Hypothesis: A tumor-negative sentinel node (SN) does not eliminate the chance of melanoma recurrence. Patterns of metastasis can be identified and characterized in patients with tumor-negative SNs.

Design: Retrospective review.

Setting: Melanoma referral center.

Patients: Patients who underwent lymphatic mapping and sentinel lymphadenectomy between 1995 and 2002 and whose SNs were negative for metastasis by hematoxylin-eosin and immunohistochemistry staining were included in the study. The SN specimens from patients with recurrent disease were reexamined for missed metastasis.

Main Outcome Measures: Differences in survival related to sites of recurrence and the rate of false-negative histopathologic SN diagnosis were determined.

Results: At a median follow-up of 36.7 months, 69 (8.9%) of 773 patients with tumor-negative SNs had recurrent disease. Three-year survival after first recurrence was 17.1% in the 37 patients with distant recurrence, 48.7% in the 19 patients with local or in-transit recurrence, and 63.5% in the 13 patients with regional basin recurrence; the difference in survival between patients with local or regional and distant recurrences was statistically significant (P < .001). Histopathologic reexamination of SNs from the 69 patients identified 9 patients with false-negative SNs; 2 of these had same-basin recurrences.

Conclusions: The SN is a valuable prognostic indicator because only 8.9% of patients with tumor-negative SNs will develop recurrence. The low incidence (1.7%) of regional basin recurrence in patients with negative SNs supports the accuracy of our current method of lymphatic mapping and sentinel lymphadenectomy to identify occult regional nodal basin metastasis.

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Before the introduction of lymphatic mapping and sentinel lymphadenectomy (LM/SL), surgeons advocated elective lymph node dissection (ELND) to identify and treat patients with melanoma who had occult regional node metastasis. Unfortunately, ELND is associated with several problems. Pathologic analysis of multiple nodes for the presence of tumor cells is time-consuming, costly, and prone to sampling error. Patients with tumor-negative regional nodes are subjected to an unnecessary operation, with its potential for the long-term risks of nerve injury and lymphedema. Furthermore, it is not clear whether ELND improves survival. Multiple prospective randomized trials of ELND have been performed, with some suggesting an improvement of survival in particular patient subgroups.1–4

In 1990, Morton et al5 first introduced the concept that a single node, the sentinel node (SN), could be identified, harvested, and examined to determine the presence of regional nodal metastasis in patients with clinical stage I/II melanoma. In their original report that used vital blue dye for intraoperative lymphatic mapping, the SN was successfully identified in 82% of 223 patients.6 Since this first published report, LM/SL has proved to be a less invasive technique that accurately assesses the tumor status of the regional lymph node basin compared with ELND, and during the past decade, it has been used routinely.7

Spread of melanoma to the SN is one of the most important determinants of prognosis in patients with early-stage cutaneous melanoma.8,9 Three-year disease-free survival rates of 88.5% for patients with tumor-negative vs 55.8% for tumor-positive SNs have been reported.8

Although a tumor-negative SN imparts a survival advantage, it does not eliminate the risk of recurrence. Several studies8–17 have examined melanoma recurrence pat-
tions and outcome in patients with tumor-negative SNs. However, many of these studies are limited by small numbers of patients, short follow-up times, and/or histopathologic assessments based only on hematoxylin-eosin (H&E) staining.

Immunohistochemistry (IHC) can increase the sensitivity of SN histopathologic analysis by identifying individual cells and small clusters of melanoma cells that might be missed by H&E staining.18 In their original study on LM/SL, Morton et al18 used IHC for SN evaluation and achieved a low false-negative rate. Despite this, some groups chose to perform SN histopathologic analysis using only H&E staining. Gershenwald et al19 reported melanoma recurrence patterns in patients with tumor-negative SNs by H&E staining. Reanalysis of the SNs in patients with same-basin recurrences by serial sectioning and/or IHC demonstrated evidence of missed occult metastases in 80%.

In this study, we retrospectively evaluated the recurrence patterns of patients whose SNs were negative for melanoma by a standardized pathologic technique that included IHC staining with antibodies to S100 and HMB-45. We investigated differences in survival based on sites of recurrence. The SNs from patients with recurrence were reevaluated by further sectioning and IHC staining. The goals of the study were to gain an understanding of the natural history of disease in patients with tumor-negative SNs as well as the accuracy of LM/SL.

METHODS

We performed a retrospective review of a prospectively acquired database to identify all patients with stage I and II melanoma who underwent successful LM/SL between January 1995 and December 2002 at our melanoma referral center. The database contained each patient's clinical characteristics, pathologic findings, and follow-up records. Excluded from this study were patients with a history of melanoma or other malignancy (other than skin cancers such as squamous cell or basal cell), those with more than 1 primary melanoma at presentation, those with same-basin recurrences by serial sectioning and/or IHC demonstrated evidence of missed occult metastases in 80%.

In this study, we retrospectively evaluated the recurrence patterns of patients whose SNs were negative for melanoma by a standardized pathologic technique that included IHC staining with antibodies to S100 and HMB-45. We investigated differences in survival based on sites of recurrence. The SNs from patients with recurrence were reevaluated by further sectioning and IHC staining. The goals of the study were to gain an understanding of the natural history of disease in patients with tumor-negative SNs as well as the accuracy of LM/SL.

RESULTS

Of the 915 patients identified from the database who met the study inclusion criteria, 773 (84.5%) had a histologically tumor-negative SN. These patients had a mean age of 54 years (range, 8-91 years) and a mean primary tumor thickness of 1.56 mm (range, 0.15-14.0 mm); other clinical and pathologic characteristics are listed in Table 1 and Table 2. Most primary melanomas were nonulcerated (83%) and superficial spreading (63%) lesions, predominantly on the trunk and extremities. Eighty percent were less than 2 mm thick.

Most SNs were harvested from the axillary or inguinal basins (Table 1). Forty-five patients (5.8%) had SNs in more than 1 lymphatic drainage basin; most of these patients had a primary melanoma on the trunk, head, or neck. The mean number of SNs harvested from patients with tumor-negative SNs was 2.3 (range, 1-8); this finding did not differ significantly from the mean number of SNs harvested from the 142 patients with tumor-positive SNs (2.2; range, 1-8).


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Table 1. Clinical Characteristics of Patients Who Had Melanoma With Tumor-Negative Sentinel Nodes and Patients Whose Melanoma Recurred

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total No. (% of Patients (N = 773))</th>
<th>No. (%) of Patients With Disease Recurrence (n = 69)</th>
<th>χ² Test P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>459 (59)</td>
<td>45 (65)</td>
<td>.30</td>
</tr>
<tr>
<td>Female</td>
<td>314 (41)</td>
<td>24 (35)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>473 (61)</td>
<td>33 (48)</td>
<td>.02</td>
</tr>
<tr>
<td>≥60</td>
<td>300 (39)</td>
<td>36 (52)</td>
<td></td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity</td>
<td>307 (40)</td>
<td>26 (38)</td>
<td>.004</td>
</tr>
<tr>
<td>Head and neck</td>
<td>156 (20)</td>
<td>24 (35)</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>310 (40)</td>
<td>19 (29)</td>
<td></td>
</tr>
<tr>
<td>Sentinel node basin</td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>Axilla</td>
<td>390 (50)</td>
<td>21 (30)</td>
<td></td>
</tr>
<tr>
<td>Inguinal</td>
<td>170 (22)</td>
<td>20 (29)</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>168 (22)</td>
<td>23 (33)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>45 (6)</td>
<td>5 (7)</td>
<td></td>
</tr>
</tbody>
</table>

*Determines statistically significant differences in clinical characteristics between patients with disease recurrence and those without disease recurrence.

Table 2. Pathologic Characteristics of Patients Who Had Melanoma With Tumor-Negative Sentinel Nodes and Patients Whose Melanoma Recurred

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total No. (% of Patients (N = 773))</th>
<th>No. (%) of Patients With Disease Recurrence (n = 69)</th>
<th>χ² or Wilcoxon Rank Sum Test P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow thickness, mm</td>
<td></td>
<td></td>
<td>.001 (Wilcoxon)</td>
</tr>
<tr>
<td>0.10-1.00</td>
<td>335 (44)</td>
<td>10 (14)</td>
<td></td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>278 (36)</td>
<td>22 (32)</td>
<td></td>
</tr>
<tr>
<td>2.01-4.00</td>
<td>108 (14)</td>
<td>25 (36)</td>
<td></td>
</tr>
<tr>
<td>&gt;4.00</td>
<td>44 (6)</td>
<td>12 (17)</td>
<td></td>
</tr>
<tr>
<td>Clark level</td>
<td></td>
<td></td>
<td>&lt;.001 (χ²)</td>
</tr>
<tr>
<td>I</td>
<td>4 (0.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>109 (14)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>305 (39)</td>
<td>16 (23)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>315 (41)</td>
<td>42 (61)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>23 (3)</td>
<td>8 (12)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td></td>
<td>&lt;.001 (χ²)</td>
</tr>
<tr>
<td>Present</td>
<td>114 (15)</td>
<td>21 (30)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>566 (73)</td>
<td>28 (41)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>93 (12)</td>
<td>20 (29)</td>
<td></td>
</tr>
<tr>
<td>Melanoma histologic findings</td>
<td></td>
<td></td>
<td>&lt;.001 (χ²)</td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>364 (47)</td>
<td>20 (29)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>118 (15)</td>
<td>20 (29)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>97 (12)</td>
<td>14 (20)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>194 (25)</td>
<td>15 (22)</td>
<td></td>
</tr>
</tbody>
</table>

*Determines statistically significant differences in pathological characteristics between patients with disease recurrence and those without disease recurrence.

PATTERNS OF RECURRENCE

At a median follow-up of 36.7 months, melanoma had recurred in 69 (8.9%) of the 773 patients (Table 1 and Table 2). The 69 patients had a mean age of 58.8 years (range, 25.9-90 years) and a mean primary tumor thickness of 2.79 mm (range, 0.77-14.0 mm). Because 1 patient had simultaneous local and distant recurrences and 3 patients had simultaneous in-transit and nodal recurrences, 73 sites of first recurrence were found. First recurrences were local in 9 patients, in transit in 14 patients, nodal in 13 patients, and distant in 37 patients. Figure 1 shows the distribution of first recurrences for all patients based on the most distant site of recurrence. For example, simultaneous local and distant first recurrences are categorized as a distant recurrence.

Approximately half (50.6%) of first recurrences were at distant sites. Twenty-eight of the 37 patients with a distant site of first recurrence died of melanoma during follow-up. Of the 32 patients who did not have a distant site of first recurrence, 11 eventually developed distant recurrences, 11 of which were fatal.

All nodal first recurrences (17.8% of all first recurrences) were in the SN basin. Thus, the incidence of same-basin recurrence was 1.7% for the total population. Same-basin recurrence was followed by distant recurrence in 9 cases, 4 of which were fatal.

Approximately one third of all recurrences were local or regional in transit. Of 14 patients who developed in-transit first recurrences, 3 had synchronous nodal recurrences and 1 developed nodal recurrence after treatment for the in-transit recurrence. The time to development of local or in-transit (median, 23 months; range, 2.5-91.8 months) vs nodal (median, 17.6 months; range, 1.1-46.3 months) vs distant (median, 25.9 months; range, 1.4-88.8 months) first recurrence was not significantly different.

Of the 69 patients with recurrence, 40 (58%) died of melanoma during follow-up. The 3-year survival rate was significantly (P<.001) higher after a first recurrence in the regional lymphatic basin (63.5%) or at a local or in-transit site (48.7%) than after a first recurrence at a distant site (17.1%) (Figure 2).

HISTOPATHOLOGIC EVALUATION OF SNS

Histopathologic reevaluation of SN specimens identified tumor-positive findings in 9 (13%) of the 69 patients based on the presence of rare isolated tumor cells or clusters no greater than 0.2 mm in largest diameter on IHC stains (8 cases) or H&E stains (1 case). In 4 cases, review of the original SN slides identified isolated tumor cells or clusters (Figure 3); 1 patient had both local and distant first recurrences (recorded as distant recurrence in Figure 3), 2 had distant first recurrences, and 1 had an in-transit first recurrence. In the remaining 5 cases, deeper sections of SN blocks demonstrated a few isolated tumor cells or clusters; 2 patients had nodal first recurrences, 1 had an in-transit first recurrence, and 2 had distant first recurrences.

The 9 patients with tumor-positive SNs included 5 women and 4 men, with ages ranging from 27 to 79 years.
H&E indicates hematoxylin-eosin; IHC, immunohistochemistry.

Recurrence

Survival, %

100

75

50

25

0

With Local or In Transit

Distant

Nodal

P<.001

Time Since First Recurrence, mo

0

10

20

30

40

50

60

70

Figure 2. Kaplan-Meier estimates of survival after local or in-transit, nodal, or distant first disease recurrences in patients with tumor-negative sentinel nodes.

Figure 3. Sites of first recurrence in 9 patients diagnosed as having missed tumor-positive sentinel nodes (SNs) on histopathologic reanalysis. H&E indicates hematoxylin-eosin; IHC, immunohistochemistry.

The ability of the SN to predict outcome depends on how accurately LM/SL identifies the presence of occult regional nodal metastases. One way to assess how successfully the SN stages the regional nodal basin would be to monitor the incidence of recurrence in lymphatic basins with tumor-negative SNs. In this study of 773 patients with tumor-negative SNs, the 3-year rate of SN basin recurrence was only 1.7%, supporting the ability of LM/SL to accurately stage the regional nodal basin in patients with melanoma.

Same-basin recurrences after tumor-negative LM/SL may result from various failures, including an error in the technique of SN identification, an inaccurate histopathologic diagnosis of tumor-negative SN, or the biological features of the melanoma. Technical aspects of LM affect the accuracy of SN identification. By analyzing data acquired from the Multicenter Selective Lymphadenectomy Trial, Morton et al demonstrated a 95.2% rate of SN identification when blue dye alone was used to perform LM. The addition of radiocolloid increased the identification rate to 99.1%. Furthermore, preoperative lymphoscintigraphy is essential to identify unsuspected drainage pathways, particularly in patients with trunk or head and neck primary tumors that may drain to multiple sites. In the present study, all patients had at least 1 SN identified by preoperative lymphoscintigraphy and intraoperative blue dye and radiopharmaceutical-directed SN localization. All LM/SL procedures were performed at 1 institution by a stable group of surgeons and nuclear medicine staff skilled in the technique. This uniformity minimized the risk of technical error.

Step sectioning and IHC staining can improve the detection of SN micrometastases and reduce the chance of inaccurately determining the SN to be tumor negative when it is truly tumor positive. In their review of 243 patients with melanoma, the tumor status of the SN is widely regarded as one of the most important prognostic indicators. By evaluating patients enrolled in the Sunbelt Melanoma Trial, Chao et al demonstrated a disease-free survival advantage in patients with tumor-negative SNs compared with patients with tumor-positive SNs. At a median follow-up of 16 months, rates of recurrence were 6% and 15.5%, respectively (P<.001). Multivariate analysis identified SN status as the most important predictor for recurrence of stage I/II melanoma (P<.001). Gershenwald et al retrospectively evaluated 612 patients with cutaneous melanoma who underwent LM/SL; rates of 3-year disease-specific survival were 96.8% and 69.9% for patients with tumor-negative and tumor-positive SNs, respectively. The SN status was again identified as the strongest predictor of disease-free survival.

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whose SNs were tumor negative by H&E staining, Gershewald et al discovered 10 patients who developed a nodal recurrence in a previously mapped basin. Serial sectioning and IHC staining of these patients’ SNs resulted in the identification of previously missed metastases in 80%. In contrast, all of our pathologists used a standardized technique in which sections of the SN were stained with H&E and antibodies to S100 and HMB-45. The 1.7% rate of same-basin recurrence for our study population is lower than that observed in other studies with similar follow-up in which the SN was evaluated only by H&E staining (Table 3). Thus, our study supports the routine use of IHC staining with antibodies to S100 and HMB-45 to aid the pathologist in identifying SN micrometastases that would otherwise be missed by H&E staining alone.

To determine the incidence and impact of errors in histopathologic SN diagnosis, we reevaluated the SNs from patients who developed recurrence. We found that 13% of all patients who developed recurrence had a tumor-positive SN that was originally misdiagnosed as tumor negative. However, 78% of the patients with missed tumor-positive SNs did not develop a recurrence within the SN basin. Our study focused on the subgroup of 69 patients who developed recurrence, and we hesitate to extrapolate these data to the parent population of 773 patients. However, if an inaccurate histopathologic SN diagnosis occurs in approximately 13% of the overall population of patients with tumor-negative SNs, then the 1.7% rate of same-basin recurrence is much lower than would be expected. One reason may be that SN removal becomes therapeutic as a means of improving disease staging, and studies are under way to examine the clinical relevance of nodal micrometastases detected by molecular techniques.

Table 3. Reported Rates of Recurrence in Patients With Tumor-Negative SNs

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Median Follow-up, mo</th>
<th>Overall Recurrence Rate, %</th>
<th>Patients With SN Basin-First Recurrences, %</th>
<th>Original Pathologic SN Analysis</th>
<th>Patients With Metastases Found on SN Reanalysis, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershewald et al, 1998†</td>
<td>243</td>
<td>35</td>
<td>11</td>
<td>4.1</td>
<td>H&amp;E</td>
<td>80</td>
</tr>
<tr>
<td>Gadd et al, 1999†</td>
<td>89</td>
<td>23</td>
<td>12</td>
<td>7.8</td>
<td>H&amp;E</td>
<td>25</td>
</tr>
<tr>
<td>Jansen et al, 2000‡</td>
<td>151</td>
<td>32</td>
<td>9.9</td>
<td>4</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Clary et al, 2001‡</td>
<td>252</td>
<td>23</td>
<td>14</td>
<td>4.4</td>
<td>H&amp;E (IHC added last year of study)</td>
<td>86</td>
</tr>
<tr>
<td>Chao et al, 2002‡</td>
<td>950</td>
<td>16</td>
<td>6</td>
<td>1.4</td>
<td>H&amp;E, IHC</td>
<td>ND</td>
</tr>
<tr>
<td>Statius Muller et al, 2002‡</td>
<td>200</td>
<td>38</td>
<td>11</td>
<td>2</td>
<td>H&amp;E, IHC</td>
<td>ND</td>
</tr>
<tr>
<td>Wagner et al, 2003‡</td>
<td>323</td>
<td>31.4</td>
<td>12.1</td>
<td>3.4</td>
<td>H&amp;E, IHC</td>
<td>ND</td>
</tr>
<tr>
<td>Fincher et al, 2003‡</td>
<td>160</td>
<td>45 (mean)</td>
<td>10</td>
<td>0.6</td>
<td>H&amp;E (IHC last 3 years of study)</td>
<td>ND</td>
</tr>
<tr>
<td>Vuylsteke et al, 2003‡</td>
<td>168</td>
<td>72</td>
<td>14</td>
<td>2.4</td>
<td>H&amp;E, IHC</td>
<td>ND</td>
</tr>
<tr>
<td>Current study</td>
<td>733</td>
<td>36.7</td>
<td>8.9</td>
<td>1.7</td>
<td>H&amp;E, IHC</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Abbreviation: H&E, hematoxylin-eosin; IHC, immunohistochemistry; ND, not done; SN, sentinel node.

*Pathologic review of SN specimens from patients whose first recurrence was in the SN basin.

By evaluating additional SN sections, pathologists may improve their ability to detect micrometastases. Of the 69 patients with recurrence, 5 (7.2%) were diagnosed as having tumor-positive SNs after 2 additional 200-µm sections were stained with H&E and IHC. However, identification of more tumor-positive SNs with additional sectioning is unlikely to affect outcome given the already low nodal recurrence rate (1.7%). Furthermore, the cost-effectiveness of the additional processing of SNs does not seem reasonable.

Recently, several centers have reported the use of reverse transcription–polymerase chain reaction (RT-PCR) assay to detect subclinical melanoma metastasis in the SN. Typically, RT-PCR is performed on a portion of the SN to detect the melanoma and melanocyte-specific marker tyrosinase. Studies have shown that 48% to 65% of histologically melanoma-negative SNs will be RT-PCR positive for tyrosinase. Kammula et al examined the clinical impact of RT-PCR findings in patients with histologically negative SNs. At a median follow-up of 42 months, a significantly higher recurrence rate was apparent in 58 patients with positive RT-PCR results than in 39 patients with negative RT-PCR results (14% vs 0%). However, when the groups were followed up for 67 months, the rates of recurrence were not statistically different. In contrast to a single-marker RT-PCR assay based on tyrosinase, a multimarker RT-PCR that uses tyrosinase in conjunction with other markers has a lower false-negative rate and seems more promising. Kuo et al used a multimarker RT-PCR for tyrosinase, melanoma antigen recognized by T cells, tyrosinase-related protein 1, and tyrosinase-related protein to upgrade 25% of histopathologically negative SNs in patients with melanoma. Eighty percent of these patients developed recurrence at a median follow-up of 55 months. Multimarker RT-PCR may be a way to eventually eliminate the need for SN histopathologic diagnosis. It also appears promising as a means of improving disease staging, and studies are under way to examine the clinical relevance of nodal micrometastases detected by molecular techniques.

Same-basin recurrence may simply reflect the biological mechanism of the disease rather than an error in SN assessment. For example, some patients may have tumor
cells located in the lymphatics that drain the primary melanoma. After wide local excision and SN biopsy, these tumor cells may remain. They then may travel to and present as a recurrence in the regional draining lymphatic basin, or they may result in in-transit recurrences. In our study, a review of SNs from the 13 patients with a regional nodal recurrence identified 2 patients who were misdiagnosed as having a tumor-negative SN. Three of the remaining 11 patients developed concurrent in-transit metastases, which suggests that tumor cells from the primary melanoma had already entered the dermal lymphatics at the time of wide local excision and SN biopsy and eventually spread to the regional nodal basin.

Most recurrences in patients with tumor-negative SNs were at distant sites, imparting a shortened survival compared with the other sites of recurrence (Figure 1). One reason for a distant recurrence is that some tumor cells may preferentially spread hematogenously. At the time of LM/SL, these cells may already have entered the bloodstream. Over time, they travel distantly and grow into a detectable metastasis. This possibility demonstrates the limitations of LM/SL for predicting outcome in a small subgroup of patients with tumor-negative SNs. Other known prognostic factors, such as Breslow level and primary tumor ulceration, may be more important in this small subgroup. In these patients, RT-PCR of blood or bone marrow for known melanoma tumor markers may also be useful.

**CONCLUSIONS**

Tumor status of the SN has been used to predict outcome, direct treatment, and follow-up in patients with melanoma. Patients with tumor-positive SNs have a higher incidence of recurrence and a worse outcome and are more likely to receive adjuvant therapy and closer follow-up than those with tumor-negative SNs. This study's 9% incidence of recurrence in patients with a tumor-negative SN supports the prognostic utility of LM/SL.

Accurate histopathologic examination of the SN is important to identify micrometastases. This study supports the use of a standardized histopathologic technique using both H&E and IHC (antibodies to HMB-45 and S100) to accurately evaluate the tumor status of the SN; only 1.7% of patients determined to have a tumor-negative SN with this technique experienced recurrence in the SN basin.

Independent, however, of how accurate we become in the identification and pathologic assessment of the SN, a small subgroup of patients with tumor-negative SNs will experience disease recurrence. The most common site of recurrence in these patients is distant rather than regional nodal (4.8% and 1.7%, respectively). Therefore, other prognostic factors, such as Breslow thickness and the presence of ulceration, should be kept in mind when trying to identify patients at high risk for recurrence. Furthermore, we must discover other methods to predict outcome, allowing us to better direct long-term follow-up and therapy for patients with melanoma.

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### REFERENCES


**DISCUSSION**

Theodore X. O’Connell, MD, Los Angeles, Calif: First of all, I would like to thank the authors for their many years of contributing to our understanding of the biology of melanoma and their pioneering and continuing work in the application of sentinel lymph node biopsy to this disease.

It has long been known that the presence of positive lymph nodes is the most important surrogate for determining the biological aggressiveness of melanoma. However, the presence of positive lymph nodes is only a surrogate for biologic activity and does not mean that the melanoma tumor cells have spread to the bloodstream and distant organs via the lymph nodes. If the lymph nodes are positive, then the tumor may have gone to the bloodstream via the lymph nodes or simultaneously to the lymph nodes and the bloodstream. Positive lymph nodes indicate a tumor with a propensity to metastasize whether by blood or lymph. In those cases with truly negative nodes, spread to distant sites is obviously solely by blood.

Although positive lymph nodes have been a powerful tool predicting metastases, it is important to define and better develop surrogates for prediction of metastases, especially as better forms of adjuvant therapy are developed. This is important both in node-positive tumors, since not all of these will develop distant metastases, and in node-negative tumors, since not all are cured.

Obviously, the presence or absence of lymph node metastases is a good predictor of future distant disease but is a long way from being totally accurate and should be refined.

When a patient fails after primary therapy, this failure may be due to technique/therapy or due to the basic biology of the tumor. Of the 69 node-negative patients who had a recurrence, 4 were positive on initial review of the slides. An additional 5 patients were deemed positive after an additional section was performed. Therefore, in 9 (13%) of the 69 cases, failure of prediction was due to improper categorization of a positive lymph node. These are really false-negative lymph nodes. Therefore, these 9 patients should be eliminated from the analysis for determining other biologic impacts, and we are left with 60 patients as the true denominator to be examined to better determine the factor of treatment failure vs biology as the cause of recurrence.

The remaining 60 patients can be further subdivided. In the 14% of patients who fail locally, it certainly could be argued that this is a failure of treatment in that not a wide enough excision was done initially. In the 14% (23%) of patients failing in-transit disease, this could be due either to the biology of the tumor or to failure of therapy again in not excising widely enough; however, in this group it is very difficult to say which is the cause of failure. In the 13% who failed in the original lymph node basin, this could be a failure of therapy; either the pathologist is not able to identify a positive lymph node even after H&E and IHC staining or this is a failure of the surgeon in not delivering the positive lymph node to the pathologist.

But now we must turn to the 37 patients (60%) who failed distantly and who obviously had aggressive tumors that were not identified by the presence of positive lymph nodes. How would we be able to better predict this failure? Certainly, there are additional predictors besides positive lymph nodes, and these have been applicable to melanomas in general as well as to node-positive melanomas. They are the Breslow and Clark classifications, the presence and absence of ulcerations, site of primary, and the cytology. Do these predictors also apply to node-negative melanomas?

It seems that they do. Of those with negative lymph nodes, only 3% of patients with a Breslow primary tumor with less than 1 mm depth of invasion recurred, increasing to 8% between 1 and 2 mm, and fully 24% recurrence for tumors over 2 mm. Similarly, in Clark level II melanomas, only 3% had failure; level III, 5%; level IV, 13%; and level V, 33%. A steady progression from level to level. Again, ulceration of the primary seems to make an impact on prognosis. In node-negative patients, only 5% with no ulceration failed, while 18% with ulceration failed distantly. Again, histology seems to be important in that only 6% of those with superficial spreading melanoma and negative nodes failed distantly, while 17% of those with nodular melanoma did. Again, mirroring previous studies with node-positive melanoma, trunk and extremity patients failed 6% and 8% of the time, respectively, while head and neck melanomas failed at a 13% rate.

Now as you can see, there is a definite trend in all these categories. I do not know how these determinants would stand up with statistical and multivariate regression analysis, but I would ask the authors using these data and these additional predictors, could there be a way to develop a formula to apply to node-negative patients to better refine the prediction of recurrences?

I have several questions for the authors: (1) In almost all studies, patients with head and neck melanomas did worse than patients with melanomas in other sites in the body. This is true whether the lymph nodes are positive or, as in this study, negative. The question with node-negative patients is whether this is due to failure to identify positive lymph nodes because of the very intricate and less predictable drainage patterns in the head and neck, or is there an inherent difference in biologic aggressiveness of head and neck tumors, or is it an anatomic difference with easier access to the rich vascular patterns in the head and neck? (2) In regard to the use of IHC analysis of lymph nodes, of which the authors have been pioneers, it obviously identifies more positive lymph nodes. The question is, do patients with lymph nodes identified only as positive by IHC act more like patients with H&E-positive lymph nodes, or more like those with truly negative nodes, or are they really a separate subcategory, and should they be treated as such?

Philip I. Haigh, MD, Los Angeles: I enjoyed that talk tremendously. I have just 1 question for the authors. In the upcoming patients whom you have from now on with T4 ulcer-
ated head and neck melanomas, should we even do the sentinel lymph node biopsy? It can be very tricky. There is some morbidity and risk, especially, for example, around the parotid gland with facial nerve injury. I'm not sure a negative node or a positive node really helps us to decide on the treatment for those patients. So I have a question about whether you still do head and neck T4 ulcerated melanomas.

Jon M. Greif, MD, San Diego, Calif: This was an excellent study, and it raises some interesting possibilities. Very few of the missed sentinel lymph node patients had nodal recurrences, and only 1 of the 12 patients who had a recurrence in the nodal basin actually had a positive sentinel lymph node. I wonder if a positive sentinel lymph node should really mandate regional lymph node dissection, potentially a very morbid procedure, or is it really a procedure meant more to help us decide on further therapy and risks?

Andrew L. DiFronzo, MD, Los Angeles: It wasn't clear to me in the 13 patients who had nodal recurrences if they were all in the same nodal basin, or were they recurrences in different basins? If they were different nodal basins, did you look back at the lymphoscintigram to see if it was a technical problem from that end?

Lawrence D. Wagman, MD, Duarte, Calif: Did you compare the survival of false-negative sentinel node patients to the patients who had positive sentinel nodes? My other question is related to the title of the paper: "10-Year Experience." What aspects of the paper were 10 years? I saw 8 years of patient accrual and an average follow-up of 3 years. I do think that the issue of 10 years of follow-up is really quite critical and would be interesting to report.

S. Eric Wilson, MD, Orange, Calif: Looking at the curves, does the annual rate of recurrence differ over the 10 years?

Dr Essner: Thank you for allowing us to present this work, which is a culmination of our experience of sentinel lymphadenectomy at the John Wayne Cancer Institute. We began performing this procedure originally at UCLA (University of California, Los Angeles) in the late 1980s, and it became standardized in 1992 and has subsequently become the procedure of choice for evaluating the regional lymph nodes in patients with early-stage melanoma. I also appreciate Dr O'Connell's insightful comments.

In response to the questions about our paper: yes, we did see particular groups of patients who tended to have recurrences, and as Dr O'Connell mentioned, increasing tumor thickness, the presence of ulceration, nodular histology, and head and neck primary sites were those factors predictive of patients who would have a recurrence. In this type of paper we can develop a predictive model of recurrence from the multivariate analysis of those factors. We have not found these models clinically useful as such because it's difficult, as you can imagine, telling our patients what is the difference between an 8% vs a 12% vs a 15% risk of recurrence with not very good adjuvant therapy and no standardized methods of following up these patients. But, yes, we have identified factors for predicting those patients who tend to have a recurrence.

Comments were made regarding IHC and H&E evaluation of the sentinel nodes. Interestingly enough, the situation appears to be different for breast cancer than melanoma, where IHC appears to be very important for determining progress. Our data suggest that the outcomes of patients with an IHC-positive node or H&E-positive nodes are very similar. When you analyze lymph nodes by RT-PCR, which was not performed on any patients in this study, the patients tend to have a prognosis in between the patients with negative nodes and those who have positive nodes by routine H&E or IHC. Certainly, these data raise other questions, such as how should pathologists analyze sentinel lymph nodes? Should we continue to use our conventional methods of evaluating the lymph nodes, or should we routinely use multiple-step sections or RT-PCR in view of the false negatives that we have found from this study?

Dr Haigh made a comment regarding the use of sentinel node lymphadenectomy for patients with thick primaries. We continue to employ it, but there is some debate in the literature regarding the outcome of these patients with thick primaries. Data from our institute suggest that patients with thick primaries have the same outcome with or without a tumor-positive sentinel node. Yet, other studies have suggested that the outcome is actually worse in patients with thick primaries and tumor-positive sentinel lymph nodes.

Another question was raised regarding the role of complete dissection after a tumor-positive sentinel. It is indeed true that appropriately 70% of patients with tumor-positive sentinel nodes have disease confined to a single lymph node, which raises the question of the therapeutic value of complete node dissection. At John Wayne Cancer Institute, we have initiated a National Institutes of Health–supported, international clinical trial in which we are evaluating the role of completion dissection after a tumor-positive sentinel node. Patients are randomized 50:50 to complete node dissection vs observation of their lymph node basin, and those who are observed undergo routine follow-up plus ultrasound of the sentinel node basin. The rationale for ultrasound is that disease in the regional lymph nodes may be picked up earlier by ultrasound than physical examination alone. All of the members of the American College of Surgeons and centers with expertise in melanoma surgery are able to participate in this study.

Dr DiFronzo made another comment regarding which patients had recurrences in the dissected basin and if any of the features from the sentinel lymph node procedure were predictive. We did go back and look at the lymphoscintigrams to see if there was anything from the images that would suggest why these patients had a recurrence. Some of the patients may have had 2 lymph nodes visualized rather than 1, leading to missed sentinel nodes. The problem with lymphoscintigraphy, and you may see it at your own institution, is that the nuclear medicine physicians often give you the lymphoscintigraphy images that they want you to see and not all of the images created in the nuclear medicine department. For instance, you could be misled, particularly in the head and neck region, where we see “lymphatic lakes” in between the primary site and an expected nodal basin, and in fact we also find unusual locations for lymph nodes in the head and neck and from the back, for instance, to interscapular sites.

We did not evaluate in this study the outcomes of our patients who failed sentinel lymph node dissection vs those with tumor-positive sentinel nodes who did not undergo completion dissection, but our expectation would be that the failures in the nodal basin would have worse prognosis than those with tumor-positive sentinel nodes who did not have a complete dissection.

Our paper probably should be retitled, because although patients were seen up to 10 years ago, most patients did not have 10 years of follow-up, with a mean follow-up of only about 36 months.

Finally, I must address Dr Wilson's comments regarding the annual rate of recurrence after tumor-negative sentinel lymph node dissection. In our experience, the earliest recurrence after a tumor-negative sentinel node is 6 months. The latest has been 6 years. And yes, they do seem to recur pretty steadily between the 6-month and 6-year period. At this point, we haven't seen any recurrences beyond 6 years, but I suspect as we get longer follow-up, we will probably have some late recurrences. In our practice, we have seen melanoma recurrences up to 20 and 30 years after primary diagnosis.