Importance of Sentinel Lymph Node Biopsy in Patients With Thin Melanoma

Byron E. Wright, MD; Randall P. Scheri, MD; Xing Ye, MS; Mark B. Faries, MD; Roderick R. Turner, MD; Richard Essner, MD; Donald L. Morton, MD

Hypothesis: The status of the sentinel node (SN) confers important prognostic information for patients with thin melanoma.

Design, Setting, and Patients: We queried our melanoma database to identify patients undergoing sentinel lymph node biopsy for thin (≤1.00-mm) cutaneous melanoma at a tertiary care cancer institute. Slides of tumor-positive SNs were reviewed by a melanoma pathologist to confirm nodal status and intranodal tumor burden, defined as isolated tumor cells, micrometastasis, or macrometastasis (≤0.20, 0.21-2.00, or >2.00 mm, respectively). Nodal status was correlated with patient age and primary tumor depth (≤0.25, 0.26-0.50, 0.51-0.75, or 0.76-1.00 mm). Survival was determined by log-rank test.

Main Outcome Measures: Disease-free and melanoma-specific survival.

Results: Of 1592 patients who underwent sentinel lymph node biopsy from 1991 to 2004, 631 (40%) had thin melanomas; 31 of the 631 patients (5%) had a tumor-positive SN. At a median follow-up of 57 months for the 631 patients, the mean (SD) 10-year rate of disease-free survival was 96% (1%) vs 54% (10%) for patients with tumor-negative vs tumor-positive SNs, respectively (P < .001); the mean (SD) 10-year rate of melanoma-specific survival was 98% (1%) vs 83% (8%), respectively (P < .001). Tumor-positive SNs were more common in patients aged 50 years and younger (P = .04). The SN status maintained importance on multivariate analysis for both disease-free survival (P < .001) and melanoma-specific survival (P < .001).

Conclusions: The status of the SN is significantly linked to survival in patients with thin melanoma. Therefore, sentinel lymph node biopsy should be considered to obtain complete prognostic information.

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Sentinel lymph node biopsy (SLNB) is a well-established method of staging the draining nodal basin in patients with malignant melanoma. The technique has most often been applied to patients with primary cutaneous melanoma who have a moderate to high risk of nodal metastasis. These primary lesions are typically greater than 1 mm in depth or have other characteristics associated with a poor prognosis. In this setting, correctly performed SLNB can accurately identify patients with occult nodal metastasis and expectedly poorer outcome that might therefore benefit from a complete lymph node dissection (CLND) and evaluation for systemic adjuvant therapies.

Prior to the widespread use and acceptance of SLNB in the management of patients with primary melanoma, indications for elective nodal staging and dissection had long been a matter of controversy. Prospective, randomized, multicenter studies demonstrated an equivalent survival benefit associated with elective lymph node dissection (ELND) in selected patients with primary melanoma 1 to 4 mm in thickness, but there was no consensus regarding its use in patients with thinner lesions. In recent years, data from phase 2 and phase 3 trials have confirmed the adverse prognostic effect of nodal recurrence in patients with intermediate-depth primary cutaneous melanoma. The clinical relevance of occult metastasis in the sentinel node (SN) and the established safety and reliability of the SN technique have led investigators to reassess the role of nodal staging in a broader group of patients with melanoma.

Although patients with thin primary lesions and no clinical evidence of nodal metastasis have done well with wide local excision, the presence of occult metastasis in the sentinel node signified a significant adverse effect on disease-free and melanoma-specific survival that was confirmed on multivariate analysis. Therefore, SLNB should be considered as an important staging tool for patients with thin melanomas, allowing for more effective planning of systemic adjuvant therapies.
cision (WLE) alone, nodal recurrence can occur and worsen patient outcome. In 2003, we described our experience with SLNB for patients with primary melanoma having a thickness of 1.5 mm or less. Our early results indicated the value of SLNB for lesions between 1.0 and 1.5 mm and possibly for thinner melanomas. Since then, several groups have advocated SLNB in patients with American Joint Committee on Cancer T1 (≤1-mm) primary cutaneous lesions, either routinely or in selected cases with adverse prognostic factors. Few articles, however, have documented the results of SLNB in this patient group, particularly the effect of nodal status on long-term outcome. To better determine the value of SLNB for primary cutaneous melanoma with a thickness of 1.00 mm or less and to test our hypothesis that the status of the SN confers important prognostic survival information for these patients, we reviewed our experience for this specific subgroup.

METHODS

Our tertiary cancer center has prospectively maintained a comprehensive melanoma database dating back more than 30 years. We conducted a review of that database to identify all of the patients who underwent SLNB for thin (≤1.00-mm) primary cutaneous melanoma since standardization of the technique in 1991. Demographics and tumor information gathered for each patient included age, sex, primary tumor characteristics (anatomical site, Clark level, Breslow depth, and presence or absence of ulceration), and tumor status of the SLNB specimen. Mitotic rate, vertical growth phase, and regression were not available for analysis in this study. Metastatic tumor burden in the SN was categorized by a maximal dimension of the largest tumor deposit as follows: 0.20 mm or less, isolated tumor cells (ITCs); 0.21 to 2.00 mm, micrometastasis; and more than 2.00 mm, macrometastasis.

Survival was determined by the Kaplan-Meier method and comparisons were made using the log-rank test. In addition, both univariate and multivariate Cox regression analyses were performed to determine the prognostic importance of SN status relative to other variables, and the Fisher exact test was used to test the correlation between patient characteristics and occult nodal metastasis (tumor-positive SN). Primary outcome measures were disease-free survival (DFS), defined as the period from the initial primary diagnosis until the first melanoma recurrence, and melanoma-specific survival (MSS), defined as the period from the initial primary diagnosis until occurrence of melanoma-specific death. In those cases where a tumor-positive SN was confirmed, the original pathology report of the primary tumor was reviewed to determine the method of biopsy. The method of biopsy was not determined for the remaining patients with thin melanoma with a tumor-negative SN (n=600) as this information was not available in our database. Of note, no changes in tumor depth or classification were made based on retrospective record review. Rather, the original tumor depth as determined by the examining melanoma pathologist at the time of the individual case was assumed to be correct. Microscopic slides for the initial biopsy specimen of the primary tumor as well as the WLE specimen were reviewed by our pathologists for essentially all patients. This study was approved by our institutional review board.

At our institution, all patients with a newly diagnosed primary cutaneous melanoma greater than 1 mm in depth are offered SLNB as part of their surgical management in the absence of clinically evident nodal disease or known distant metastasis. Those with thin primary lesions are offered SLNB on a more select basis. These patients are not selected for SLNB according to a specific protocol or institutional criteria, however. Rather, the options and rationale for SLNB are discussed individually between each patient and his or her respective dedicated melanoma surgeon. A large number of factors contribute to specific recommendations regarding SLNB, including patient age, tumor location and depth, presence or absence of ulceration, and other variables thought to affect nodal status. Also of great importance are the patient’s concerns regarding nodal status and desire to undergo SLNB despite a relatively low risk of occult nodal metastasis.

Our technique for SLNB in melanoma has been described in detail. In brief, patients undergo same-day lymphatic mapping with technetium Tc 99m filtered sulfur colloid injected intradermally around the primary site. Skin markers are then placed to identify SN sites and the patient is transported to the operating room. Ten minutes prior to the skin incision, up to 1 mL of Lymphazurin (Tyco International, Norwalk, Connecticut) is injected intradermally followed by brief dermal massage. The SNs are identified by levels of radioactivity measured with a handheld gamma probe and by visualization of blue dye. Pathologic handling of the SNs used paraffin sections at 2 levels (the sections were separated by 40 µm prior to 2000 but by 200 µm in subsequent years) of each paraffin block. Sections were stained with hematoxylin-eosin and with immunohistochemical stains for S-100 protein, HMB-45, and Melan-A (Melan-A was added in 2002). All cases deemed positive were reevaluated by a single melanoma pathologist (R.R.T.) to confirm nodal status and assess nodal tumor burden. Known ocular field diameter was used to measure metastatic deposits in the greatest dimension, which were characterized as ITCs, micrometastasis, or macrometastasis according to American Joint Committee on Cancer, 6th edition guidelines for breast carcinoma and previously described histologic criteria. For all patients found to have tumor-positive SNs, CLND was recommended.

RESULTS

We identified 1592 patients with complete information regarding tumor depth in our database who underwent SLNB in conjunction with WLE for primary cutaneous melanoma. Six hundred thirty-one (40%) of those patients had primary lesions classified as thin melanoma (≤1.00 mm), and 31 of those 631 patients (5%) had a tumor-positive SN. Three hundred thirty-eight of the 631 patients (54%) were male, and 10 of those 338 patients (3%) had a tumor-positive SN. Two hundred ninety-three of the 631 patients (46%) were female, and 21 of those 293 patients (7%) had a tumor-positive SN. The median patient age was 44 years in the tumor-positive group compared with 52 years in the tumor-negative group (P=.02). Patients aged 50 years and younger were more likely to have tumor-positive SNs than their older counterparts (P=.04). Demographics and tumor-specific variables of both tumor-negative and tumor-positive patients are shown in Table 1. Univariate analysis confirmed the negative effect of tumor-positive SN(s) on MSS (P<.001). This adverse effect was also significant on multivariate analysis (P<.001) as was the presence of primary tumor ulceration (P=.003) and head or neck as the primary tumor site (P<.001).

Pathologic examination of the SN(s) demonstrated ITCs in 14 patients, micrometastasis in 15 patients, and...
macrometastasis in 2 patients. Of the 631 patients who underwent SLNB, 453 (72%) had a primary tumor thicker than 0.50 mm, but the ratio of tumor-negative to tumor-positive SNs was similar across tumor depth as shown in Table 2. Melanoma recurrence occurred more frequently in patients with tumor-positive nodes (42%) than patients with tumor-negative nodes (3%), and the patterns of recurrence for each group are shown in Table 3. Twenty-six of the 31 patients with nodal metastasis detected on SLNB underwent CLND. Reasons for failure to undergo CLND were based largely on patient decisions after discussion of SLNB results. Of the 5 patients who did not undergo CLND, 4 had micrometastasis and 1 had ITCs in the SN; 1 of the 5 patients developed distant recurrence. Twenty-eight patients had a single tumor-positive node, 1 patient had 2 tumor-positive nodes, 1 patient had 3 tumor-positive nodes, and 1 patient had 4 tumor-positive nodes, for a nodal average of 1.2 tumor-positive nodes per case.

At a median follow-up of 57 months, the mean (SD) 10-year DFS rate was 54% (10%) for patients with a tumor-positive SN compared with 96% (1%) for patients with a tumor-negative SN (P < .001) (Figure 1). In addition, the mean (SD) 10-year MSS rate was 83% (8%) for patients with a tumor-positive SN compared with 98% (1%) for patients with a tumor-negative SN (P < .001) (Figure 2). The mean (SD) 5-year DFS rate according to intranodal tumor burden was 73% (14%), 43% (13%), and 0% for ITCs, micrometastasis, and macrometastasis, respectively (P = .03) (Figure 3). Patients with micrometastasis in the tumor-positive SN trended toward decreased 10-year MSS when compared with patients with only ITCs in the tumor-positive node (mean [SD], 77% [12%] and 86% [13%], respectively; P = .64). Neither of the 2 patients with macrometastasis in the tumor-positive SN has had a melanoma-related death.

Of the 31 patients who had tumor-positive SNs, 15 (48%) underwent shave biopsy, 4 (13%) underwent excisional biopsy, and 12 (39%) underwent an unspecified biopsy procedure. Despite the frequent use of shave biopsy, the deep margin was in question after the initial biopsy in only 4 of 31 cases (13%). In 2 of those 4 cases, residual melanoma was identified following WLE of the primary site with adjustment of tumor thickness from 0.7 mm to 0.9 mm in a single patient.

**COMMENT**

Sentinel lymph node biopsy has become standard procedure for staging the regional lymph nodes in primary cutaneous melanoma and for identifying those patients who might benefit from a CLND. The technique,

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**Table 1. Comparison of Clinical Variables and Demographics According to Status of the Sentinel Node in Patients With Thin Primary Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tumor-Negative SN No. (%)</th>
<th>Tumor-Positive SN No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>272 (93)</td>
<td>21 (7)</td>
<td>.02</td>
</tr>
<tr>
<td>Male</td>
<td>328 (97)</td>
<td>10 (3)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>273 (93)</td>
<td>20 (7)</td>
<td>.94</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>327 (97)</td>
<td>11 (3)</td>
<td></td>
</tr>
<tr>
<td>Site of primary melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head or neck</td>
<td>85 (94)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>259 (95)</td>
<td>13 (5)</td>
<td>1.95</td>
</tr>
<tr>
<td>Extremity</td>
<td>256 (95)</td>
<td>13 (5)</td>
<td></td>
</tr>
<tr>
<td>Clark level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>194 (97)</td>
<td>5 (3)</td>
<td>.03</td>
</tr>
<tr>
<td>3</td>
<td>283 (94)</td>
<td>17 (6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>111 (93)</td>
<td>8 (7)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>No</td>
<td>521 (95)</td>
<td>27 (5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (93)</td>
<td>3 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SN, sentinel node.

**Table 2. Distribution of Tumor-Negative and Tumor-Positive Sentinel Nodes According to Depth of Primary Melanoma and Intranodal Tumor Burden for Patients With Thin Primary Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Tumor Burden</th>
<th>Depth of Primary Melanoma, mm</th>
<th>Tumor-Negative SN No. (%)</th>
<th>Tumor-Positive SN No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.25 (n=13)</td>
<td>12 (92)</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>0.25-0.50 (n=165)</td>
<td>158 (96)</td>
<td>7 (4)</td>
</tr>
<tr>
<td></td>
<td>0.51-0.75 (n=194)</td>
<td>186 (96)</td>
<td>8 (4)</td>
</tr>
<tr>
<td></td>
<td>0.76-1.00 (n=259)</td>
<td>244 (94)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Tumor-negative SN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor-positive SN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITCs, No.</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Micrometastasis, No.</td>
<td></td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Macrometastasis, No.</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ITCs, isolated tumor cells; SN, sentinel node.

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**Table 3. Patterns of First Recurrence for Patients With Tumor-Negative and Tumor-Positive Sentinel Nodes With Thin Primary Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>Tumor-Negative SN No.</th>
<th>Tumor-Positive SN No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional nodal basin</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Soft tissue or distant nodal basin</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other visceral</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total, No. (%)</td>
<td>18 (3)</td>
<td>13 (42)</td>
</tr>
</tbody>
</table>

Abbreviation: SN, sentinel node.
originally described by Morton et al in 1992, was initially adopted by surgeons working mostly in high-volume melanoma centers. As the technique became refined and data demonstrated its reliability, the popularity and acceptance of SLNB increased worldwide. The primary reason is that the technique has proven both highly reliable and reproducible in correctly locating the SN(s) with an acceptably low false-negative rate and a negligible incidence of “skip” metastases. In addition, associated surgical morbidity is quite low with very few related major long-term complications. Local complications do occur, however, at a rate consistent with other elective, clean operations. For example, Morton and colleagues reported a 10% total wound complication rate in 937 patients who underwent SLNB in conjunction with WLE for malignant melanoma but only a 1% rate of either regional or systemic complications in this same group of patients.

The management of clinically tumor-negative nodal basins in patients with primary cutaneous melanoma had been...
a matter of controversy long before the development and widespread use of SLNB.5,6 Prior to the initiation of several large, prospective, randomized studies, a number of smaller retrospective reports had provided conflicting data on the survival benefit of ELND.24-26 Initial randomized studies from the World Health Organization and others addressed the benefit question in patients with early-stage melanoma and failed to demonstrate any survival advantage for immediate ELND in comparison with observational management (delayed lymph node dissection).27-29 Criticisms regarding the inability of these studies to identify potential survival benefit in specific patient subsets as well as conflicting results from several other studies led to the initiation of the Intergroup Melanoma Trial. In this multi-institutional study, 740 patients with clinically localized, intermediate-thickness (1- to 4-mm) melanoma were randomized to either ELND or nodal observation.5 Initial results4 reported in 1996 and follow-up results6 reported in 2000 demonstrated a significant survival benefit for ELND in patients younger than 60 years with early, nonulcerated primary lesions 1 to 2 mm in depth. The study also confirmed the importance of both tumor depth and ulceration as predictors of occult nodal involvement and the importance of nodal status as the best single predictor of patient outcome.6

As the SLNB era arrived, these reports and others formed the foundation for guidelines regarding the indications for SLNB in patients presenting with primary cutaneous melanoma. Proposed cutoffs paralleling the American Joint Committee on Cancer recommendations regarding tumor thickness staging (T stage) took shape; tumor depth of 1.0 mm or less in the absence of other significant factors was a relative contraindication for SLNB given the low yield of tumor-positive nodes and the expected outstanding survival of these patients.14

The incidence of melanoma, however, is increasing worldwide, and up to 70% of new cases are thin lesions.30 Although these patients continue to do well overall, good outcomes are far from ensured.7,8 Multiple studies have demonstrated that 5% to 10% of these patients harbor occult nodal metastasis that will often result in recurrent disease. For example, Karakousis et al11 examined their experience with 472 patients diagnosed with thin cutaneous melanoma in the pre-SLNB era. Patients were included in the study if they were found to have no clinical evidence of nodal disease at the time of WLE and if they had been followed up reliably for a minimum of 10 years. A total of 67 patients developed recurrent disease, and roughly half of those recurrences (or 7% of the total) were in a regional nodal basin. The strongest predictor of a disease-specific death was nodal recurrence. In the past, both the cost and significant morbidity of ELND balanced against a theoretical benefit argued for a largely observational approach in patients with thin primary lesions. The emergence of selective lymphatic sampling as a safe and reliable technique to identify patients who might benefit from CLND, however, has led clinicians to challenge conventional indications for nodal sampling and staging.2,31

In an attempt to better identify those patients with thin melanoma who might best benefit from SLNB, some investigators have studied patients with thin melanoma who experienced a poor outcome. They attempted to identify adverse prognostic factors that might better predict patients suitable for more aggressive staging and management. Kalady et al8 reviewed their 30-year experi-
Table 4. Reported Results of Sentinel Lymph Node Biopsy in Patients With Thin (≤1.00-mm) Primary Cutaneous Melanoma and Factors Correlated With a Tumor-Positive Sentinel Node

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients No.</th>
<th>Tumor-Positive Sentinel Node, %</th>
<th>Factors Associated With Tumor-Positive Sentinel Node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecchi et al, 2007</td>
<td>631</td>
<td>5</td>
<td>Clark level, age, sex</td>
</tr>
<tr>
<td>Ranieri et al, 2006</td>
<td>184</td>
<td>6.5</td>
<td>Clark level, tumor thickness, mitotic rate</td>
</tr>
<tr>
<td>Wong et al, 2006</td>
<td>223</td>
<td>3.5</td>
<td>None</td>
</tr>
<tr>
<td>Hershko et al, 2006</td>
<td>64</td>
<td>8</td>
<td>Clark level, tumor thickness</td>
</tr>
<tr>
<td>Kesmodel et al, 2005</td>
<td>181</td>
<td>5</td>
<td>Tumor thickness, mitotic rate</td>
</tr>
<tr>
<td>Sitzenberg et al, 2004</td>
<td>146</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>Jacobs et al, 2003</td>
<td>65</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Lowe et al, 2003</td>
<td>46</td>
<td>6.5</td>
<td>Clark level</td>
</tr>
<tr>
<td>Oliveira Filho et al, 2003</td>
<td>77</td>
<td>8</td>
<td>Mitotic rate, ulceration, vertical growth phase</td>
</tr>
</tbody>
</table>

There is strong evidence that nodal status provides extremely relevant prognostic information for patients with thin melanoma. Perhaps the more pertinent issue when weighing the cost and morbidity of SLNB against the admittedly low yield (5% in our series) of the procedure in these patients is whether minimizing nodal recurrence through SLNB and appropriate CLND improves outcome in terms of DFS and/or overall survival in this patient group (ie, what are the consequences of nodal recurrence in patients with thin cutaneous melanoma who do not undergo selective nodal staging at the time of original diagnosis and surgical treatment?). The Multicenter Selective Lymphadenectomy Trial Group addressed this question in a prospective, randomized study of patients with intermediate-thickness primary cutaneous melanoma. The findings from this trial included results and outcomes for 1269 eligible patients who underwent either WLE plus SLNB with immediate CLND if indicated or WLE alone followed by nodal observation with delayed CLND if indicated. In the patients randomized to nodal observation, results for those with nodal metastases demonstrated disease progression relative to the involved nodal basin as well as a decrease in 5-year survival and an increase in melanoma-specific death. Although patients in the Multicenter Selective Lymphadenectomy Trial had a higher incidence of nodal involvement than did our patients with thin primary cutaneous melanoma (16% vs 9%, respectively), given that the prognostic effect of nodal metastasis seems as significant in patients with thin primary melanoma as in other groups, it seems likely that the effect of delayed nodal management and disease progression in the setting of nodal metastasis will be significant as well, albeit in a smaller group of patients.

While it is clear from our study and others that most patients with a newly diagnosed, thin primary cutane-
ous melanoma will not derive any benefit from SLNB as part of their initial surgical management, it seems equally clear that for the small number of patients with occult nodal metastasis at the time of their initial diagnosis, correct identification provides critical prognostic information that can be obtained only with SLNB. In addition, patients with tumor-negative SNs can be reassured that their risk of recurrence and melanoma-related death is extremely low. As yet there is no reliable noninvasive technique to determine which thin primary melanomas are likely to have metastasized to the regional lymphatic basin. Therefore, all patients with invasive thin primary melanoma should be counseled regarding the implications of occult nodal metastasis and the ability of SLNB to reliably identify patients with this more advanced disease. Younger patients with deeper lesions characterized by other adverse prognostic factors such as ulceration, elevated mitotic rate, and evidence of a vertical growth phase should be made aware of available evidence suggesting that they have a greater risk of occult nodal metastasis at the time of initial diagnosis and therefore might be more likely to benefit from SLNB. Patients should further be informed, however, that the correlation of these different variables with SN status from one study to the next has been poor. Future studies should focus on the development of a more reliable system of risk stratification that will more readily assist clinicians in identifying the relatively few patients with thin primary cutaneous melanoma who could benefit from SLNB.

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Author Contributions: Study concept and design: Wright, Essner, and Morton. Acquisition of data: Wright, Scheri, Faries, Turner, and Essner. Analysis and interpretation of data: Wright, Ye, Faries, and Morton. Drafting of the manuscript: Wright, Scheri, Ye, Turner, Essner, and Morton. Critical revision of the manuscript for important intellectual content: Wright, Faries, and Morton. Statistical analysis: Ye and Faries. Administrative, technical, and material support: Wright, Turner, Essner, and Morton. Study supervision: Wright, Scheri, Essner, and Morton.

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REFERENCES

James E. Goodnight Jr, MD, Sacramento, California: It is certain-ly an important and correct truism at this point that sen-tinel lymph node biopsy has revolutionized staging for malignant melanoma and breast carcinoma. The procedures are true, practice-changing events in the management of these patients. The arguments over sentinel lymph node biopsy are now generally how, not whether. By its use, thousands and thou-sands of patients have been spared the morbidity of lymph node dissection. It is a singular contribution brought about by the leaders of the John Wayne group, certainly Dr Essner being prominent in that group.

Having said that, are you and your colleagues telling me now that no melanomas, patients may be spared, that all must under-gone sentinel lymph node biopsy? When I was younger, Wallace Clark and Alexander Breslow sort of promised me that some prominant in that group.

The first question was regarding how we found these 631 patients, my nuclear medicine people will be happy. So will the isotope salesman. My OR [operating room] schedule will suffer, and I will further deplete the scarce supply of isoullan blue dye, plus I will create some morbidity. The question is, will I be doing these folks any good? Now actually this complaint is a little tongue in cheek since others have made similar and consistent observations to yours, and I can easily recall in my own cases of patients with lesions in the 0.9-mm range who ultimately showed tumor in the regional lymph nodes and it went on to distant spread and death. So I have liberalized my indications for sentinel lymph node biopsy to include patients with melanomas less than 1 mm in thickness. But the question is, how much less? At this point I don't expect that I will do sentinel lymph node biopsy for patients with melanoma in the 0.5-mm range despite your data. Time may make me change that.

Basically, my obvious major questions are how can we make better identification of patients with thin melanomas who are at risk for occult lymph node metastases? It seems that we ought to be able to get closer to who the baddies are.

My first question actually is why did 631 patients in your database with tumors 1 mm or less actually undergo sentinel lymph node biopsy? Moreover and in particular, why did 178 patients with melanomas less than 0.5 mm undergo sentinel lymph node biopsy? Your surgeons must have had a reason, and do we know what those reasons were, and, in fact, do you still employ those reasons?

The most disturbing finding for me in your data is that Bres-low thickness in this large group of thin melanomas was not a guide to risk of occult tumor in the regional nodes. Younger age was suggestive of greater risk, deeper Clark level was suggestive, anatomic site and ulceration were not helpful. I would ask, did you examine mitotic rate or the designation of vertical growth phase as a histologic feature associated with risk?

In this series of thin melanomas, one-half of your patients with a positive sentinel lymph node biopsy had a shave biopsy of the primary lesion. We all know the problems with a shave biopsy. Is shave biopsy in fact a risk factor in thin melanomas that would impel us to do a sentinel lymph node biopsy?

My final question is, what clinical approach to thin melano-mas and sentinel lymph node biopsy do you recommend from your study? Are you in fact doing them all?

So I am going to close with a brief digression. In your manuscript, very nicely done, there are 5 patients in your series who had a positive sentinel lymph node biopsy but did not go on to complete lymph node dissection. Only 1 of those patients went on to progression of disease. This is in contrast to your very cogent observation that in this group of thin melanomas, ulceration of the primary and anatomic location in the head and neck does confer an adverse survival risk, but it does not predict for sentinel lymph node biopsy. So basically, this dichotomy, that is, a positive sentinel lymph node patient not progressing vs an anatomic factor and histologic factor that predict for survival but don't predict for sentinel lymph nodes, I think simply underscores the vagaries and variable genome of this exasperating disease.

Dr Essner: As Dr Goodnight has discussed already, the concept of sentinel node dissection not being new anymore has revolu-tionized the care of our melanoma patients, allows us to stage them with a minimum morbid procedure, and with increasing surgical experience has become an outpatient procedure done in the main OR, occasionally in a surgery center setting, or even under local anesthesia alone.

Nevertheless, the question of the biology of melanoma continues to confound us as we struggle with determining which factors are predictive of patient outcome, and in the era of molecular biology, we have failed to learn much about the primary tumors; because of their small size, we have little access to fresh tumor tissue. Nevertheless, we examined this group of 631 patients from our institution who underwent sentinel node biopsy as a follow-up from a paper that we published in 2003 when we noted the observation of about a 5% incidence of tumor-positive sentinel nodes in the thin primary group. Yet in this initial study, there were essentially no patient deaths, which suggested the biology of lymph node metastases from thin primaries varied from thicker lesions. Nevertheless, in this study, it is clear that these patients with thin primary melanomas and tumor-positive lymph nodes do have a long-term prognosis similar to patients with thicker lesions, suggesting that the biology is more indolent but equally dangerous with thin primaries than thicker lesions.

The first question was regarding how we found these 631 patients to be considered for sentinel node dissection. It represents about half of the patients we saw during this era, and in fact many of the patients present to our institution for a variety of reasons. The first is because of our wide range of referrals we get from all over the country and occasionally from abroad. The second is that we have had a number of adjuvant
therapy trials during this time, and patients would undergo sen-
tinel lymph node dissection to be considered for entry into ad-
juvant therapy studies. Occasionally, patients noted our work
on using molecular profiling of the sentinel nodes and would
find their way to our institution for molecular staging, al-
though it was not performed on these patients. So there was a
rather large group of patients not generally considered for sen-
tinel node dissection yet nevertheless made it to our institu-
tion and ultimately had a sentinel node biopsy.

The second question was regarding the 178 patients with
very thin primaries. A lot of these patients wanted to have their
lymph nodes evaluated, although the risk of metastases was rela-
tively low.

As you can see from the data, there are a number of factors
predictive of sentinel node positivity, including female gender,
younger age, and increasing Clark level; these factors have been
shown in other reports to be relevant. Yet as Dr Goodnight
pointed out, prognosis of our patients related to the sentinel
node status, head and neck primary site, and ulceration. We
and others have examined these factors and found that head
and neck primaries seem to be underrepresented for the total
number of positive sentinel nodes, yet many of the patients will
develop distant disease as did some of our patients with thin
primaries or those who had ulcerated primaries. While ulcer-
ation is not very common in this group, it does predict poor
outcome.

Another point was raised regarding mitotic rate and verti-
cal growth factor of the primary. The group from the Univer-
sity of Pennsylvania has used mitotic rate and vertical growth
phase to classify the risk of metastases for thin primaries and
found these factors to be predictive. Yet, we have not found
mitotic rate and vertical growth phase to be reproducible fac-
tors or always relevant when evaluating the primary tumors.

Indeed, about half of the patients had shave biopsies. This
is very common in our melanoma patient population as many
dermatologists refer patients after shave biopsies. In fact, a
number of papers suggest that a shave biopsy is an adverse
prognostic factor because in many cases it underestimates the
true primary thickness. So it’s not the shave biopsy itself, but
it’s in fact this method of excising the nevus which may cause
the pathologist to underestimate the metastatic potential of
the primary.

Our recommendation currently at this point is that we rec-
ommend doing sentinel node biopsy in patients with thin pri-
maries who are younger, are female, and have an increasing Clark
level. We didn’t use regression of the primary with as much cer-
tainty. Patients with nonulcerated primaries and non-head
and-neck lesions should be considered for sentinel node biopsy.

So the question is, what is the true biology of melanoma? Well, I think we are only starting to learn, and certainly in pa-
tients who have a thin primary melanoma and have a negative
sentinel node, the prognosis is so good we may change our meth-
ods of following up these patients, ie, we rarely use blood work,
and examination by chest x-ray may be the only imaging that
is necessary. There is no defined role for whole-body PET [posi-
tron emission tomographic] scanning or other costly scan-
ning techniques for these patients. It also appears that patients
with a tumor-positive sentinel node in this thin group may not
require completion dissection, as the risk of nonsentinel lymph
nodes containing metastases is reportedly low.

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