studies.10,12–14 On the other hand, 5-year survival probabilities from all-cause death and cancer death among men with clinically diagnosed uveal melanoma were better compared with men with microscopically diagnosed uveal melanoma. These findings support the idea that early detection of ocular melanoma could increase the survival probability in men. In addition, the proportion of men with clinically diagnosed uveal melanoma has increased by 10 times from 4.6% in 1999 to 2005 to 46.2% in 2006 to 2012 (Supplementary Table S2). This might be because, in recent decades, the Korean health care system has achieved overall improvements and increased the
numbers of ophthalmologists, retinal specialists, and ocular oncology specialists. Moreover, in 1999, the Korean government initiated a national screening program for cancer, and providers frequently offer fundus photography for screening chorioretinal diseases. Improvements in the health care system and increasing frequency of medical checkups might also affect health behaviors differently in a sex-specific manner (e.g., screening examination might be more effective in men who are less likely to complain of symptoms). However, as we were unable to assess differences in tumor characteristics, metastatic behavior, and health care utilization patterns between men and women in the KCCR database, further investigation is warranted to elucidate the longer survival duration among Korean women with uveal melanoma.

In the present study, we reported 5-year survival probabilities from all-cause death as an overall picture of prognosis and survival outcomes in uveal melanoma patients in Korea. Survival estimates of the period 2006 to 2012 is based on the follow-up available, and some of patients may not have complete 5-year follow-up but contributed to the survival intervals up to their follow-up times. Although observed survival reflects all-cause mortality of uveal melanoma patients, it did not reflect the net cancer-specific survival for uveal melanoma. In population-based cancer registry studies, relative survival or cause-specific survival is often estimated as a net measure of survival. In this study, our findings also showed that 5-year survival probabilities from cancer death in women was better than in men, and sex differences of hazard ratio from cancer death were also observed in the Cox-proportional hazards model after adjusting covariates. Although we did not show in this study, the estimated 5-year relative survival rates for the study population were 70% (95% CI, 57%–73%) in men and 87% (95% CI, 76%–88%) in women, which were similar to the all-cause observed survival rates. In addition, after adjusting for multiple covariates, HR for cancer death in women was significantly lower than in men.

Our study has several limitations. First, the KCCR database lacks information regarding detailed tumor characteristics,

<table>
<thead>
<tr>
<th>Variables</th>
<th>All, 5-y Survival Rate (95% CI)</th>
<th>Sex, 5-y Survival Rate (95% CI)</th>
<th>P Value* (Log-Rank Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Men (N = 169)</td>
<td>Women (N = 175)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–54 years</td>
<td>75 (69–79)</td>
<td>66 (58–75)</td>
<td>83 (76–88)</td>
</tr>
<tr>
<td>≥55 years</td>
<td>66 (57–74)</td>
<td>56 (41–68)</td>
<td>76 (65–85)</td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Choroid (C69.2–69.3)</td>
<td>75 (68–80)</td>
<td>67 (57–75)</td>
<td>83 (74–89)</td>
</tr>
<tr>
<td>Ciliary body and iris (C69.4)</td>
<td>75 (61–84)</td>
<td>62 (41–78)</td>
<td>86 (66–94)</td>
</tr>
<tr>
<td>Year at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999–2005</td>
<td>69 (60–76)</td>
<td>59 (46–69)</td>
<td>80 (67–88)</td>
</tr>
<tr>
<td>2006–2012</td>
<td>80 (73–86)</td>
<td>75 (64–83)</td>
<td>85 (75–92)</td>
</tr>
<tr>
<td>Diagnostic verification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>70 (64–76)</td>
<td>59 (49–68)</td>
<td>83 (74–89)</td>
</tr>
<tr>
<td>Clinical/other</td>
<td>87 (76–93)</td>
<td>91 (77–96)</td>
<td>83 (67–92)</td>
</tr>
</tbody>
</table>

* Log-rank test was used to test the differences of the survival distribution between men and women.  † Bonferroni correction was applied and the level of significance was set as P < 0.025.
Sex Disparity in Uveal Melanoma Survival

**Table 4.** Hazard Ratios for Cancer Death Among Patients With Uveal Melanoma in Korea

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted Model, Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Fully Adjusted Model, Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Selected Model,* Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.52 (0.32–0.85)</td>
<td>0.008</td>
<td>0.49 (0.30–0.81)</td>
<td>0.005</td>
<td>0.50 (0.30–0.81)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Age, year</strong></td>
<td></td>
<td></td>
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<tr>
<td>1999–2005</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>2006–2012</td>
<td>0.70 (0.42–1.15)</td>
<td>0.16</td>
<td>0.93 (0.55–1.57)</td>
<td>0.78</td>
<td></td>
<td></td>
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<tr>
<td><strong>Year at Diagnosis</strong></td>
<td></td>
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<tr>
<td>1999–2005</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>2006–2012</td>
<td>0.70 (0.42–1.15)</td>
<td>0.16</td>
<td>0.93 (0.55–1.57)</td>
<td>0.78</td>
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<tr>
<td><strong>Tumor site</strong></td>
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<tr>
<td>Choriocapillary stroma (C69.2-69.3)</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Ciliary body and iris (C69.4)</td>
<td>1.37 (0.79–2.37)</td>
<td>0.26</td>
<td>1.21 (0.69–2.12)</td>
<td>0.50</td>
<td></td>
<td></td>
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<tr>
<td><strong>Diagnostic verification</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Clinical/other</td>
<td>0.35 (0.17–0.75)</td>
<td>0.005</td>
<td>0.40 (0.18–0.87)</td>
<td>0.02</td>
<td>0.37 (0.18–0.78)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Fully adjusted model is modeled after adjusting for age, year of diagnosis, tumor sites, and diagnostic verification methods.

Histopathologic features, metastatic behavior, and information regarding treatment. Second, we could not investigate sex differences in health behavior (i.e., screening rates, health care utilization pattern, extent of complain of symptoms or pain). Third, increases in the number of ocular melanoma cases from 1999–2005 to 2006–2012 seems to be mainly attributed to increasing general longevity, but some are likely to be partly due to improvement of completeness of cancer registration. Fourth, it cannot be ruled out that retinal melanoma might be metastatic skin melanoma to the eye, although the trained registrar thoroughly reviewed the medical chart and pathologic report before classifying the corresponding case as primary cancer site or metastatic site, and retinal melanoma was quite rare (4 [1.2%] of 344 uveal melanoma cases) in the KCCR database. Finally, we considered cancer death as a surrogate variable for uveal melanoma death. The cause of death was classified using ICD-10 code by the national statistics office. It was limited to identify the uveal melanoma death from cause of death data, because cause of death data were coded using the ICD-10 code, which contains only tumor site and does not include morphologic information. However, most cases were the first and only primary cancer. Furthermore, the patients who were diagnosed secondary cancer and died from the secondary cancer death were excluded from cancer deaths. Therefore, we treated cancer death from cause of death data as uveal melanoma death.

Notwithstanding these limitations, our data showed that women with uveal melanoma had a better survival probability compared with men in the Korean population using the nationwide, population-based national cancer registry. Better survival probabilities from all-cause death and cancer death in women with uveal melanoma were consistently observed in the results of the Kaplan-Meier method and the Cox-proportional hazards model. In Korea, there have been survival disparities by sex—women have a better survival probability than men—among uveal melanoma patients, suggesting that more careful medical examination is needed to detect ocular melanoma earlier for men. Future study is needed to unravel the exact mechanism underlying sex differences in the survival probability of patients with uveal melanoma.

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