Head and Neck Melanoma in the Sentinel Lymph Node Era

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Objective: To determine whether, in the era of sentinel lymph node (SLN) biopsy, head and neck melanoma (HNM) has a poorer outcome than melanomas at other sites (OMS).

Design: Prospective database, 1994 to 2004. Characteristics and outcomes of patients with HNM vs those with OMS were analyzed by Fisher test, paired t test, and χ² test.

Setting: Tertiary referral center.

Patients: A total of 755 patients with melanoma who had undergone SLN biopsy.

Main Outcome Measures: Differences between patients with HNM and those with OMS.

Results: A total of 17.4% of patients had HNM vs 82.6% with OMS. There was a male HNM preponderance: 68.7% vs 50.3% for females (P < .01). Patients with HNM were older (mean [SD] age, 57.1[16.6] years vs 53.3[16.2] years; P < .01). There were fewer cases of superficial spreading melanoma in patients with HNM (29.0% vs 53.7%; P < .01). There were more diagnoses of lentigo maligna in patients with HNM (26.0% vs 1.9%; P < .01). The mean thickness of the primary lesion was 2.32 (1.9) mm vs 2.31 (2.9) mm; P = .49. Fewer patients with HNM had Clark level involvement lower than level IV (13.3% vs 24.0%; P < .01). More SLNs were harvested from patients with HNM (3.72 [3.2] vs 2.89 [2.6]; P < .01), but a lower percentage of positive SLNs was found (9.2% vs 16.0%; P < .05). There was no difference in local, regional, or distant recurrence (5.3%, 6.9%, and 5.3%, respectively, in patients with HNM and 3.4%, 5.5%, and 6.7%, respectively, in patients with OMS). The 2- and 5-year survival rates for patients with HNM were 96.2% and 72.6%, respectively, in patients with OMS (P = .40).

Conclusions: Most patients with HNM are older males with more SLNs harvested. They do not seem to have poorer outcome than patients with OMS.

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MALIGNANT MELANOMA will be diagnosed in 1 in 59 men and women at some time during their lifetime. The American Cancer Society estimates that in 2007, 59,940 new cases of melanoma will be diagnosed (33,910 in men and 26,030 in women) and that 10,850 individuals will die of melanoma. A number of prognostic indicators have been described, the most important of which are the thickness of the primary lesion, the presence or absence of ulceration, the number of metastatic lymph nodes, and the presence or absence of satellitosis or in-transit disease. A number of investigators have reported that the anatomic site of the primary lesion has important prognostic implications. Garbe et al followed a series of 5093 patients with malignant melanoma from 1970 through 1988 at 4 university centers in Germany to determine the importance of anatomic location for survival. These investigators found that individuals with melanoma of the scalp and neck had lower 10-year survival rates than those with melanomas of the extremities. A prognostic model created by the Pigmented Lesion Group (Schuchter et al) at the University of Pennsylvania also found that those with melanomas of the axis (defined as the head, neck, trunk, and volar and subungual sites) had a poorer outcome than those with primary lesions of the extremities, although no subset analysis looking specifically at the head and neck primary melanomas was performed. Similarly, a population-based study from Sweden found that patients...
with primary melanomas of the extremities had an improved survival compared with patients with lesions at other primary sites, including the head and neck.

These data, however, were largely collected in the era before sentinel lymph node (SLN) biopsy. The routine use of the SLN procedure to more accurately stage melanoma, and these more accurate, minimally invasive staging techniques, may eliminate the perceptions of poorer outcome of melanomas of the head and neck region (HNM). In addition, assessment of the nodal status may have been used less frequently, particularly in the head and neck region, prior to the availability of a minimally invasive technique to evaluate patients at elevated risk for nodal metastasis. We therefore sought to determine the significance of the head and neck as a primary melanoma site in the era of SLN biopsy, when SLN biopsy became the standard of care for the management of intermediate thickness melanoma.

**Table. Clinical and Histopathologic Characteristics of the HNM and OMS Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HNM Group (n=131)</th>
<th>OMS Group (n=624)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>90 (68.7)</td>
<td>314 (50.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>57.1 (16.6)</td>
<td>53.3 (16.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Type of lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>34 (26.0)</td>
<td>12 (1.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Nodular</td>
<td>19 (14.5)</td>
<td>81 (13.0)</td>
<td>.50</td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>38 (29.0)</td>
<td>335 (53.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Acral lentiginous</td>
<td>0</td>
<td>20 (3.2)</td>
<td>.20</td>
</tr>
<tr>
<td>Thickness, mean (SD), mm</td>
<td>2.32 (1.9)</td>
<td>2.31 (2.9)</td>
<td>.90</td>
</tr>
<tr>
<td>Clark level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>3 (0.5)</td>
<td>.60</td>
</tr>
<tr>
<td>II</td>
<td>4 (3.1)</td>
<td>20 (3.2)</td>
<td>.60</td>
</tr>
<tr>
<td>III</td>
<td>10 (7.6)</td>
<td>99 (15.9)</td>
<td>.008</td>
</tr>
<tr>
<td>IV</td>
<td>82 (62.6)</td>
<td>364 (58.3)</td>
<td>.20</td>
</tr>
<tr>
<td>V</td>
<td>9 (6.9)</td>
<td>23 (3.7)</td>
<td>.08</td>
</tr>
<tr>
<td>Ulceration present</td>
<td>16 (12.2)</td>
<td>85 (13.6)</td>
<td>.30</td>
</tr>
<tr>
<td>Regression present</td>
<td>24 (18.2)</td>
<td>179 (28.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>16 (12.2)</td>
<td>50 (8.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SLNs harvested, mean (SD)</td>
<td>3.72 (3.2)</td>
<td>2.89 (2.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥1 Mitoses/10 HPFs, %</td>
<td>79.4</td>
<td>72.8</td>
<td>.007</td>
</tr>
<tr>
<td>Positive SLNs, %</td>
<td>9.2</td>
<td>16.0</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: HNM, head and neck melanoma; HPF, high-power field; OMS, melanomas at other sites; SLN, sentinel lymph node.

This database was approved by the institutional review board involving human subjects at The Ohio State University. A melanoma SLN database was established at The Ohio State University in August 1994 and is prospectively maintained. This database was approved by the institutional review board involving human subjects at The Ohio State University.

Of note, more than 85% of cases in the database were reviewed by 1 of 2 dermatopathologists (one of whom was C.M.). The SLN biopsies were offered as a staging procedure to all patients with melanomas more than 1 mm in depth of invasion and in individuals with melanomas less than 1 mm in depth and associated adverse prognostic features, such as the presence of ulceration or regression and Clark level IV or V involvement. Although the indications for SLN biopsy remained fairly constant, the use of the technique may have increased over the course of the study owing to growing acceptance of the technique. This database was examined to evaluate the clinical and histopathologic characteristics and outcomes of individuals diagnosed with primary HNM compared with melanomas at other primary sites (OMS). The query was discontinued in December 2004 to allow adequate follow-up. The age and sex of the affected individuals and the site of the primary lesion were examined. The type of melanoma (superficial spreading, nodular, lentigo maligna, and acral lentiginous), depth of invasion, Clark level, ulceration, regression, presence or absence of mitoses, and results of SLN biopsy were recorded. Local, regional, and distant recurrences were examined, as were 2- and 5-year survival rates. Data were analyzed using χ² analysis, Fisher exact test, and paired t test analysis.

**RESULTS**

From August 1994 to December 2004, a total of 2039 patients with melanoma were evaluated at The Ohio State University; 83% were evaluated by the surgical oncology service, and 37% underwent SLN biopsy. A total of 755 patients underwent wide excision and SLN biopsy for malignant melanoma at the Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard M. Solove Research Institute at The Ohio State University, from August 1994 to December 2004. Of these, 131 (17.4%) had primary HNM (hereinafter, HNM group) and 624 (82.6%) had OMS (hereinafter, OMS group). The clinical characteristics of these 2 groups are shown in the Table. Of the HNM group, 49 (37.4%) were located on the face, 37 (28.2%) on the neck, 29 (22.1%) on the ear, and 16 (12.2%) on the scalp. There was a male predominance in the HNM group (P<.01), and these patients were older, with a mean (SD) age of 57.1 (16.6) years vs 53.3 (16.2) years for the OMS group (P<.01). There were fewer cases of superficial spreading melanoma among the HNM group and, as expected, more cases of lentigo maligna melanoma. Fewer patients in the HNM group had a Clark level lower than IV compared with the OMS group (14/105 [13.3%] vs 122/509 [24.0%]; P<.01). In 107 cases of HNM and 493 cases of OMS, data regarding mitoses were available. There was at least 1 mitosis per 10 high-power fields in more patients in the HNM group (85 [79.4%]) than in the OMS group (358 [72.6%]; P=.007).

There were significantly more SLNs harvested from the HNM group than from the OMS group (3.72 [3.2] vs 2.89 [2.6]; P<.01). In spite of this, however, the percentage of positive nodes was significantly lower in the HNM group vs the OMS group (9.2% vs 16.0%; P=.03). Failure to localize the SLN occurred in 1.5% of the HNM group and in 0.6% of the OMS group (P=.30). There was no notable difference in local, regional, or distant recurrence between groups (5.3%, 6.9%, and 5.3%, respectively, for the HNM group vs 3.4%, 5.5%, and 6.7%, respectively, for the OMS group). There was a total of 23 recurrences in the HNM group (17.5%) and 97 in the OMS group (15.5%). Interestingly, 18 (78.3%) and 62 (63.9%) of the recurrences in HNM and OMS groups, respectively, were in individuals with a negative SLN biopsy. In the HNM group, there were 5 distant (27.8%), 7 regional (38.9%), and 6 local recurrences (33.3%) in those
with a negative SLN biopsy and 2 distant (40%), 1 regional (20%), and 2 local recurrences (40%) in those with a positive SLN biopsy. In the OMS group, there were 24 distant (38.7%), 23 regional (37.1%), and 15 local recurrences (24.2%) after a negative SLN biopsy and 17 distant (48.6%), 12 regional (34.3%), and 6 local recurrences (17.1%) after a positive SLN biopsy. There were 12 individuals in the HNM group with a positive SLN (9.8%), 8 of whom underwent a completion lymph node dissection (66.7%) and 3 of whom had additional involved nodes discovered at the time of operation (37.5%). In the OMS group, 100 patients had a positive SLN (16%); 92 underwent completion node dissection (92.0%) and 17 had additional positive nodes discovered at the time of operation (18.5%). The false-negative rate of sentinel lymphadenectomy in the HNM and OMS groups was not statistically different between the 2 groups, (5.9% and 4.4%, respectively; P = .12). With a mean (median) follow-up of 3.2 (2.8) years, there was no notable difference in time to first recurrence or overall survival (Figure 1 and Figure 2).

**COMMENT**

A number of important prognostic indicators exist in melanoma. The most important of these are thickness and nodal status. Anatomic site, however, has also been considered a prognostic factor, with lesions of the head and neck showing a worse outcome.1-3 Of course, many of these models were formulated in the era before routine SLN biopsy, and whether there is a true difference in outcome based solely on anatomic site in this era of routine SLN biopsies is unclear. In multivariate models, however, anatomic site does remain an important predictor of outcome (central associated with a poorer prognosis than extremity), and the external ear, scalp and neck, and trunk are associated with increasing relative hazard.4,5 Our analysis, however, did not identify a worse prognosis associated with the primary HNMs compared with OMS.

The reasons for the worse prognosis previously seen in HNMs are unclear. The HNMs arising at less visible areas, such as the scalp and posterior neck, are generally thicker at presentation.4 Certainly, as at other sites, thicker lesions, those associated with ulceration, and those in which the SLNs are involved with metastasis have a worse outcome.5 No difference in thickness or ulceration was seen in our cohort of patients. And, although more SLNs were harvested for primary HNMs, the SLN was less likely to be involved with metastatic disease.

In the era predating lymphoscintigraphy and SLN biopsy, the treatment of HNMs was complicated by the high rates of discordant drainage patterns and the possibility of drainage to bilateral cervical basins.6-13 The performance of SLN biopsy in HNMs is technically challenging and associated with lower sensitivity.14 More recent studies,6,13,15-16 however, have demonstrated identification rates of SLNs in HNMs ranging from 93% to 100%, although acknowledging that the procedure may be technically challenging. In our series of patients, with a mean duration of follow-up of 3.2 years, the false-negative rate of SLN biopsy for HNM (5.9%) was not different than the false-negative rate for OMS (4.4%). In addition, no difference in outcome was observed, and no overall difference in recurrence was observed. Our rate of SLN positivity (9.2%) was slightly lower than that reported in the literature (10.1%-16.7%),6,16 which may, in part, explain the fact there was no difference in outcome between HNMs vs OMS in our series of patients.

In addition, the predominance of facial primary lesions in the HNM group (37.4%) and relative paucity of scalp lesions (12.2%) may account for the improved outcome seen in our patient population, because previous analysis of the site of HNMs has shown that a primary melanoma of the scalp was associated with a 3-fold greater mortality than tumors on the face.6,8 Many of the earlier articles suggesting a worse outcome with HNMs did not include the data regarding the location of primary sites.6,8 Some studies7,14 looking exclusively at HNMs have also described a predominance of facial lesions (36%-60%), whereas in another, smaller study,14 neck and scalp lesions were more common than facial and ear lesions.

It seems that lesions of the scalp and posterior neck behave somewhat more aggressively than lesions of the
face, analogous to the difference between truncal and extremity lesions. The head and neck area has always been thought to have richer, more interrelated lymphatic channels, and therefore it is difficult to relate these lesions to the trunk and extremity lesions. There were not sufficient numbers in the HNM group to perform an adequate comparison, but this topic would be an interesting area for future study.

In summary, despite differences in the age and sex distribution of individuals with HNMs in the era of routine SLN biopsy, these individuals did not seem to have a notably poorer outcome than individuals with OMS.

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Author Contributions: Drs Agnese, Tillman, Pozderac, Magro, and Walker and Ms Maupin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Walker. Acquisition of data: Maupin, Tillman, Pozderac, Magro, and Walker. Analysis and interpretation of data: Agnese, Maupin, and Walker. Drafting of the manuscript: Agnese. Critical revision of the manuscript for important intellectual content: Maupin, Tillman, Pozderac, Magro, and Walker. Administrative, technical, and material support: Maupin and Walker. Study supervision: Walker.

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REFERENCES


