Testicular cancer in Europe and the USA: survival still rising among older patients

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Abstract
Despite high curability, some testicular cancer (TC) patient groups may have increased mortality. We provide a detailed age- and histology-specific comparison of population-based relative survival of TC patients in Europe and the USA. Design Using data from 12 European cancer registries and the USA Surveillance, Epidemiology and End Results 9 database, we report survival trends for patients diagnosed with testicular seminomas and nonseminomas between 1993-1997 and 2003-2007. Additionally, a model-based analysis was used to compare survival trends and relative excess risk (RER) of death between Europe and the USA adjusting for differences in age and histology.

Reference

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Testicular cancer in Europe and the USA: survival still rising among older patients


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Background: Despite high curability, some testicular cancer (TC) patient groups may have increased mortality. We provide a detailed age- and histology-specific comparison of population-based relative survival of TC patients in Europe and the USA.

Design: Using data from 12 European cancer registries and the USA Surveillance, Epidemiology and End Results 9 database, we report survival trends for patients diagnosed with testicular seminomas and nonseminomas between 1993–1997 and 2003–2007. Additionally, a model-based analysis was used to compare survival trends and relative excess risk (RER) of death between Europe and the USA adjusting for differences in age and histology.

Results: In 2003–2007, the 5-year relative survival of patients with testicular seminoma was at least 98% among those aged <50 years, survival of patients with nonseminoma remained 3%–6% units lower. Despite improvements in the relative survival of nonseminoma patients aged ≥50 years by 13%–18% units, survival remained markedly lower than the survival of seminoma patients of the same age. Model-based analyses showed increased RERs for nonseminomas, older, and European patients.

Conclusions: There remains little room for survival improvement among testicular seminoma patients, especially for those aged <50 years. Older TC patients remain at increased risk of death, which seems mainly attributable to the lower survival among the nonseminoma patients.

Key words: cancer registries, nonseminomas, population-based, relative survival, seminomas, testicular cancer

introduction

Testicular cancer (TC) is one of the most curable cancers nowadays, mainly due to the effective cisplatin-based chemotherapy for advanced disease that was introduced in the 1970s [1, 2]. Although the majority of the TC patients are 15–44 years old at the time of diagnosis, 18% of the patients are aged >45 years at the time the TC is diagnosed and 7% are aged >55 years [2]. Histopathologically, testicular germ cell tumors are divided into two major groups: seminomas and nonseminomas. Seminomas tend to grow more slowly and have a better prognosis than nonseminomas [3]. The age-specific incidence of nonseminomas peaks earlier, around the age of 25 years, than that of the seminomas, in which the incidence peaks ~10 years later [3, 4]. In TC patients aged >40 years, the vast majority of the tumors are seminomas [5]. Both histology and stage are important factors for choice of treatment and prognosis [6].

Relative survival has been increasing for both histologies of TC since the 1970s, although more pronounced for the nonseminomas than for the seminomas [7]. In the period 1988–2001, 5-year relative survival of American seminoma and nonseminoma patients was 98% and 93%, respectively. This is quite comparable to Dutch survival estimates in the same period [7, 8]. Relative survival of TC patients >50 years of age has been shown to be lower than that of younger patients [2, 9]. This could be due to suboptimal treatment, comorbidities, a lower tolerance to chemotherapy, a different biological behavior of the tumor or a less favorable stage distribution in the elderly [2, 9, 11]. However, the exact pattern in which the survival...
decreases by age is unknown, and recent detailed international comparisons of trends in TC survival are not available.

The aim of this study was to estimate and compare the trends in population-based relative survival of TC between Europe and the USA and to present age- and histology-specific relative survival for both continents.

methods
data

For Europe, the database of the European Network for Indicators on Cancer (EUNICE) Survival Cooperation was used, which includes information on the incidence and follow-up of cancer cases from 12 European population-based cancer registries from 1985 onwards. General inclusion criteria and data preparation procedures were described in detail in a previous publication [12]. For the USA, the Surveillance, Epidemiology and End Results (SEER) 9 limited-use database was used, with the same selection and inclusion criteria [13].

We have included all TC cases aged 15–84 years who were diagnosed in 1988–2007 from both the EUNICE and the SEER 9 database, along with corresponding age, sex, race (USA only), and calendar period-specific life tables to enable calculation of relative survival estimates. For all analyses, patients from the European registries as well as the SEER9 registries were considered together. Patients aged ≥85 years at diagnosis were excluded from this study due to very small numbers in this age group and possible problems with follow-up of vital status.

To have an impression of the stage distribution of TC among the different age groups, the stage distribution of the American TC patients diagnosed in the most recent period is calculated according to age group.

survival analyses

Five-year relative survival estimates were calculated separately for the European and American registries. Relative survival estimates were derived as ratios of the observed survival of the TC patients and the expected survival of the underlying general population with a similar sex and age distribution [14]. The survival estimates were calculated according to the Ederer II method [15]. All survival estimates were period estimates, which are exclusively based on the survival experience of patients during the specific calendar period for which they were derived [16]. This method has been shown to closely predict survival later observed for patients diagnosed in that period [17–19].

First, 5-year period-based relative survival estimates were calculated for the calendar periods 1993–1997, 1998–2002, and 2003–2007, using a period-specific saturated Poisson regression model for relative survival [20]. To derive a test for survival trends, the periods 1993–1997, 1998–2002, and 2003–2007 were additionally included as numerical terms. In instances where registries had data available on incident cases until 2005 or 2006, but follow-up of vital status until 2007, hybrid analysis was used. This method enables estimation of up-to-date survival for situations where follow-up data are available for more recent years than incidence [21, 22]. Standard errors of the survival estimates were calculated with the delta method. α = 0.05 was used as a level of significance for the different tests.

age- and histology-specific trend analyses

For the detailed age-specific analysis, the age groups 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–64, and 65+4 years were considered. For analyses according to histology, the tumors were grouped into seminomas (ICD-O-3 morphology codes: 9060–9064) and nonseminomas (ICD-O-3 morphology codes: 9065–9085, 9100–9102, 9105). The tumors that could not be grouped as seminoma or nonseminoma were excluded from analyses according to histology (EUNICE: n = 559, SEER: n = 217). The age groups 15–29, 30–49 and 50+ were considered.

modeling

In order to examine and compare survival trends between registries from Europe and the USA over time while adjusting for histology and age, we extended the previously described survival model, to include period of diagnosis (numerical variable, 1 = 1993–1997, 2 = 1998–2002, and 3 = 2003–2007), age [categorical variable, four age groups (15–29, 30–39, 40–54, and 55–84)], histology (seminoma or nonseminoma), and continent (dichotomous variables). The output of this relative survival multiple regression analysis was fully adjusted relative excess risks (URRE) of death with a 95% Wald confidence intervals (95% CI).

results

Overall, data from 15 559 and 14 435 TC patients were selected from the EUNICE and SEER 9 databases, respectively, for this study (Table 1). In Europe the number of cases contributed by each cancer registry varied between 275 (Estonia) and 4373 (Norway), in the USA this varied between 573 (Hawaii) and 2590 (Seattle).

Detailed age-specific 5-year relative survival of TC patients from the EUNICE and SEER databases in the period 2003–2007 is presented in Table 2. For both the European and the American patients, the 5-year relative survival was high, i.e. mostly 96% or higher for the age groups up to 54 years. For those aged 55–64 years, 5-year relative survival seemed to be somewhat lower compared with the patients aged 54 years or less, while 5-year relative survival was markedly poorer for the small group of patients aged ≥65 years in both Europe and the USA, with survival estimates of 72% and 83%, respectively.

The stage distribution of the American patients diagnosed in the period 2003–2007 is presented according to age groups in supplementary Table S1, available at Annals of Oncology online. The youngest patients (15–24 years) were the most often diagnosed with distant disease. Patients aged ≥55 years were more often registered with unstaged disease.

The histological distribution of TC is presented in Table 3. In both populations, the proportion of patients with nonseminoma made up the majority in the age group 15–29 years, while in the two older age groups 65%–83% of the cases had a seminoma. The proportion of patients with seminoma was marginally higher in each age group and period in the USA. While the proportion of seminomas may have increased slightly among patients aged 15–29 years in Europe, proportions were rather stable in the other age groups as well as in the USA.

The 5-year relative survival of seminoma patients in the age groups 15–29 and 30–49 years was generally very high in both the USA and Europe (Table 4) in all three periods, and by 2003–2007, estimates reached at least 98.6% both populations. A significant improvement was seen among European seminoma patients for the age groups 15–29 and 30–49 years. While no significant improvement was found for the USA patients, in which the already very high survival in the first period left little scope for further improvement.
The survival for nonseminoma patients in the age groups 15–29 and 30–49 years varied between 90% and 95%, with little change over time and very little difference between Europe and the USA. For the age groups 15–29 and 30–49 years, the 5-year relative survival of nonseminoma patients was consistently between 2% and 6% units lower than that of the seminoma patients within the same age group in all three periods of diagnosis.

In both Europe and the USA, the largest percentage units change in 5-year relative survival was seen in the age group 50–84 years, for whom a significant increase in survival over time was seen in Europe for seminoma patients and in the US for nonseminoma patients. The survival of American patients was slightly higher than that of patients in the EUNICE registries in all three examined periods for both histology groups, except for nonseminoma patients in 1998–2002.

<table>
<thead>
<tr>
<th>Registry</th>
<th>Country</th>
<th>Registry underlying population (millions)</th>
<th>National coverage (%)</th>
<th>Number of testicular cancers (1988–2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cracow</td>
<td>Poland</td>
<td>0.8</td>
<td>1.9</td>
<td>303</td>
</tr>
<tr>
<td>Estonia</td>
<td>Estonia</td>
<td>1.4</td>
<td>100</td>
<td>275*</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Lithuania</td>
<td>3.4</td>
<td>100</td>
<td>576*</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Slovenia</td>
<td>1.9</td>
<td>100</td>
<td>1461</td>
</tr>
<tr>
<td>Turin</td>
<td>Italy</td>
<td>1.0</td>
<td>1.8</td>
<td>432*</td>
</tr>
<tr>
<td>Tuscany</td>
<td>Italy</td>
<td>1.2</td>
<td>2.1</td>
<td>421*</td>
</tr>
<tr>
<td>Eindhoven</td>
<td>The Netherlands</td>
<td>1.0</td>
<td>6.6</td>
<td>1134</td>
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<tr>
<td>Scotland</td>
<td>UK</td>
<td>5.1</td>
<td>100</td>
<td>3703</td>
</tr>
<tr>
<td>Finland</td>
<td>Finland</td>
<td>5.2</td>
<td>100</td>
<td>1702</td>
</tr>
<tr>
<td>Norway</td>
<td>Norway</td>
<td>4.5</td>
<td>100</td>
<td>4373</td>
</tr>
<tr>
<td>Geneva</td>
<td>Switzerland</td>
<td>0.4</td>
<td>5.3</td>
<td>314</td>
</tr>
<tr>
<td>Saarland</td>
<td>Germany</td>
<td>1.0</td>
<td>1.3</td>
<td>865</td>
</tr>
<tr>
<td>Total EUNICE</td>
<td></td>
<td></td>
<td></td>
<td>4.5b</td>
</tr>
<tr>
<td>Atlanta</td>
<td>USA</td>
<td>2.9</td>
<td>1.0</td>
<td>1153</td>
</tr>
<tr>
<td>Connectic</td>
<td>USA</td>
<td>3.4</td>
<td>1.2</td>
<td>1907</td>
</tr>
<tr>
<td>Detroit</td>
<td>USA</td>
<td>4.0</td>
<td>1.4</td>
<td>2058</td>
</tr>
<tr>
<td>Hawaii</td>
<td>USA</td>
<td>1.2</td>
<td>0.4</td>
<td>573</td>
</tr>
<tr>
<td>Iowa</td>
<td>USA</td>
<td>2.9</td>
<td>1.0</td>
<td>1632</td>
</tr>
<tr>
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<td>USA</td>
<td>1.8</td>
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<tr>
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<tr>
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<tr>
<td>Utah</td>
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<td>1322</td>
</tr>
<tr>
<td>Total SEER 9</td>
<td>USA</td>
<td>26.7</td>
<td>9.5</td>
<td>14 435</td>
</tr>
</tbody>
</table>

*For Estonia and Tuscany, data were available up to 2005, for Turin up to 2006, while for Lithuania, data were available since 1990.

As percentage of Europe (not including Russia, Turkey, Kazakhstan, Azerbaijan, Armenia and Georgia).

Table 2. Age-specific 5-year relative survival of patients with testicular cancer from the EUNICE and SEER 9 registries in the period 2003–2007

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Five-year relative survival EUNICE</th>
<th>Five-year relative survival SEER 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>PE</td>
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<tr>
<td>15–19</td>
<td>143</td>
<td>96.2</td>
</tr>
<tr>
<td>20–24</td>
<td>518</td>
<td>96.0</td>
</tr>
<tr>
<td>25–29</td>
<td>789</td>
<td>96.0</td>
</tr>
<tr>
<td>30–34</td>
<td>853</td>
<td>95.8</td>
</tr>
<tr>
<td>35–39</td>
<td>796</td>
<td>97.5</td>
</tr>
<tr>
<td>40–44</td>
<td>576</td>
<td>97.1</td>
</tr>
<tr>
<td>45–49</td>
<td>343</td>
<td>93.1</td>
</tr>
<tr>
<td>50–54</td>
<td>209</td>
<td>96.1</td>
</tr>
<tr>
<td>55–64</td>
<td>195</td>
<td>93.2</td>
</tr>
<tr>
<td>65–84</td>
<td>120</td>
<td>72.3</td>
</tr>
<tr>
<td>Total</td>
<td>4542</td>
<td>95.7</td>
</tr>
</tbody>
</table>

PE, point estimate; SE, standard error.
Among patients aged ≥50 years, the 5-year relative survival of nonseminoma patients was 8%–10% units lower than that of seminoma patients in the period of 2003–2007, a larger difference than seen for younger age groups, but smaller than seen in previous periods.

The relative survival multiple regression model for TC is presented in Table 5. The model confirms, after adjusting for age and histology, a statistically significant reduction in excess mortality over time, an increasing excess mortality for older (≥30 years) compared with younger patients (<30 years), and a highly increased excess mortality for those aged ≥55 years. A much lower excess mortality was found for seminomas compared with nonseminomas (RER = 0.28, \( P < 0.01 \)). Overall, a statistically significantly increased RER of 1.20 was found for the EUNICE registries in comparison to the SEER registries.

### discussion

Our analysis of recent trends in TC survival in Europe and the USA found consistently higher 5-year relative survival for seminoma compared with nonseminoma patients, with the biggest differences among these groups seen among patients in the oldest age group (50–84 years). Despite considerable rises in the relative survival in the oldest age group, the multiple regression analysis showed that relative survival of the patients aged ≥55 years remained considerably poorer than that of younger patients. The analysis suggests that mainly patients with nonseminoma TC remain at an increased risk for mortality in all age groups.

While survival of European TC patients aged <50 years was somewhat lower than that of the American patients diagnosed during the first study period (1993–1997), due to improvement of survival of the European patients, essentially equal 5-year relative survival was found for European and American TC patients younger than 50 years diagnosed during the last study period (2003–2007). While survival of patients with TC during the early 1990s was already very high in some parts of Europe and the USA [8, 23], it is likely that rapid improvement in TC survival in Eastern European countries after their socioeconomic transition in the 1990s contributed to the further improvement of TC relative survival in Europe [24].

The results of this study indicate that mainly nonseminoma TC patients remain at increased risk of mortality. The survival differences between the two histologies are rather consistent with previously reported survival differences [7–9]. The results of a previous high-resolution study [10] suggest that the large difference in survival between the two histology groups is mainly explained by the greater propensity of the nonseminomas to metastasize. Owing to more rapid growth and more aggressive behavior, nonseminomas tend to have a less favorable stage distribution than seminomas, and within the group of metastasized patients, they also have a poorer prognosis than seminomas [8, 25]. It is therefore not expected...
that the nonseminoma patients have a somewhat lower relative survival than seminoma patients.

The results of the age-specific as well as histology stratified analyses suggest that the largest difference in relative survival between the European and the American patients was seen among the oldest patients (Tables 2 and 3), and the results of the multiple regression analysis are also consistent with this. The large, if imprecise, difference seen between the European and the US patients aged 65–84 years may have contributed to the increased risk of mortality for European patients in contrast to American patients, which was detected in the multiple regression analysis. Also, based on the high relative survival of seminoma patients aged 50–84 years, it seems that the poorer survival of TC patients aged ≥55 years is mainly attributable to the nonseminoma patients in that age group. The rather large rises in the survival of patients aged 50–84 years in the recent decade further suggests that increasing effectiveness of therapy was achieved among these patients.

The remaining poorer survival for older TC patients could have been caused by a number of reasons, such as a less favorable stage distribution, possibly due to delayed diagnosis, less tolerability to specific therapy modalities such as chemotherapy, comorbidities, and/or suboptimal treatment [9]. The stage distribution of the American TC patients aged ≥50 years included in our study was rather similar to that of younger patients (supplementary Table S1, available at Annals of Oncology online), and the existing small differences between the age groups can probably not explain the large differences in survival between the age groups. In addition, a previous study based on SEER data showed that, except for the localized seminomas, the worse survival for TC patients over 50 years of age was still present after stratification for histology and stage (localized versus metastasized) [9]. Less favorable stage or histology distributions can thus not solely explain the worse survival in older TC patients. The main three chemotherapeutic agents for TC (cisplatin, etoposide, and bleomycin) have been associated with increased toxicity in the elderly [26]. One of the most important toxic effects is bleomycin-related pulmonary toxicity, which can be fatal. Several studies have reported that bleomycin-related (fatal) pulmonary toxicity is increased in patients over the age of 40 and in patients with poor renal function [27, 28]. Older TC patients might have received dose reductions due to (expected) toxic effects, which could have affected their long-term survival or they could have died due to the toxicity. In addition, there is a general tendency to assume that tolerance to chemotherapy is lower in older people, which may result in undertreatment of elderly patients with cancer for fear of excessive toxicity [26]. However, a reduction of the doses of chemotherapy is generally not recommended for elderly patients with cancer [26, 29].

Limitations of this study include the lack of availability of data on stage and treatment, which could have been used to investigate further the causes of the lower survival in the older patients. Because of the lack of information on treatment, it was also impossible to compare differences in therapeutic strategies in the USA and Europe. Current European and American guidelines are however quite similar, suggesting that there should be relatively few differences in the treatment of TC in Europe and the USA [6, 30].

Furthermore, both the EUNICE and the SEER-9 database do not cover the total populations of Europe and the USA, respectively. The SEER-9 population is more affluent, more highly educated, has a lower unemployment rate and is substantially less rural than the remainder of the USA [31], and these differences may affect survival estimates. Comparable studies have not been carried out for the EUNICE registries. It is possible that survival estimates obtained in the current study may thus not be entirely representative for the whole of Europe and the USA, and regional variation may also exist in both areas.

conclusions

The trends in relative survival of TC patients appear to be comparable between Europe and the USA. Survival for seminoma patients, particularly for the age groups 15–49 years, has come extremely close to the maximum possible by 2003–2007, representing an essentially total lack of cancer-specific mortality among these patients, and leaving very little if any further room for further improvement of survival in these patients.

Survival of nonseminoma patients was consistently lower than that of seminoma patients. Although the largest improvement of survival of nonseminoma patients was noted in patients aged ≥50 years, the nonseminoma patients in this age group still have the largest survival difference compared with seminoma patients and the highest risk of mortality. Future research into the lower survival of older TC patients should thus focus on these patients, to first establish why they have poorer survival and secondly address the problem of the causes of the lower survival so that these patients can also benefit fully from the excellent opportunities that are available to cure TC.

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disclosure

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references