The Contribution of Nodular Subtype to Melanoma Mortality in the United States, 1978 to 2007

Waqas R. Shaikh, BS; Michael Xiong, BA; Martin A. Weinstock, MD, PhD

Objective: To gain insight into reducing melanoma mortality by examining epidemiologic trends by subtype with emphasis on the contribution of each subtype to melanoma-related death.

Design: Retrospective population-based cohort study.

Setting: Original 9 registries of the Surveillance, Epidemiology, and End Results Program from 1978 to 2007.

Participants: A total of 111,478 patients with histologically confirmed invasive melanoma.

Main Outcome Measure: Proportion of ultimately fatal melanomas by subtype.

Results: Among melanomas of known subtype, superficial spreading melanoma comprised 66% of incident melanomas and 46% of ultimately fatal melanomas; nodular melanoma comprised 14% of incident melanomas and 37% of ultimately fatal melanomas. For superficial spreading melanoma, overall incidence per 100,000 per year increased (from 4.28 to 6.63), ultimately fatal incidence remained stable (at 0.56 to 0.51), and 10-year relative survival increased (from 90.6% to 96.5%) when comparing successive 5-year intervals. In contrast, for nodular melanoma, the overall incidence (1.30-1.32), ultimately fatal incidence (0.46-0.44), and 10-year relative survival rate (61.8%-61.5%) remained stable. Epidemiologic trends of melanoma, not otherwise specified, were similar to superficial spreading melanoma. There was a strong negative correlation between the proportion of melanoma, not otherwise specified, among all melanomas, and the proportion of superficial spreading melanoma, among melanomas of known subtype ($r = -0.80$; $P = .01$), across the registries.

Conclusions: Superficial spreading and nodular melanoma constitute similar proportions of ultimately fatal melanomas. Although incidence of and survival from superficial spreading melanoma have increased from 1978 to 2007, neither the incidence of nor survival from nodular melanoma has changed. Public health efforts should include a focus on nodular melanoma for maximum reduction of melanoma mortality.

attle–Puget Sound, Washington; and Utah), which were established in the 1970s and comprise approximately 10% of the US population. Other SEER registries, which were added later, were not included in the analysis because of the interest in looking at trends over decades. Information on the data collection, reporting, and quality control methods for the SEER Program can be found at http://www.seer.cancer.gov. Institutional review board approval was not required because the data used were from a publicly available US government database.

**DEFINITIONS**

The International Classification of Diseases for Oncology, Third Edition, histology codes were used to define grouped histologic subtypes as followed: SSM (code 8743), NM (code 8721), lentigo maligna melanoma (LMM; code 8742), acral lentiginous melanoma (ALM; code 8744), amelanotic melanoma (AM; code 8730), other subtypes (Other; codes 8722, 8723, 8728, 8740, 8741, 8745, 8746, 8761, 8770-8774, and 8780), and melanoma, not otherwise specified (NOS; code 8720). Incident melanoma was defined as a case of incident melanoma in which the patient died during the study period, and the cause of death listed on the death certificate was melanoma.

Relative survival is the probability of survival in the absence of other causes of death. It is calculated by dividing the observed survival of a cohort group by the expected survival of a similar group while controlling for race, sex, age, and date at which the age was coded (SEER*Stat software, version 6.6.2; available at the SEER Program, National Cancer Institute, Web site: http://seer.cancer.gov/seerstat). Standard SEER exclusion criteria for survival analysis were applied (ie, cases that were coded as death certificate only, autopsy only, ≥2 primary cancers, and alive with no survival time). Because overall relative survival for melanoma stabilizes after 9 years (data not shown), analysis was limited to melanomas diagnosed during the period 1978 to 1997 with follow-up through 2007 when evaluating relative survival and rates of ultimately fatal melanoma. When evaluating incident cases and overall incidence rates, cases were analyzed from 1978 to 2007.

**STATISTICAL ANALYSIS**

The overall incidence and ultimately fatal incidence age-adjusted to the 2000 US population standard and the 10-year relative survival for invasive melanoma with 95% CIs were calculated using SEER*Stat software, version 6.6.2. Incidence of ultimately fatal melanomas was purposefully used instead of the melanoma mortality rate. The former tabulates death using the year of diagnosis, allowing for year-to-year comparison with the overall incidence, which also uses year of diagnosis. The latter tabulates death using the year of death, which does not allow for year-to-year comparison with the overall incidence because there is a lag between year of diagnosis and year of death. Relative survival was calculated using the Kaplan-Meier method. Stata SE software (version 8; StataCorp, College Station, Texas) was used to calculate correlation coefficients between the proportion of melanoma NOS, among all melanomas, and the proportion of each other grouped subtype, among known subtypes, across the SEER 9 registries. P values for correlation coefficients were calculated using a t test with the null hypothesis being that for each correlation, the correlation coefficient equals zero. All P values were 2-sided with statistical significance set as P < .05.

**RESULTS**

**INCIDENT CASES AND ULTIMATELY FATAL CASES BY SUBTYPE**

In the SEER 9 registries from 1978 to 2007, 111 478 incident cases of invasive melanoma were reported, including 9904 cases of ultimately fatal invasive melanoma initially diagnosed from 1978 to 1997. Superficial spreading melanoma and NM constituted 66% (43 427 cases) and 14% (8973 cases) of incident melanomas of known subtypes, respectively. From 1978 to 2007, there was no substantial change in the proportions of known subtypes. **Table 1** provides details of the frequency and proportions for all subtypes, including melanoma NOS in 5-year time periods. In contrast to incident melanomas, SSM and NM constitute an approximately similar number and percentage (2343 cases [46%] and 1854 cases [37%], respectively) of ultimately fatal melanomas of known subtypes; no other subtype accounts for more than 6% of the total. The proportions remained relatively stable from 1978 to 1997. The fact that at least 1 in 5 cases of NM (1854 of 8973) is ultimately fatal and at least 1 in 19 cases of SSM (2343 of 43 427) is ultimately fatal is accounted for by the 10-year relative survival rates of NM and SSM of 61.3% and 96.3%, respectively. Proportions of ultimately fatal cases by subtype did not vary when stratified by sex: from 1978 to 1997, SSM and NM accounted for 45% (1458 cases) and 37% (1186 cases) of ultimately fatal melanomas, respectively, for males.

**Table 1. Melanoma Frequency Trends by Subtype in 111,478 Patients in SEER 9 Registries**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>SSM (%)</th>
<th>NM (%)</th>
<th>LMM (%)</th>
<th>ALM (%)</th>
<th>AM (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-1982</td>
<td>4139 (66.4)</td>
<td>1226 (19.7)</td>
<td>653 (10.5)</td>
<td>NA</td>
<td>97 (1.6)</td>
<td>118 (1.9)</td>
</tr>
<tr>
<td>1983-1987</td>
<td>5576 (68.9)</td>
<td>1303 (16.1)</td>
<td>867 (10.7)</td>
<td>44 (0.5)</td>
<td>109 (1.3)</td>
<td>196 (2.4)</td>
</tr>
<tr>
<td>1988-1992</td>
<td>6727 (69.8)</td>
<td>1342 (13.9)</td>
<td>955 (9.9)</td>
<td>183 (1.9)</td>
<td>100 (1.0)</td>
<td>333 (3.5)</td>
</tr>
<tr>
<td>1993-1997</td>
<td>8229 (68.0)</td>
<td>1543 (12.8)</td>
<td>1394 (11.5)</td>
<td>226 (1.9)</td>
<td>118 (1.0)</td>
<td>586 (4.8)</td>
</tr>
<tr>
<td>1998-2002</td>
<td>9354 (66.5)</td>
<td>1708 (12.2)</td>
<td>1833 (13.0)</td>
<td>238 (1.7)</td>
<td>83 (0.6)</td>
<td>840 (6.0)</td>
</tr>
<tr>
<td>2003-2007</td>
<td>9402 (61.1)</td>
<td>1851 (12.1)</td>
<td>2339 (15.3)</td>
<td>294 (1.9)</td>
<td>97 (0.6)</td>
<td>1267 (8.3)</td>
</tr>
<tr>
<td>Total, 1978-2007</td>
<td>43 427 (66.4)</td>
<td>8973 (13.7)</td>
<td>8041 (12.3)</td>
<td>985 (1.5)</td>
<td>604 (0.9)</td>
<td>3340 (5.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ALM, acral lentiginous melanoma; AM, amelanotic melanoma; LMM, lentigo maligna melanoma; NA, not applicable; NM, nodular melanoma; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; SSM, superficial spreading melanoma.

* Data on ALM were collected after 1986.
and 48% (884 cases) and 36% (668 cases) of ultimately fatal melanomas, respectively, for females. Proportions of incident melanomas by subtype were also similar between sexes: SSM and NM contributed to 62% (22,051 cases) and 15% (5321 cases) of incident melanomas, respectively, for males, and 71% (21,376 cases) and 12% (3652 cases) of incident melanomas, respectively, for females. Table 2 provides details of the frequency and proportions for all subtypes, including melanoma NOS among ultimately fatal cases in 5-year time periods from 1978 to 1997.

**Epidemiologic Trends by Subtype**

For NM and ALM, the overall incidence, ultimately fatal incidence, and 10-year relative survival were all relatively stable during the 30-year study period. This contrasted with SSM and LMM, for which overall incidence increased, ultimately fatal incidence remained stable, and 10-year relative survival increased during the study period. Tables 3, 4, and 5 provide details of the epidemiologic trends for all melanomas of known subtype and for melanoma NOS.

**Analysis of the Composition of Melanoma NOS**

From the SEER 9 registry data set, melanoma NOS accounted for 46,108 cases of all incident melanomas (41%) and 4832 cases of all ultimately fatal melanomas (49%). Because melanoma NOS comprises such a high proportion of diagnosed cases, attempts were made to find clues to its composition. Trends in overall incidence, ultimately fatal incidence, and 10-year relative survival were similar between melanoma NOS and SSM and LMM (Tables 3–5). The proportion of melanoma NOS, among all incident cases, negatively correlated most closely with LMM and AM, respectively, for males. Proportions of melanoma NOS, among ultimately fatal cases, negatively correlated most closely with NM and ALM, respectively, for females.
COMMENT

This study has several major findings. First, NM accounts for a high proportion of ultimately fatal cases of invasive melanoma (37%). Second, over the past 30 years the overall incidence, ultimately fatal incidence, and relative survival for NM have not changed. However, for SSM the overall incidence and relative survival have gradually increased, whereas the ultimately fatal incidence has not changed. Third, there are similarities between melanoma NOS and SSM, as demonstrated by similar trends in overall incidence, ultimately fatal incidence, and relative survival; further support is demonstrated by the statistically significant, strong, negative correlation between melanoma NOS and SSM among both incident and ultimately fatal cases across the SEER registries.

Nodular melanoma accounts for a disproportionate fraction of ultimately fatal cases compared with incident cases (37% vs 14%). Because NM accounts for 37% of ultimately fatal cases of melanoma, early detection of NM is needed to reduce melanoma mortality. This finding is consistent with those of previous studies that have associated NM with proxies for case fatality, such as tumor thickness,29 biologic aggressiveness,39 rate of growth,22 mitotic rate,11 ulceration,11 Clark level,11 and incidence of recurrence in the sentinel lymph node bas-

sin.22,23 These “aggressive” characteristics may be associated with distinct genetic pathways of NM compared with other subtypes, although more research is needed. Nodular melanoma is more likely to have loss of p16 expression14 and lower rates of BRAF mutation35 compared with SSM. In addition, NM compared with other subtypes is associated with NRAS mutation20 and over-expression of securin, a protein encoded by proto-oncogene hPTTG.27 The association between melanoma subtype and genetic mutations may provide the framework for a new classification system that not only highlights the different clinical presentations of melanoma but also predicts therapeutic response.14,15

This study’s results show that the overall incidence, ultimately fatal incidence, and relative survival for NM have been relatively stable during the past 30 years. Evaluation of the progress against cancer is made by simultaneously interpreting trends in overall incidence, ultimately fatal incidence, and relative survival.26 Analysis of NM trends shows that there has been a lack of progress concerning NM both in terms of detection and treatment. Awareness and early detection campaigns have generally used the ABCD criteria.29 Although these criteria can sometimes detect NM, oftentimes they fail to detect NM.30,31 Thus, a lack of progress in detecting NM may not be surprising. In addition, melanoma treatment has made only marginal advances in survival.32 In a major academic center in the United States, there were no changes in NM tumor thickness or ulceration status between the time periods 1972 to 1982 and 2002 to 2007.33 Similar results for thickness trends for NM were found in Italy.34 The findings of both studies are consistent with this study’s results of an unchanged ultimately fatal incidence and relative sur-

Table 5. Trends in 10-Year Relative Survival Rate (95% CI) by Subtype in 50,491 Patients in SEER 9 Registriesa

<table>
<thead>
<tr>
<th>Time Period</th>
<th>SSM</th>
<th>NM</th>
<th>LMM</th>
<th>ALM</th>
<th>AM</th>
<th>Other</th>
<th>NOS</th>
<th>All Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-1982</td>
<td>0.906</td>
<td>0.618</td>
<td>0.881</td>
<td>NA</td>
<td>0.369</td>
<td>0.667</td>
<td>0.724</td>
<td>0.797</td>
</tr>
<tr>
<td></td>
<td>(0.890-0.920)</td>
<td>(0.581-0.653)</td>
<td>(0.802-0.929)</td>
<td></td>
<td>(0.244-0.494)</td>
<td>(0.532-0.772)</td>
<td>(0.705-0.744)</td>
<td>(0.785-0.809)</td>
</tr>
<tr>
<td>1983-1987</td>
<td>0.937</td>
<td>0.536</td>
<td>0.956</td>
<td>NA</td>
<td>0.373</td>
<td>0.787</td>
<td>0.769</td>
<td>0.842</td>
</tr>
<tr>
<td></td>
<td>(0.924-0.948)</td>
<td>(0.599-0.761)</td>
<td>(0.885-0.983)</td>
<td></td>
<td>(0.258-0.488)</td>
<td>(0.674-0.864)</td>
<td>(0.750-0.786)</td>
<td>(0.831-0.852)</td>
</tr>
<tr>
<td>1988-1992</td>
<td>0.946</td>
<td>0.679</td>
<td>0.960</td>
<td>0.686</td>
<td>0.486</td>
<td>0.792</td>
<td>0.812</td>
<td>0.868</td>
</tr>
<tr>
<td></td>
<td>(0.934-0.957)</td>
<td>(0.640-0.715)</td>
<td>(0.859-0.989)</td>
<td>(0.565-0.780)</td>
<td>(0.350-0.609)</td>
<td>(0.707-0.854)</td>
<td>(0.795-0.827)</td>
<td>(0.859-0.877)</td>
</tr>
<tr>
<td>1993-1997</td>
<td>0.965</td>
<td>0.615</td>
<td>0.994</td>
<td>0.699</td>
<td>0.498</td>
<td>0.868</td>
<td>0.845</td>
<td>0.888</td>
</tr>
<tr>
<td></td>
<td>(0.954-0.974)</td>
<td>(0.577-0.651)</td>
<td>(&lt;0.001-1.000)</td>
<td>(0.586-0.785)</td>
<td>(0.366-0.616)</td>
<td>(0.800-0.915)</td>
<td>(0.830-0.859)</td>
<td>(0.879-0.924)</td>
</tr>
</tbody>
</table>

Abbreviations: ALM, acral lentiginous melanoma; AM, amelanotic melanoma; LMM, lentigo maligna melanoma; NA, not applicable; NM, nodular melanoma; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; SSM, superficial spreading melanoma.

Table 6. Relationship Between Melanoma NOS and Each Known Subtype in SEER 9 Registries: Correlation Between the Proportion of Melanoma NOS Among All Melanomas and the Proportion of Each Subtype Among Known Melanoma Subtypes

<table>
<thead>
<tr>
<th>Correlation</th>
<th>SSM</th>
<th>NM</th>
<th>LMM</th>
<th>ALM</th>
<th>AM</th>
<th>Other</th>
<th>NOS</th>
<th>All Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among incident cases</td>
<td>−0.80</td>
<td>0.54</td>
<td>−0.12</td>
<td>0.74</td>
<td>0.77</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.13</td>
<td>.76</td>
<td>.02</td>
<td>.01</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among ultimately fatal cases</td>
<td>−0.66</td>
<td>0.18</td>
<td>0.46</td>
<td>0.80</td>
<td>0.58</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.05</td>
<td>.64</td>
<td>.21</td>
<td>.01</td>
<td>.09</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALM, acral lentiginous melanoma; AM, amelanotic melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; NOS, not otherwise specified; SEER, surveillance, epidemiology, and End Results; SSM, superficial spreading melanoma.
vival for NM and further underscore the importance of making progress against NM.

If the goal is to reduce melanoma mortality, then a key challenge is to detect thin NMs. Nodular melanomas commonly occur in men older than 50 years on the head and neck. Because those lesions often do not meet the ABCD criteria, the E criterion (evolving) was added to help detect NM, among other reasons. In addition, the EFG criteria were introduced to highlight important clinical features of NM. These additional diagnostic aids are relatively new, and time will tell if they can help to detect NM at an early stage of development. Geller et al analyzed clinical characteristics of NM and discovered that in comparison with SSM, thick NM tended to be pale, with no color, blisterslre, and raised or lumpy, and discovered in patients who had not been examined by a physician within the past 3 years. Changes in size, shape, or color were more likely in thin NMs than in thick NMs. Warycha et al found that most NMs were elevated and reported a shorter median duration of change in comparison with SSM (5 months vs 9 months, respectively). One case series evaluated 11 cases of thin NMs. They concluded that NMs often possess unremarkable clinical features and that physicians need to be suspicious of new or changing lesions as a key warning sign. Furthermore, they found that dermoscopic features, such as “homogenous disorganized pattern, asymmetry, a blue-white veil, structureless areas, and atypical vascular structures,” provided clues to the cancerous nature of the lesion. Further research is needed about the early warning signs of NM.

Superficial spreading melanoma is the most common subtype and accounts for the largest number of fatal cases. Progress in the detection and treatment of SSM is suggested by an improved relative survival. Controversies have arisen as to the discrepancy between a rising overall incidence rate and a stable overall mortality rate. One explanation is overdiagnosis or misdiagnosis of indolent melanomas owing to increased rates of biopsy and a lowered histologic threshold for the diagnosis of malignant disease. However, this argument does not explain the increase in thicker melanomas, especially among lower socioeconomic groups. The likely explanation is both a rise in overdiagnosis or misdiagnosis of indolent melanomas and a real rise in the burden of invasive melanomas. Despite the ultimately fatal incidence remaining relatively stable, the 10-year relative survival has improved. Survival rates provide a good measure of progress against cancer. This improvement in survival is believed to be related to a combination of education, screening, early detection, and excision of primary tumors in the early stage of development as there have been no major advancements in melanoma treatment.

To understand the composition of the melanoma NOS category, a comparison of epidemiologic trends of melanoma NOS with known subtypes was made. The overall incidence, ultimately fatal incidence, and relative survival trends for melanoma NOS were similar to those of SSM. Further analysis revealed a statistically significant, strong, negative correlation between the proportion of SSM, among known subtypes, and the proportion of melanoma NOS, among all melanomas, across the SEER registries. Presuming that the proportion of each known melanoma subtype is constant throughout the different SEER registries, then any change in the proportion of melanoma NOS with a corresponding reciprocal change in the proportion of a known subtype suggests the transfer of that subtype into the melanoma NOS category. Both of these findings suggest that a significant proportion of SSM is included in the melanoma NOS subcategory. A previous study that analyzed the same SEER database found that “the distribution and median thickness of melanoma NOS resembled that of SSM rather than that of NM. Although not conclusive, all these findings suggest that a high proportion of melanoma NOS are SSM. If this is true, then the true proportion of NM among ultimately fatal cases would be lower than was calculated.

There are several limitations. First, 41% of incident and 49% of ultimately fatal melanomas were recorded as melanoma NOS. These numbers are high, and, depending on the subtype composition of melanoma, NOS can greatly influence the ultimate relative proportions of each subtype among incident and ultimately fatal cases. There are suggestions that melanoma NOS is composed mainly of SSM, but no firm conclusion can be reached. The second limitation is that there is underreporting and delayed reporting to the SEER registries. Given that there is some controversy regarding NM as a distinct entity, some pathologists may not be recording NM in pathology reports, which in turn would make this study’s results for NM more pronounced. Third, there is no independent verification as to the accuracy of the subtype coding by the SEER registries. Finally, Breslow thickness was not included in the analysis because it does not have the practical relevance in optimizing clinical detection.

Despite these limitations, this study has major strengths. The use of the SEER population-based database provides quality-controlled data with a high number of cases across geographically diverse areas over a 30-year period, which is largely characteristic of the US population. The use of ultimately fatal incidence instead of mortality rate allows for fair year-to-year comparisons to the overall incidence. Finally, the use of relative survival instead of melanoma-specific survival captures both direct and indirect causes of mortality while circumventing reliance on the accuracy of death certificate coding.

Given the recent plateauing of melanoma mortality, new strategies are needed. Based on the results of this study that NM makes a substantial contribution to melanoma mortality with no change in overall incidence, ultimately fatal incidence, and relative survival over the past 3 decades, the authors recommend that public health efforts should include a focus on NM for maximum reduction of melanoma mortality. Although the classification of melanoma into subtypes does not correlate to prognosis as well as tumor thickness, ulceration status, and mitotic activity, it does identify clinically relevant and unique forms of melanoma. Emphasis on the E...
criterion and the EFG rule may be useful since the ABCD warning signs preferentially detect SSM. Widespread use and competence in dermoscopy may also allow for earlier detection when historical or clinical features are limited. Individuals at high risk for NM (especially men > 50 years) can be targeted. Given that NMs often have a history of change with a median duration of 5 months, recommendation of the monthly thorough skin self-examination11,17 to patients is even more crucial. Finally, given the relatively high proportion of melanoma NOS in the SEER database, we recommend the complete and accurate reporting of cases to the SEER registries, which is essential for detailed characterization of melanoma.

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Author Contributions: Dr Weinstock had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Shaikh, Xiong, and Weinstock. Acquisition of data: Weinstock. Analysis and interpretation of data: Shaikh, Xiong, and Weinstock. Drafting of the manuscript: Shaikh and Weinstock. Critical revision of the manuscript for important intellectual content: Shaikh, Xiong, and Weinstock. Statistical analysis: Shaikh, Xiong, and Weinstock. Obtained funding: Weinstock. Administrative, technical, and material support: Weinstock. Study supervision: Weinstock.

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