Objective: To define the percentage of positive sentinel lymph node biopsies and identify risk factors for the presence of lymph node disease in patients with melanomas less than or equal to 1 mm in depth.

Design: Retrospective chart review.

Setting: Washington University School of Medicine and Barnes-Jewish Hospital, St Louis, Mo, a melanoma referral center with outpatient surgical care.

Patients: Forty-six patients with melanomas less than or equal to 1 mm in depth undergoing sentinel lymph node biopsy at our institution between 1996 and 2002.

Results: The procedure was well tolerated and there were no reported complications. Of the 46 patients, 3 (7%) (95% exact confidence interval, 1.3%-17.8%) were found to have positive sentinel lymph nodes or micrometastatic disease. The finding of a positive sentinel lymph node was associated with a Clark level of III or more (P≤.07).

Conclusions: Conclusions from this study are limited by the small sample size. The results of our study suggest that sentinel lymph node biopsy of patients with melanomas less than or equal to 1 mm in depth may be indicated when the Clark level is III or more.

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From the Divisions of Dermatology (Drs Lowe, Hurst, and Cornelius) and Surgical Oncology (Dr Moley), Washington University School of Medicine, St Louis, Mo. The authors have no relevant financial interest in this article.
Controversy exists regarding the utility of SLNB for primary tumors that are nonulcerated and less than 1 mm in depth, particularly those with a Clark level of II or III. According to Dubois et al,²¹ SLNB is inappropriate for nonulcerated lesions 0.75 mm or less in depth, with a Clark level of II or III. In one study of 75 persons undergoing SLNB with primary tumors less than 0.9 mm in depth, Statius Muller et al²² found that none of the sampled nodes was positive.

It has been demonstrated, however, that patients with a positive sentinel node are more likely to have a primary lesion that is axially located, thick, or ulcerated.²⁰ In patients with tumors of similar depth, axial location has been associated with a worsened prognosis, as has male sex.¹⁹ Axial location has been correlated with metastasis in thin melanomas as well.¹⁴,¹⁵ Ulceration is believed to be related to rapid tumor growth, increased tumor doubling time, compromised blood supply,¹² and worsened prognosis.¹¹ Although rarely seen in tumors thinner than 1 mm, ulceration has, in fact, been correlated with metastases in thin lesions.²⁶ In tumors thinner than 1 mm, a Clark level of IV or greater is associated with higher rates of metastasis²⁴ and increased mortality.¹³,¹⁵,²⁷ Melanomas in the vertical growth phase, or infiltrating into the dermis and subcutaneous tissue, have been reported to have an increased incidence of disease metastasis,²⁸,²⁹ although conflicting reports exist.²³

Host tumor response may result in histologic evidence of tumor regression and partial destruction of the tumor.³⁰,³¹ Clinically, areas of depigmentation within the tumor may be seen.³²,³³ Tumor regression may be associated with a worsened prognosis, possibly reflective of more aggressive biological behavior³⁴ or underestimation of tumor depth.³⁰ Consequently, in patients with lesions of similar depth, regression has been associated with metastasis and a worsened prognosis.¹⁴,¹⁶,¹⁸,¹⁹,³⁵,³⁹ although these findings have been refuted.¹³,¹⁵,⁴⁰,⁴³

Our study was undertaken to describe the incidence of sentinel lymph node metastasis in our patient population, and to identify the risk factors for sentinel node disease in patients with a Breslow depth of less than or equal to 1 mm.

METHODS

PATIENT DATA

Charts of patients treated at Washington University School of Medicine and Barnes-Jewish Hospital, St Louis, Mo, for melanoma between 1996 and 2002 were reviewed for age at diagnosis; tumor location, depth, presence of regression or ulceration, and histologic subtype; methods of treatment; and patient outcome. Permission for this study was obtained from the Human Studies Committee at Washington University School of Medicine under approval No. 01-0589. Two hundred fifty-one patients with primary lesions that were less than or equal to 1 mm in depth on original histopathologic examination were treated at our institution during this time.

Of the 251 patients with thin tumors, 140 of the original biopsies were performed at outside institutions, then the patients were referred to our institution for definitive management and follow-up. As a routine practice, tissue specimens from outside institutions were reviewed by dermatopathologists at our institution before any management decisions were made.

At the time of wide reexcision, 21 of the patients had residual disease at the site of the original primary tumor. The corresponding subjects were excluded from this study.

SENTINEL LYMPH NODE BIOPSY

A review of 230 subjects with lesions equal to or thinner than 1 mm treated at our institution between July 1, 1996, and August 31, 2002, showed that 46 patients underwent SLNB. In each case, the decision to undergo SLNB was based on the clinical presentation and was made jointly by the physician and the patient. Factors that influenced the decision to have an SLNB included the lesion depth, the Clark level of invasion, and presence of regression or ulceration on histopathologic examination of the primary lesion. In most cases, SLNB was performed at the time of wide local excision, after identification of the sentinel node by means of lymphoscintigraphy. No intraoperative complications were associated with the procedure in any of these patients.

Initially described by Morton et al in 1992,⁴⁴ the technique of SLNB has been previously reported.⁴⁵-⁴⁷ Briefly, at our institution, once the diagnosis of a melanoma 1 mm or greater in depth or Clark level IV is confirmed on histopathologic examination, the patient returns for a wide excision, lymphatic mapping, and SLNB. Evaluation of the sentinel node begins with injection of a radioactive tracing agent at the site of the resected tumor. After the radioactive agent has been given sufficient time to drain into the nodal basin, the location of the sentinel node is detected by radiography and marked on the patient. This mark, along with a radioactive probe for confirmation in some cases, is used to localize the incision and identify the sentinel node. Before the incision is made, isosulfan blue is injected into the site of the previous resection and allowed to drain to the nodal bed, serving as an additional guide and a confirmation that the correct node has been isolated. The sentinel node is sent to the pathology department for histologic examination.

In all cases, sentinel nodes were evaluated by a board-certified pathologist using standard histologic examination with hematoxylin-eosin staining. In addition, beginning in 2000, all nodes that were negative by histologic examination were also evaluated for micrometastases by immunohistochemical staining, primarily the MART-1 antibody. In all, 25 cases were reviewed by histologic examination alone and 21 cases were reviewed with both histologic examination and immunohistochemistry.

STATISTICAL EVALUATION

The relationship between sentinel node positivity and age, sex, level of invasion, depth of lesion, tumor regression, and tumor ulceration was analyzed by means of Cox simple regression model. Similar comparisons were made between these variables and death by means of Cox simple regression. The relationships of node positivity and death with lesion location and histogenic subtype were analyzed by means of analysis of variance. All statistical analysis was performed with the Minitab Statistical software package, version 13 (Minitab Inc, State College, Pa).

RESULTS

A total of 230 subjects with lesions equal to or less than 1 mm thick were included in this study. Of the subjects, 131 were male and 99 were female. The mean age of sub-
Patient characteristics are listed in Table 1.

Consistent with previous data, primary lesions were most commonly located on the trunk in male patients (52.3%) and the extremities in female patients (49.5%). The dominant histologic types of lesions were lentigo maligna and superficial spreading in male subjects (36.6% and 38.2%, respectively) and superficial spreading melanoma in female subjects (50.5%).

In all, 59 patients with primary tumors less than or equal to 1 mm in depth were referred for tumor reexcision and SLNB. However, 13 of these patients were excluded from this study, either because the original pathology specimen was not available for review (n = 2) or because residual tumor was found at the time of the tumor reexcision, making the true depth of the lesion less definitive (n = 11).

The study population, therefore, consisted of 46 individuals, 26 men and 20 women, with a mean age of 50 years (range, 20-75 years). Of those undergoing SLNB, 8 subjects had in situ lesions. The mean lesion depth in the remaining subjects was 0.74 mm. Of the original biopsies, 32 were performed at outside institutions and the patients were subsequently referred to Washington University School of Medicine for definitive treatment. Other patient characteristics are listed in Table 2.

TUMOR CHARACTERISTICS

Of the patients undergoing SLNB, 15 had tumors with histologic evidence of regression and 1 with ulceration. Fifteen were vertical growth-phase melanomas, 15 were in radial growth phase, and 16 did not have the growth phase specified. Twelve of the tumors were Clark level I or II, 19 were level III, and 15 were level IV. Of the 46 subjects undergoing SLNB, 3 (7%) had disease in the sentinel node (95% exact confidence interval, 1.3%-17.8%).

Of the 3 patients found to have sentinel node metastases, 2 were male and 1 was female. Two of the patients had histologic evidence of metatatic lymph node disease, and one subject had immunohistochemical evidence alone. None of the primary lesions with positive sentinel nodes had evidence of regression or ulceration on histopathologic examination. Two of the primary lesions were in the radial growth phase; the growth phase of the third was not designated in the pathological report. Invasion to Clark level III or greater was associated with lymph node metastasis (P = .07), but this did not reach statistical significance because of the small sample size. Table 3 lists other patient information.

PATIENT FOLLOW-UP

The 3 patients with sentinel node metastases underwent lymph node dissections of the appropriate nodal basin. The completion lymphadenectomies were negative for metastatic disease, and all patients remained disease free. The 43 patients who were not found to have disease in the sentinel node at the time of SLNB remained alive and disease free at last follow-up.

Table 1. All Patients With Melanomas Less Than or Equal to 1 mm in Depth

<table>
<thead>
<tr>
<th>Mean age, y</th>
<th>All Patients (n = 230)</th>
<th>Male (n = 131)</th>
<th>Female (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of disease, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>23.4</td>
<td>27.7</td>
<td>17.5</td>
</tr>
<tr>
<td>Trunk</td>
<td>43.6</td>
<td>52.3</td>
<td>32.0</td>
</tr>
<tr>
<td>Extremity</td>
<td>32.2</td>
<td>19.2</td>
<td>49.5</td>
</tr>
<tr>
<td>Sole</td>
<td>0.9</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Histologic subtype, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>43.5</td>
<td>38.2</td>
<td>50.5</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>33.5</td>
<td>36.6</td>
<td>29.3</td>
</tr>
<tr>
<td>Nodular</td>
<td>1.3</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Acral lentiginous</td>
<td>0.9</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Other, not otherwise specified</td>
<td>20.0</td>
<td>22.8</td>
<td>17.2</td>
</tr>
</tbody>
</table>

Table 2. Patients With Melanomas Less Than or Equal to 1 mm in Depth Undergoing SLNB

<table>
<thead>
<tr>
<th>Mean age, y</th>
<th>All Patients (n = 46)</th>
<th>Male (n = 26)</th>
<th>Female (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of disease, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>5 (11)</td>
<td>4 (15)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Trunk</td>
<td>22 (48)</td>
<td>16 (62)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Extremity</td>
<td>18 (39)</td>
<td>5 (19)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Sole</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Histologic subtype, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>32 (70)</td>
<td>16 (62)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>7 (15)</td>
<td>5 (19)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Nodular</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acral lentiginous</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Other, not otherwise specified</td>
<td>5 (11)</td>
<td>4 (15)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Table 3. Information for Patients With Melanomas Less Than or Equal to 1 mm in Depth and Positive Sentinel Nodes*

<table>
<thead>
<tr>
<th>Patient Age, y/Sex</th>
<th>Location</th>
<th>Breslow Depth, mm</th>
<th>Clark Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>36/F</td>
<td>Arm</td>
<td>0.56</td>
<td>III</td>
</tr>
<tr>
<td>64/M</td>
<td>Back</td>
<td>0.96</td>
<td>III</td>
</tr>
<tr>
<td>47/M</td>
<td>Arm</td>
<td>0.50</td>
<td>III-IV</td>
</tr>
</tbody>
</table>

*All 3 patients: (1) had excisional biopsies for diagnosis, (2) had superficial spreading melanoma histologic subtypes without regression or ulceration, (3) underwent elective lymph node dissection, and (4) were disease free at last follow-up.

COMMENT

Melanoma nodal metastasis has been reported to occur as an orderly event, with initial spread to the sentinel node and subsequent progression to other nodes.57 Sentinel node biopsy, originally described by Morton et al in 1992,44 is currently recommended for all patients with melanoma tumors greater than 1 mm in depth without clinical evidence of metastasis at the time of diagnosis. In addition, SLNB is presently recommended in lesions less than 1 mm in depth with ulceration or invasion to a
Clark level of IV or greater.\textsuperscript{20,21} Subjects with nodal metastasis detected on SLNB are then advised to undergo completion lymph node dissection and be considered for interferon therapy. Previous studies have reported positive sentinel node rates of 4.7% for patients with lesions 0.76 to 1.49 mm in depth, 19% for lesions 1.51 to 4 mm, and 34% to 36% for lesions greater than 4 mm.\textsuperscript{20,46}

The benefit of complete lymphadenectomy in patients with melanoma has been debated. Initially, several studies found no overall survival advantage in patients with melanoma who underwent elective lymph node dissection.\textsuperscript{49-51} However, subgroup analysis has found that elective lymph node dissection improves survival in selected subgroups, specifically in those younger than 60 years, with lesions 1 to 2 mm in thickness, and particularly in subjects with nonulcerated lesions.\textsuperscript{49,50} In addition, in subjects with tumors greater than 1.5 mm in depth and with occult nodal metastases, it has been reported that subjects undergoing immediate elective lymph node dissection have increased survival compared with subjects undergoing nodal dissection after the appearance of clinical disease.\textsuperscript{31}

In this study, we reviewed the outcomes of 46 subjects with lesions equal to or less than 1 mm in depth undergoing SLNB. Fifteen had tumors with histologic evidence of regression and 1 with ulceration. Fifteen of the tumors were in the vertical growth phase, 15 were in the radial growth phase, and 16 did not have the growth phase specified. Twelve of the tumors were Clark level I or II, 19 were level III, and 15 were level IV.

Of the 46 subjects undergoing SLNB, 3 (7%) had disease in the sentinel node (95% exact confidence interval, 1.3%-17.8%). This percentage is slightly higher than that previously reported.\textsuperscript{22} All 3 tumors were of the superficial spreading melanoma subtype. Two of the primary tumors were in the radial growth phase, and the growth phase of the third was not designated. None of these subjects had lesions that were ulcerated or re- gressed on histopathologic evaluation, although the prognostic significance of ulceration in stage I and II melanoma is well recognized.\textsuperscript{11} None of the 8 patients with in situ lesions had micrometastatic disease.

The only factor predictive of a positive SLNB in these 3 patients was the presence of a Clark level of III or more (P=.07). Given the limited number of patients in this study, this did not reach statistical significance. Although this is consistent with previous recommendations of Clark level IV as a criterion for SLNB, our data suggest that in tumors of 1 mm or less, SLNB could be considered for Clark level III lesions.

The outcomes of our study were limited by the small size of our study group. Our study substantiates the findings of other groups, where thin melanomas have been demonstrated to have the potential to metastasize to the regional nodal basin. In our experience, SLNB is a useful adjunct to prognosis and treatment in thin melanomas with a Breslow depth of 1 mm or less and a more invasive Clark level, in this case III or more. The results of our study also support the reporting of Clark level for T1 (<1-mm) melanomas, as included in the new American Joint Committee on Cancer staging for cutaneous melanoma.\textsuperscript{11} Our future studies will include compari-

\section*{REFERENCES}


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42. Wanebo HJ, Cooper PH, Hagar RW. Thin (less than or equal to 1 mm) melanomas of the extremities are biologically favorable lesions not influenced by regression. Ann Surg. 1985;201:499-504.