Uveal Melanoma Survival in Sweden from 1960 to 1998

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PURPOSE. To investigate the crude and relative survival rates in patients with uveal melanoma in Sweden during the period from 1960 to 1998.

METHODS. A population-based national survey revealed 2997 cases of uveal melanoma in the Swedish Cancer Registry. The survival rates were calculated by the Hakulinen life-table method, using relative survival as an estimate for deaths due to uveal melanoma. The excess mortality rates were calculated with confidence intervals for the first 5 years after diagnosis. Multivariate regression analysis was undertaken to evaluate the influence of gender, age, and calendar period on relative survival the first 5 years after diagnosis. The underlying causes of deaths in the patients with uveal melanoma, as found in the Cause of Death Registry were also investigated.

RESULTS. Up to December 31, 1998, 2003 patients had died. The 5-year crude survival rate was 60.3% and the relative survival 70.1%. After 10 years, the rates were 42.5% and 59.4%, respectively. Significant excess mortality existed up to 5,5 years after diagnosis. In the multivariate model, younger age (P < 0.001) and later calendar period (P = 0.002), but not gender (P = 0.117), were associated with better relative survival. Deaths due to uveal melanoma were misclassified in the Cause of Death Registry in more than half of the cases.

CONCLUSIONS. This study, covering more than 95% of the uveal melanoma cases in the Swedish population revealed an improvement in relative survival rates for patients with uveal melanoma over time and a significant excess mortality up to 5.5 years after diagnosis. (Invest Ophthalmol Vis Sci. 2003;44: 3282–3287) DOI:10.1167/iovs.03-0081

Uveal melanoma is the only primary malignancy of the eye that can be considered life threatening to the population above the age of 15 years. The mortality rate is high despite modern treatment modalities and the clinical course is in many ways unpredictable. The 5-year mortality rates vary from 6% to 53%,2–5 depending on patient selection. Late metastases have been reported several decades after diagnosis.5,6 Within 10 years of diagnosis of uveal melanoma, approximately 40% of the patients have metastases, predominantly to the liver. Life expectancy after clinical detection of metastases is poor. Without treatment, a median survival time of 2 to 6 months7–9 is expected. A modest improvement has been experienced in recent years, with a prolonged median survival time up to 1 year with different combinations of systemic or intrahepatic delivery of chemo- and immunotherapy.10–13

Published studies have often focused on comparing recently introduced treatments with each other or with the former standard treatment, enucleation.14–18 The patients have therefore been sampled and randomized prospectively, as in the collaborative ocular melanoma study (COMS) or compared with historical controls. The observed all-cause mortality has in many instances been used as a measurement for the overall outcome in uveal melanoma. Several sources such as death certificates, hospital files, with or without histopathologic specimens of metastases, have been used to capture the melanoma-specific mortality rate with a varying level of certainty.

The purpose of our study was to investigate the all-cause mortality and the mortality due to uveal melanoma, with a minimal loss to follow-up in an unselected population of patients with uveal melanoma emanating from a nationwide population-based survey in Sweden, covering almost four decades.19 The melanoma-specific mortality rates were further analyzed in subgroups, with respect to gender, calendar period, and patient age at diagnosis. In this uveal melanoma population, an evaluation was also undertaken of the validity of the underlying causes of deaths as reported to the Cause of Death Registry.

MATERIALS AND METHODS

A national population-based survey in Sweden revealed 2997 cases of uveal melanoma (including iris, choroid, and ciliary body melanomas) during the period from 1960 to 1998 and is estimated to have captured more than 95% of the cases.19 The survey was based on reports to the Swedish Cancer Registry and hospital files from the two centers where eye-sparing treatments have been performed since the late 1970s. The latter search was performed to ensure inclusion of patients with no histologic specimen available. Since 1979, 387 patients had received 192–198 ythanium episcleral plaques as the initial treatment, and during the period 1989 to 1991 another 20 patients underwent treatment with proton beam irradiation.

Through an individual national registration number, linkage between the annual population census, the Cancer Registry, and the Cause of Death Registry can be achieved so that loss to follow-up is minimized. The Cause of Death Registry reports the underlying cause of death, according to the International Classification of Diseases (ICD) code used in Sweden at the time of the death of each respective patient (1960–1968: ICD-7; 1969–1986: ICD-8; 1987–1996: ICD-9; 1997–ICD-10). The method of establishing the cause of death is coded as autopsy, clinical examination, or forensic investigation, along with a more specified subgrouping of the clinical examination. After approval of the research protocol by the Human Ethics Committee at the Karolinska Institute in accordance with the statutes of the World Medical Association’s Declaration of Helsinki, a combined database was set up consisting of 2997 patients with uveal melanoma, including their survival status at the cutoff date of December 31, 1998. To further investigate the cause of death, the database was cross checked against other diagnoses in the Cancer Registry, because it appeared that many patients had died with a diagnosis of other cancers that might have

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been related to uveal melanoma—especially cutaneous melanoma and unspecified pulmonary and hepatic tumors. Also, a search against hospital files was performed in the cancer cases in which the underlying cause of death was difficult to classify (119 patients, mainly with secondary hepatic and pulmonary tumors of unspecified origin), but many of the patients could not be found because Swedish law stipulates that medical records must be preserved for only 10 years after the death of a patient. Thirty files could be traced and were reviewed, and in 20 cases the diagnosis of uveal melanoma–related death was classified with varying degrees of certainty (verified through autopsy, liver imaging, or biopsy). The autopsy rate over time in the total uveal melanoma population was also investigated.

Survival was analyzed by the life-table method described by Hakulinen and Abeywickrama,21 in which relative survival is used as an estimate of cause-specific mortality. The relative survival rate is defined as the ratio of the survival rate observed in a patient group of interest to the survival rate expected in a group of people similar to the patient group in all factors (age, gender, and calendar period) affecting survival, except the disease of interest. Survival in cancer is often measured by this quantity, which is adjusted for the effect on mortality attributable to competing risks of death. The Swedish life tables,22 with annual reports and covering the ages 0 to 99 years gender specifically, were used in the calculations. The annual excess mortality rate was estimated with the following formula: excess mortality rate during year \(0 \leq i \leq n-1 = \frac{1}{n} - \frac{1}{i} \) cumulative relative survival rate year \(0 \leq i \leq n-1\). For the following years: (cumulative relative survival \(i-1\) - cumulative relative survival \(i, i/n\)) cumulative relative survival \(i\), where \(i\) is year 0-1, 1-2, 2-3, . . . .

The annual excess mortality rate was calculated for the first 15 years with 95% confidence intervals. Univariate analyses of survival classified by age group (0–44, 45–59, 60–74, and 75+ years), calendar periods (1960–1969, 1970–1979, 1980–1989, and 1990–1998), and gender (male, female) for the first 5 years after diagnosis were undertaken. A multivariate model was set up for analysis of the simultaneous influence of gender, age group, and calendar period on relative survival for the first 5 years after diagnosis. Regression analysis of relative survival rates was performed according to the life-table proportional hazards model suggested by Hakulinen and Tenkanen.23 This is a fixed-interval grouped version of the Cox model, and the Generalized Linear Interactive Modelling (GLIM) software package24 was used to fit the model. The fitted model included a constant and the categorical variables of the four age groups; four time periods; follow-up years 1, 2, 3, 4, and 5; and gender. Relative risk ratio with 95% confidence intervals was estimated for each factor, taking the first level as baseline. The level of significance was set at \(P \leq 0.05\) or less.

**RESULTS**

**Validity of the Coded Underlying Causes of Death in the Uveal Melanoma Population**

During the period 1960 through 1998, 2997 uveal melanoma cases were identified in Sweden, in which 2003 persons had died at the end point of the study on December 31, 1998. Information was unavailable about survival status in only nine patients because of emigration. The Cause of Death Registry reported 474 (24%) patients with uveal melanoma as the underlying cause of death, but as many as 574 (29%) patients were registered with cutaneous melanoma as the underlying cause (Table 1).

Of these 574 patients, only 25 patients were included in the Cancer Registry with a separate registration of cutaneous melanoma. A sample was drawn from the remaining 549 patients (with uveal melanoma and cause of death registered as cutaneous melanoma) consisting of the patients who died after 1989 and lived in the Stockholm area (57 patients). Hospital files from the regional oncology clinics were analyzed, because many patients received palliative treatment for melanoma metastases, and in no instance could the diagnosis of cutaneous melanoma be verified. The 549 patients were considered to have died of uveal melanoma and to have been originally misclassified, either by the clinician or at the registration office. Nonmelanoma cancers were the underlying cause of death in 291 patients, and information about the cause of death was unavailable for two patients. The autopsy rate of the patients with uveal melanoma declined throughout the investigation period, from 44% to 15%. We chose not to enter these findings into further analysis of survival, because the level of uncertainty was considerable, with the risk of over- or understimating the melanoma-related mortality rate.

**Relative Survival as a Measurement for Uveal Melanoma-Related Mortality**

During the first 5 years of follow-up, 620 men and 491 women died, and at 10 years, 842 men and 691 women had died. The crude (observed) survival rate after 5 years was estimated to be 60.3% (57.2% in men and 63.6% in women). The 10-year crude survival rate was 42.5% (39.0% and 46.4%, respectively). The relative survival rate, taken as the estimate for the deaths due to uveal melanoma was 70.1% for the first 5 years (68.3% in men and 71.9% in women). After 10 years, the rates were 59.4% (57.8% in men and 60.9% in women), with the overall rates shown in Figure 1. The tendency toward a better 5-year relative survival for women, as estimated with a risk ratio of 0.88 (95% CI: 0.73–1.05) did not reach statistical significance. The excess mortality rate in the uveal melanoma population was significantly elevated for the first 5.5 years after diagnosis, as estimated from the confidence intervals (Fig. 2). The peak excess mortality (8.0%) occurred during years 3 to 4 after diagnosis. The cumulative excess mortality rate was 29.9% at 5.5 years. Between 6 and 10 years after diagnosis, a statistically nonsignificant trend toward prevailing excess mortality was observed. In the univariate analysis, younger age at diagnosis (\(P < 0.001\); Fig. 3) and later calendar periods (\(P = 0.002\); Fig. 4), but not gender (\(P = 0.123\)), correlated with improved survival.

The multivariate model, which measured the simultaneous effect of calendar period, patient age at diagnosis, gender, and follow-up years on relative survival, was performed with regression analysis. Again, the factors age (\(P < 0.001\)) and calendar period (\(P = 0.002\), but not gender (\(P = 0.117\)), were statistically significant, with better survival in younger age groups and in later calendar periods (Table 2).

**DISCUSSION**

In this population-based survey, the calculations were based on the relative survival rates as a measure of melanoma-specific mortality, because the validity of death certificates was questionable. In analyzing mortality, the risk of misclassification of the underlying cause of death is a considerable matter of concern.25 The validity of death certificates has been analyzed in many papers and both over- and underreporting of
diagnoses occur. A common error is that a broader definition or a nonspecific site is overrepresented as an underlying cause of death in the certificates. Percy found in a survey of more than 48,000 cancer deaths that sites common for metastasis, such as bone, were overrepresented, whereas deaths caused by of ocular cancer were correctly classified in only 49% of cases. In our study, we found the same pattern, with an accurate classification rate of 46%. In the death certificates, 474 patients were classified with ocular cancer, but as many as 549 patients had been classified as dying of cutaneous melanoma, but there were no previous registrations or records of this disease in hospital files of these patients.

The formula chosen in this study to estimate the uveal melanoma-related mortality rate, the relative survival method described by Hakulinen and Abeywickrama, has gained wide acceptance in cancer epidemiology, because it deals with competing death risks. The method allowed us to calculate the mortality rates of this rare disease in a whole population, without having the true underlying causes of death established. Because uveal melanoma has a peak incidence in the age group of more than 65 years in the Swedish population, the patients are at high risk of dying of other causes. Kroll et al. found, however, that patients with uveal melanoma are not at higher risk than expected of dying of nonmelanoma causes. The
expected mortality rates from life tables are calculated from all causes of death, including the studied disease of interest, but this specific disease constitutes a negligible fraction of the total mortality, and the use of population life tables can therefore be justified.30 Also, choosing a population-based approach avoided case selection, such as the patterns of referral to ocular oncology clinics, which can be a possible source of bias in analyzing survival rates from referral centers.

In this Swedish survey, covering a 39-year period and with no loss to follow-up, we found that within 5 years after diagnosis of uveal melanoma, 30% of the patients had died of the disease, and after 10 years 40%. For the first 5 years after diagnosis, we found a yearly excess mortality rate of 5% to 8%, supporting the concept that dissemination of the disease can take place years before detection of ocular melanoma.31,32

The death rates due to uveal melanoma in the present study are comparable with the rates in previous studies.1–4 Compared with the steadily improving survival noted over decades in patients with cutaneous melanoma, with a 5-year relative survival rate of 80%,33 the reported survival rate in patients with uveal melanoma has remained substantially unchanged over time. However, in our study, we actually found an improvement over time in the 5-year relative survival rate.
TABLE 2. Multiple Regression on Relative Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>df</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up year*</td>
<td>4</td>
<td>1.00</td>
<td></td>
<td>0.015†</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>1</td>
<td>1.34</td>
<td>1.02–1.75</td>
<td>0.033</td>
</tr>
<tr>
<td>1 vs. 3</td>
<td>1</td>
<td>1.44</td>
<td>1.10–1.89</td>
<td>0.008</td>
</tr>
<tr>
<td>1 vs. 4</td>
<td>1</td>
<td>1.54</td>
<td>1.17–2.04</td>
<td>0.001</td>
</tr>
<tr>
<td>1 vs. 5</td>
<td>1</td>
<td>1.26</td>
<td>0.93–1.72</td>
<td>0.142</td>
</tr>
<tr>
<td>Period*</td>
<td>5</td>
<td>0.99</td>
<td>0.80–1.24</td>
<td>0.952</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>1</td>
<td>0.82</td>
<td>0.65–1.03</td>
<td>0.090</td>
</tr>
<tr>
<td>1 vs. 3</td>
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<td>0.58</td>
<td>0.43–0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age*</td>
<td>3</td>
<td>2.05</td>
<td>1.41–2.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>1</td>
<td>2.77</td>
<td>1.93–3.96</td>
<td>&lt;0.001</td>
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<tr>
<td>1 vs. 3</td>
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<td>3.89</td>
<td>2.59–5.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender*</td>
<td>1</td>
<td>0.88</td>
<td>0.73–1.05</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Relative risks of excess mortality and 95% confidence intervals (CI).
† Overall test.

In the Swedish Cancer Registry no information about tumor size, histopathology, or other clinical parameters, including treatment, is available, although before 1979, more or less the only treatment was enucleation. Since then, eye-sparing treatments have become widely used for small- to medium-sized tumors. In our data from 1979 and onward, 27% of the patients had been treated with ruthenium plaques or proton beam irradiation as the initial therapy. Although the 5-year relative survival rates were significantly better in later time periods in our study, care should be taken when drawing conclusions regarding the impact of eye-sparing treatments on survival, because the data could not be adjusted for different treatments or for staging of the uveal melanoma. As found in many studies, treatment modalities appear to have little influence on survival.1.2.14–16 In view of the survival rates of the entire population of Swedish patients with uveal melanoma the shift from enucleation toward eye-sparing treatments has not so far adversely affected survival.

An explanation for the improved survival could be that elderly people in recent years have engaged in more visually demanding activities and seek medical advice earlier for decreasing vision. Visual disturbances are common initial symptoms of uveal melanoma and were found in 72% to 87% of patients at presentation.54,55 Also, during the last decades, screening for diabetic retinopathy has been introduced, along with an expansion of cataract surgery to more than 50,000 operations annually,56 and this may have captured some cases of uveal melanoma. During the same period (1960–1998), however, the incidence of uveal melanoma declined significantly in the male and was stable in the female Swedish population.15 This finding, together with an improved relative survival rate indicates that a change toward a comparatively earlier recognition of small uveal melanomas is unlikely.

Even though competing causes of death were omitted in the analysis of the relative mortality rate, younger age was found to be a strong predictor of better survival and was statistically significant in the multivariate analysis. The patients with melanoma in this survey had a median age of 64 years, which should be compared with the mean life expectancy in Sweden (for that specific age group) of another 17 years for men and 21 years for women in 1998.22

The conclusion is that uveal melanoma carries mortality rates in the Swedish population comparable to rates reported in other studies, but an improvement in the 5-year relative survival rate over time was found. The reason for this improvement remains unclear. The high excess mortality rate after the first years after diagnosis of uveal melanoma calls for further investigation, both by identifying patients with elevated risks for metastatic death and by evaluation of the efficacy of adjuvant therapy for these patients.

References