Role of Sentinel Lymph Node Biopsy in Patients with Thin Melanoma

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Abstract
Sentinel lymph node (SLN) biopsy has emerged over the past 2 decades as a rational approach for staging regional lymph nodes in patients with clinically node-negative melanoma (stage I and II disease). Large multi-institutional studies have confirmed that when performed by experienced surgeons, it is an accurate, reliable technique for identifying occult regional nodal disease, and that SLN status is the most important prognostic factor in patients with stage I and II melanoma. However, the incidence of occult regional nodal metastasis in patients with thin melanoma (≤ 1.0 mm; approximately 70% of patients with newly diagnosed melanoma) is low, and whether to perform SLN biopsy in these patients remains controversial. Several predictors of SLN metastasis in patients with thin melanoma have been suggested, but none widely accepted. This article reviews current literature on these predictors in patients with thin melanoma. Although the ability to draw conclusions was limited by the size and design of the available studies, the authors tentatively conclude that SLN biopsy can be considered for patients with melanomas 0.75 mm or larger, those with T1b melanomas (i.e., ≤ 1.0 mm; Clark level IV/V and/or ulcerated), and those with thin melanomas with an increased tumor mitotic rate (especially ≥ 1 mitosis/mm²). Including younger age (e.g., ≤ 40 years) in the decision also seems reasonable, particularly if the primary tumor is associated with a high tumor mitotic rate. Tumor regression does not seem to be associated with an increased risk for SLN metastasis. Firm conclusions on the predictive value of vertical growth phase, absence of tumor-infiltrating lymphocytes, or male gender were not possible, particularly if used as a sole criterion for offering this procedure. SLN biopsy should be discussed with all patients with newly diagnosed thin melanoma. (JNCCN 2009;7:308–317)

The incidence of cutaneous melanoma is increasing more rapidly than that of any other cancer in the United States. The lifetime risk for developing invasive melanoma among individuals in the United States is estimated at 1 in 50. Between 1950 and 2001, the incidence of cutaneous melanoma increased more than 600%, largely because of an increase in the incidence of thin melanoma, clinically defined as having a Breslow thickness of 1.0 mm or less. During the past 15 years, nearly 70% of all melanomas reported to the Surveillance, Epidemiology, and End Results (SEER) program were thin melanomas; thus, thin melanoma most likely accounts for more than 40,000 new cases per year.

According to the 2002 American Joint Committee on Cancer (AJCC) sixth edition of the melanoma staging system, thin melanomas are classified as T1 lesions. If it has no evidence of ulceration or extension into Clark level IV or V, it is subclassified as T1a; if either ulceration or Clark IV/V extension is present, the melanoma is subclassified as T1b. T1a lesions are AJCC stage IA, and T1b lesions are AJCC stage IB.

Although most patients with thin melanoma have a very good prognosis, some develop clinically evident regional metastasis, which classically occurs after a protracted period of observation, usually years after initial diagnosis. The database analysis on which the 2002 AJCC melanoma staging system is based indicated that the 10-year mortality rates for stage IA (T1a) and IB (T1b + T2a) disease were 12% and 17%, respectively. Thus, in a small group of patients with early-stage...
disease, disseminated disease and death from melanoma can occur. Given the high incidence of thin melanoma, these relatively low mortality rates nonetheless translate into an important national health problem.

Several studies indicate that the most important predictor of prognosis in melanoma patients with clinically negative regional lymph nodes is subclinical microscopic lymph node involvement. Sentinel lymph node (SLN) biopsy has emerged as a powerful tool for identifying patients with this involvement, who may benefit from early therapeutic lymphadenectomy and adjuvant therapy. SLN biopsy is generally recommended for patients whose melanoma is 1 mm or thicker.

Use of SLN biopsy in patients with thin melanoma is controversial. Experts have suggested that it is not indicated in these patients because of the low incidence of nodal metastasis, uncertain prognostic value of a positive sentinel node independent of other factors predicting mortality in patients with thin cutaneous melanoma, risk for morbidity (albeit low) associated with the procedure, and associated cost. However, several studies investigating the risk for SLN involvement in patients with thin melanoma (mostly small single-institution studies) have shown that a subset of patients are at sufficient risk (sometimes defined as ≥ 5%) for positive SLNs at initial diagnosis to justify SLN biopsy. A key challenge is how best to define this patient subset.

No clear consensus exists regarding which prognostic factors best predict the risk for SLN metastasis, what constitutes a high risk for SLN metastasis, and which prognostic factors should be used in clinical decision making about SLN biopsy in patients with thin melanoma. Because the incidence of SLN positivity in patients with thin melanoma is low, and because different institutions use different clinicopathologic criteria for determining which patients with melanomas less than 1 mm thick should be offered SLN biopsy, even sizeable single-institution analyses have limited potential to unravel these complex clinical issues. This article reviews the current literature on SLN biopsy in thin melanoma to try to clarify predictors of SLN metastasis and resolve some of the uncertainty about which patients with thin melanomas should be offered SLN biopsy.

Methods
A search of PubMed and MEDLINE was performed. Search terms included all or a combination of the following: melanoma, thin, T1, < 1.0 mm, sentinel lymph node, biopsy, nodal, predictor, metastasis, recurrence, and survival. The search results identified English-language studies that focused entirely or partially on thin melanoma. Data were also included from the database analyses on which the 2002 6th edition and proposed 7th edition of the AJCC melanoma staging system are based. Thin melanoma was defined according to the 2002 AJCC staging system: primary cutaneous melanoma with a Breslow thickness ≤ 1.0 mm or thinner.

Results
Twenty-four English-language studies were identified in which predictors of SLN involvement were analyzed among various cohorts of patients with thin melanoma who underwent SLN biopsy (Table 1). All 24 studies were retrospective, although in some the data analyzed was collected prospectively. The incidence of a positive SLN ranged from 1.1% to 13.5%; overall, 184 (5.1%) of the 3635 patients with thin melanomas had 1 or more positive SLNs. Only 11 of the 24 studies evaluated more than 100 patients with thin melanomas, and in only 5 of the studies were more than 10 patients with SLN metastasis identified. Given the small cohort sizes and low incidences of positive SLNs, coupled with the lack of information on which clinicopathologic criteria were used to identify and select patients for most studies, only limited statistical analysis designed to explore factors predictive of SLN metastasis in patients with thin melanoma was possible. Further complicating definitive analysis of the studies in this review was the fact that the specific potential risk factors analyzed varied greatly among studies (Table 1). Thus, for each of the potential risk factors discussed, the summary is based on information from only a subset of the 24 studies included in the review.

Breslow Thickness
Beginning with the 2002 AJCC melanoma staging system, regional nodal staging with SLN biopsy has been recommended for all patients with stage IB or II disease (i.e., Breslow thickness > 1.0 mm or ≤ 1.0 mm but with evidence of ulceration and/or Clark level IV
Table 1 Predictors of SLN Involvement in Patients With Thin Melanomas (< 1.0 mm)

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Patients with Positive SLN</th>
<th>% Positive</th>
<th>Breslow depth &lt; 0.75 mm vs. ≥ 0.75 mm or as continuous variable</th>
<th>CL</th>
<th>Ulc</th>
<th>TMR</th>
<th>VGP</th>
<th>Regression</th>
<th>TIL</th>
<th>Gender</th>
<th>Age</th>
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<tbody>
<tr>
<td>Thompson and Shaw</td>
<td>187</td>
<td>9</td>
<td>4.8</td>
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<tr>
<td>Agnese et al.</td>
<td>91</td>
<td>1</td>
<td>1.1</td>
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<tr>
<td>Bedrosian et al.</td>
<td>71</td>
<td>4</td>
<td>5.6</td>
<td>1/40 = 2.5%</td>
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<tr>
<td>Bleicher et al.</td>
<td>272</td>
<td>8</td>
<td>2.9</td>
<td>2/118 = 1.7%</td>
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<td>No</td>
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<td>No</td>
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<tr>
<td>Cecchi et al.</td>
<td>50</td>
<td>2</td>
<td>4.0</td>
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<tr>
<td>Cecchi et al.</td>
<td>59</td>
<td>2</td>
<td>3.4</td>
<td></td>
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<td></td>
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<tr>
<td>Hershko et al.</td>
<td>64</td>
<td>5</td>
<td>7.8</td>
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<td>Jacobs et al.</td>
<td>63</td>
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<td>3.2</td>
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<tr>
<td>Kesmodel et al.</td>
<td>181</td>
<td>9</td>
<td>5.0</td>
<td>1/191 = 0.5%</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Koskinen et al.</td>
<td>56</td>
<td>3</td>
<td>5.4</td>
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<tr>
<td>Kruer et al.</td>
<td>251</td>
<td>13</td>
<td>5.2</td>
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<tr>
<td>Lowe et al.</td>
<td>46</td>
<td>3</td>
<td>6.5</td>
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<tr>
<td>Morris et al.</td>
<td>193</td>
<td>9</td>
<td>4.7</td>
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<tr>
<td>Nahabedian et al.</td>
<td>24</td>
<td>2</td>
<td>8.3</td>
<td>0/13 = 0%</td>
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<tr>
<td>Oláh et al.</td>
<td>89</td>
<td>12</td>
<td>13.5</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Oliveira Filho et al.</td>
<td>77</td>
<td>6</td>
<td>7.8</td>
<td></td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Puleo et al.</td>
<td>409</td>
<td>20</td>
<td>4.9</td>
<td>20/409 = 4.9%</td>
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<tr>
<td>Ranieri et al.</td>
<td>184</td>
<td>12</td>
<td>6.5</td>
<td>2/86 = 2.3%</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Sondak et al.</td>
<td>42</td>
<td>4</td>
<td>9.5</td>
<td></td>
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<tr>
<td>Stitzenberg et al.</td>
<td>146</td>
<td>6</td>
<td>4.1</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Taylor et al.</td>
<td>135</td>
<td>7</td>
<td>5.2</td>
<td></td>
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<td></td>
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<tr>
<td>Vaquerano et al.</td>
<td>91</td>
<td>6</td>
<td>6.6</td>
<td></td>
<td>No</td>
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<tr>
<td>Wong et al.</td>
<td>223</td>
<td>8</td>
<td>3.6</td>
<td>0/109 = 0%</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Wright et al.</td>
<td>631</td>
<td>31</td>
<td>4.9</td>
<td>16/372 = 4.3%</td>
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<td>Yes</td>
<td>No</td>
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</tbody>
</table>

Primary Tumor and Patient Characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria Used to Recommend SLN Biopsy in Thin Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson and Shaw</td>
<td>Breslow; 0.75–1.0 mm; age &lt; 45 y</td>
</tr>
<tr>
<td>Agnese et al.</td>
<td>CL IV/V; Ulc; Reg; vascular invasion</td>
</tr>
<tr>
<td>Bedrosian et al.</td>
<td>VGP</td>
</tr>
<tr>
<td>Bleicher et al.</td>
<td>No*</td>
</tr>
<tr>
<td>Cecchi et al.</td>
<td>No</td>
</tr>
<tr>
<td>Cecchi et al.</td>
<td>No</td>
</tr>
<tr>
<td>Hershko et al.</td>
<td>Breslow; Ulc; VGP</td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Kesmodel et al.</td>
<td>No</td>
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<tr>
<td>Koskinen et al.</td>
<td>No</td>
</tr>
<tr>
<td>Kruer et al.</td>
<td>No</td>
</tr>
<tr>
<td>Lowe et al.</td>
<td>No</td>
</tr>
<tr>
<td>Morris et al.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Nahabedian et al.</td>
<td>Breslow ≤ 1 mm; CL IV/V; Ulc; Reg</td>
</tr>
<tr>
<td>Oláh et al.</td>
<td>CL IV/V; Ulc; TMR &gt; 5/mm²; Reg</td>
</tr>
<tr>
<td>Oliveira Filho et al.</td>
<td>CL IV/V; Ulc; TMR &gt; 5/mm²; Reg</td>
</tr>
<tr>
<td>Puleo et al.</td>
<td>Breslow ≥ 0.75 mm</td>
</tr>
<tr>
<td>Ranieri et al.</td>
<td>Unknown thickness; CL IV or V; Ulc; TMR: “high”; Reg; truncal location</td>
</tr>
<tr>
<td>Sondak et al.</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Stitzenberg et al.</td>
<td>Yes</td>
</tr>
<tr>
<td>Taylor et al.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Vaquerano et al.</td>
<td>Breslow &gt; 0.75 mm; if ≤ 0.75 mm, SLN biopsy performed on; CL IV/V; Ulc; Reg; patient demand</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>CL IV/V; Ulc</td>
</tr>
<tr>
<td>Wright et al.</td>
<td>Female ≤ 50 Breslow; Ulc; tumor location; age</td>
</tr>
</tbody>
</table>

Abbreviations: Breslow, Breslow tumor thickness; CL, Clark level; H&E, hematoxylin and eosin; IHC, immunohistochemistry; Reg, regression; SLN, sentinel lymph node; TIL, tumor-infiltrating lymphocytes; TMR, tumor mitotic rate; VGP, vertical growth phase; Ulc, ulceration.

*The absence of tumor infiltrating lymphocytes was only predictive of SLN involvement in melanomas thicker than 1.0 mm.
or V involvement). The NCCN Clinical Practice Guidelines in Oncology on melanoma encourage SLN biopsy for stage IB and II disease and state that SLN biopsy should be considered for patients with stage IA melanoma with potentially adverse features, such as Breslow thickness greater than 0.75 mm, young patient age, positive deep margin, lymphovascular invasion, or mitotic rate of 1 or more mitoses/mm². In nearly all melanoma centers worldwide, patients whose melanomas are 1.0 mm or thicker are routinely offered SLN biopsy, regardless of other clinicopathologic factors. Before the 2002 AJCC staging system, the cutoff for thin melanoma was 0.75 mm, and some centers recommend SLN biopsy when Breslow thickness is 0.75 mm or thicker.

This review indicates that SLN metastases in patients with Breslow thickness less than 0.75 mm are rather uncommon. In the 7 studies that reported the rate of SLN metastasis in 829 patients with melanomas smaller than 0.75 mm, only 22 (2.7%) had positive SLNs (Table 1). If, 12,13,18,23,27,32,33 Of these 7 studies, 6 reported SLN metastasis rates of 2.5% or less in patients with melanomas thinner than 0.75 mm; the 4.3% incidence reported by Wright et al.33 was the notable exception to this general observation. The reason for the higher incidence in the Wright study is unknown, although variations in the eligibility criteria for SLN biopsy among various institutions may play a role (Table 1).

In the 8 studies reporting the rate of SLN metastasis in 1166 patients with Breslow thickness 0.75 to 1.0 mm, 72 (6.2%) had positive SLNs.12,13,18,23,26,27,32,33 In the 10 studies analyzing the effect of increased Breslow thickness as a continuous or dichotomous variable on the rate of SLN metastasis, 3 found that Breslow thickness of 0.75 to 1.0 mm versus less than 0.75 mm was a predictor of SLN involvement; 14,18,27 the other studies found no relationship.

Clark Level
Of the 10 studies in this review that assessed the relationship between Clark level and risk for SLN metastasis, 2 found that Clark level predicted SLN involvement.27,33 In an analysis of 631 patients, Wright et al.33 found that the rate of SLN involvement was 7.4% for patients with Clark level IV or V and 4.4% for those with Clark level II or III. In an analysis of 184 patients, Ranieri et al.27 found that the rate of SLN involvement was 12.3% for patients with Clark level IV or V and 3.5% for those with Clark level II or III. The remaining 8 studies concluded that Clark level did not predict SLN involvement.

In the largest of these series, an analysis of 409 patients with thin melanoma (0.75–1.0 mm) who underwent SLN biopsy at H. Lee Moffitt Cancer Center & Research Institute, Puleo et al.26 found that 20 patients (4.9%) had SLN metastases and the risk for metastasis was not statistically different in patients with Clark level II or III (4.4%) and those with Clark level IV (5.7%). The authors conjectured that if Clark level IV or V were used as the sole selection criterion for SLN biopsy in patients with melanomas 1.0 mm or smaller, as the AJCC recommends, a substantial number of patients with SLN metastasis would be missed.

Ulceration
In the large database analysis on which the 2002 AJCC melanoma staging system is based, ulceration was present in 6% of the 5596 patients with thin melanoma (≤ 1.0 mm) and associated with a poorer prognosis and disease progression.4

In the 10 studies analyzed for this review that evaluated the relationship between ulceration and risk for SLN metastasis, ulceration was present in 4% to 9% of thin melanomas.13,17,18,24–27,29,32 Only 1 relatively small study 25 found that ulceration predicted SLN metastasis in thin melanoma. In many studies, none of the thin melanomas with SLN involvement was associated with ulceration.18,27,32 Several authors cautioned that, despite its well-established prognostic significance with respect to survival, if ulceration alone were used as the selection criterion for SLN biopsy in patients with thin melanoma, many patients with SLN metastases would be missed.

Tumor Mitotic Rate
In 4 of the 5 studies in this review that evaluated the relationship between mitotic rate and risk for SLN metastasis, higher mitotic rate was associated with higher risk for SLN involvement.18,25,27 The authors developed a classification tree consisting of 4 risk groups. At greatest risk for SLN metastasis (16.1%
SLN-positive) were men with tumors thicker than 0.75 mm with a mitotic rate greater than 0/mm².

Only one study that analyzed tumor mitotic rate concluded that it did not have an impact on SLN metastasis. The lack of relationship between mitotic rate and SLN involvement in this study may have been related to the small size of the series and the unknown tumor mitotic rate in 2 of the 8 patients with SLN metastasis.

**Vertical Growth Phase**

Vertical growth phase involves the invasion of melanoma cells from the epidermis into the dermis. Early vertical growth phase is distinguished from the radial growth phase by the presence of a dominant nest within the papillary dermis that is conspicuously larger than any nest within the epidermis and that forms an expansile nodule. The presence of vertical growth phase has been associated with metastatic potential.

The value of vertical growth phase as a predictor of SLN metastasis was evaluated in 4 studies reviewed, with vertical growth phase found to predict SLN involvement in 2.

**Tumor Regression**

Primary tumor regression, a histopathologic finding of tumor loss associated with varying degrees of stromal inflammatory changes, is observed in 10% to 35% of all cutaneous melanomas. Although the biology of tumor regression is not entirely clear, at least 2 potential interpretations have been proposed. Tumor regression may indicate that the primary melanoma was previously thicker, in which case the "true" Breslow thickness may be underestimated through histologic assessment of the tumor, and a wider excision and SLN biopsy may be advisable. Alternatively, tumor regression may represent a protective host immune response to the tumor, in which case patients with tumor regression may actually be at decreased risk for metastasis.

The importance of regression as a predictor of nodal metastasis remains controversial. Although some reports suggest that regression has an adverse impact on survival, others have found no effect or a beneficial effect.

Of the 7 studies in this review evaluating the relationship between tumor regression and risk for SLN involvement, 6 did not identify regression as a predictor of SLN metastasis in patients with thin melanoma. In the study that found that regression was a predictor of SLN metastasis, 11 of the 12 patients with SLN metastasis had primary tumor regression; interestingly, the primary tumor was not ulcerated or Clark level IV in any of the patients with a positive SLN.

**Tumor-Infiltrating Lymphocytes**

The presence of tumor-infiltrating lymphocytes (TILs) in the vertical growth phase of melanoma has been linked with a host immune response to melanoma. In some reports, the presence of TILs has been associated with a better prognosis. In 1 of the 4 studies in this review evaluating the relationship between TILs and SLN metastasis, the absence of TILs was an independent predictor of SLN involvement in patients with thin melanoma. Taylor et al. found that TILs were absent in 20% of patients, and compared with the presence of nonbrisk or brisk TILs, the absence of TILs increased the risk for SLN metastasis approximately threefold.

**Gender**

Of the 5 studies evaluating the relationship between patient gender and the risk for SLN involvement, 4 found that gender did not predict SLN metastasis. Interestingly, however, when gender was combined with mitotic rate greater than 0/mm² and Breslow thickness greater than 0.75 mm in a classification tree, Kesmodel et al. observed a 16.1% SLN metastasis rate in men, compared with 8.8% in women. Because of the relatively small size of the study, this difference was not statistically significant. One study observed a statistically higher likelihood of SLN metastasis in women (women, 7.2%; men, 3.0%; P = .02).

**Patient Age**

Although the impact of age on SLN metastasis in thin melanoma is not established, several studies identified younger age as an independent predictor in patients who underwent SLN biopsy. However, 6 of 8 studies evaluating the influence of age on risk for SLN metastasis in patients with thin melanoma showed that it was not a predictor. In most of the studies, the small number of younger patients made evaluating the impact of age
impossible. Sondak et al.\textsuperscript{28} found that age younger than 35 years (particularly in patients whose primary melanoma was associated with a high tumor mitotic rate) was an independent risk factor for SLN metastasis. Wright et al.\textsuperscript{33} found that patient age 50 years or younger was an independent risk factor for SLN metastasis in all patients evaluated. This risk also persisted in patients with thin melanomas.

Other Factors
Among a few studies evaluating the impact of primary tumor location\textsuperscript{16,18,29,32} and patient race\textsuperscript{29} on risk for SLN metastasis in patients with thin melanoma, these were not found to be predictive of SLN involvement. However, many of these studies were small, and the true impact of these factors remains undetermined.

Discussion
In an analysis of 24 studies investigating the predictors of SLN metastasis in patients with thin melanoma, the reported incidence of SLN metastasis varied substantially, from 1.1% to 13.5%. Most of the studies analyzed were single-institution and relatively small. Only 11 of the 24 studies evaluated more than 100 patients with thin melanoma, and only 5 of the studies identified more than 10 patients with SLN metastasis. Because the prognostic factors analyzed differed among studies, analysis of each potential prognostic factor was based only on a subset of the studies presented (Table 1). Accordingly, formal statistical assessment of factors predictive of SLN metastasis was often limited; direct comparisons among studies were challenging, if not impossible. Another important limitation is that in some of the studies, tumor thickness was not the sole criterion used to determine whether to offer patients SLN biopsy. Thus, potential confounders are present even within cohorts of patients with a given tumor thickness.

Despite these limitations, the authors’ analysis supports some preliminary recommendations. First, offering SLN biopsy to patients with melanomas 0.75 mm or thicker seems reasonable, especially if other poor prognostic factors are present. The risk for SLN metastasis in patients with melanomas 0.75 mm or thicker was at least 5% in most studies, and the overall rate when the studies were combined was 6.2%. Second, routine use of SLN biopsy cannot be justified in patients with melanomas thinner than 0.75 mm if no poor prognostic factors are present. (Definitive identification of such prognostic factors, however, remains elusive.) Among patients with melanomas thinner than 0.75 mm, the risk for SLN metastasis was 2.7%. The cost-effectiveness of SLN biopsy in patients with thin melanoma has also been raised,\textsuperscript{11} and routine use of SLN biopsy in patients with melanomas thinner than 0.75 mm is unlikely to be cost-effective.

A third, somewhat more tentative conclusion is that SLN biopsy is appropriate for patients with T1b melanomas (i.e., ≤ 1.0 mm; Clark level IV/V and/or ulcerated). In the AJCC analysis, T1b melanomas were associated with adverse prognosis and a higher incidence of lymph node involvement.\textsuperscript{3,4} In this review, neither Clark level IV/V nor ulceration individually seemed to be sufficiently predictive to recommend SLN biopsy. However, most studies in this review probably had insufficient power to detect an effect of ulceration on SLN metastasis risk. Also, in a preliminary analysis from a large multi-institutional study (discussed later),\textsuperscript{52} Clark level IV or V and ulceration were univariate predictors of SLN metastasis in patients with melanomas 2 mm or thinner. Importantly, although T1b tumor may be an appropriate criterion for SLN biopsy, use of it as the sole criterion for SLN biopsy would omit the subset of patients that are not Clark IV or V or ulcerated but nonetheless have a risk for SLN metastasis of 5% or greater.

A fourth conclusion from this analysis is that SLN biopsy may be recommended for patients who have thin melanomas with an increased tumor mitotic rate, particularly if defined in terms of the proposed AJCC definition of 1 mitosis/mm\textsuperscript{2} or more.\textsuperscript{34} As mentioned previously, Kesmodel et al.\textsuperscript{18} developed a classification tree predicting the risk for SLN metastasis in thin melanoma and found that men with thin melanomas thicker than 0.75 mm and a tumor mitotic rate greater than 0/mm\textsuperscript{2} had the highest risk (16.1%) for SLN metastasis. This classification tree and the prognostic importance of increased tumor mitotic rate were subsequently validated in a multiple covariate regression model for regional nodal disease as a surrogate for SLN positivity developed from a cohort of 882 patients with thin melanoma treated in the pre-SLN biopsy era.\textsuperscript{53}

Further support for using high mitotic rate as a criterion for SLN biopsy in patients with thin melanoma is the database analysis for the 7th edition AJCC
melanoma staging system, which identified increased mitotic activity as an independent adverse prognostic factor in T1 lesions and led to the proposed classification of T1 melanomas with a tumor mitotic rate of 1 mitosis/mm² or more as T1b lesions.34

Given the limited data on the predictive value of vertical growth phase and the conflicting findings among the few studies addressing this question, the authors were unable to draw conclusions on the value of vertical growth phase as a sole selection criterion for SLN biopsy in patients with thin melanoma. The presence of vertical growth phase in primary tumors can be difficult to determine, and lack of interobserver consistency has been reported.54

The impact of primary tumor regression on the risk for SLN metastasis and survival remains controversial. However, this review suggests that tumor regression is not associated with an increased risk for SLN metastasis in patients with thin melanoma. This preliminary conclusion must be confirmed in larger studies. Because of interstudy variations in the definition and reporting of primary tumor regression, coupled with the unclear relevance of the specific extent of regression, determining the true impact of regression is difficult. Notably, although some centers continue to use extensive regression (usually defined as > 75% of the primary tumor) as a criterion for performing SLN biopsy in patients with thin melanoma, many centers do not, a practice reflected in the most recent NCCN Clinical Practice Guidelines in Oncology: Melanoma (in this issue; to view the most recent version, visit the NCCN Web site at www.nccn.org).35

Based on available literature, significant evidence does not exist to recommend using absence of TILs, male gender, or younger age as a primary criterion for SLN biopsy in patients with thin melanomas. However, because younger age was an independent predictor of SLN metastasis in several studies that examined predictors of SLN metastasis among all patients who underwent SLN biopsy,28,49–51 including younger age (≤ 40 years may represent a reasonable cut point) in the decision-making process on SLN biopsy for patients with thin melanoma seems reasonable, particularly if the primary tumor is associated with a high tumor mitotic rate or other adverse feature.

Challenges in determining predictors of SLN metastasis in patients with thin melanomas include the 1) low overall incidence of SLN metastasis in these patients, 2) lack of consistency in the potential predictors analyzed, 3) lack of consistency across institutions (even among clinicians within an institution) with respect to the factors considered in the decision whether to offer SLN biopsy, and 4) preponderance of small single-institution studies. In an effort to overcome some of these challenges, Gershenwald et al.52 initiated a study comprising 12 institutions in the United States, Australia, and Europe and assembled a large international dataset of 5830 patients (including patients from a subset of the 24 studies evaluated in this review) with primary cutaneous melanoma with Breslow thickness up to 2 mm who underwent SLN biopsy, approximately one third with melanomas thinner than 1 mm. Using the 2002 AJCC definitions, SLN positivity rates were 2.3%, 8.1%, 3.6%, and 8.4% for patients with primary tumors thinner than 0.75 mm, 0.75 to 0.99 mm, T1a, and T1b, respectively. Ongoing multiple covariate analyses, including those limited to patients with Breslow thickness up to 1 mm, will hopefully shed light on the possible interplay among various prognostic factors and facilitate a better understanding of risk factors for patients with thin melanoma. A prospective registry of thin melanomas with clear definitions of assessed variables would also provide invaluable information with which to determine independent predictors of SLN metastasis and prognosis.

In addition to which patients with thin melanoma should be offered SLN biopsy, another important question remains: whether completion lymph node dissection (CLND) is necessary in patients with thin melanoma and SLN metastasis. CLND is currently standard care, outside of a clinical trial, for these patients, and in most series, the incidence of non-SLN involvement in these patients is 8% to 33%.55–59 The authors recently reported55 on 343 patients with melanoma and SLN metastasis who underwent CLND and found that no patients with primary melanoma 2.0 mm or thinner, 3 or more SLNs removed, and largest SLN tumor focus less than 0.5 mm in diameter had additional non-SLN metastases. Furthermore, among the 29 patients with primary melanoma 1.0 mm or thinner, only 1 (3.4%) was found to have non-SLN involvement on CLND (Andtbacka et al., unpublished data). The need for CLND in patients with thin melanoma requires further evaluation; the ongoing randomized Multicenter Selective Lymph-
which the patient is interested; and 5) morbidity and risks for SLN biopsy are acceptable to the physician and the patient. Most of the panelists said they would offer SLN biopsy to patients with melanomas 1.0 mm or thinner with characteristics that increase the likelihood of regional node micrometastasis.

Although unanimous consensus on these characteristics was not reached, most panelists said they would consider recommending SLN biopsy to patients with melanomas 1.0 mm or thinner with primary tumor ulceration, a mitotic rate 1/mm² or greater, or Clark level IV/V invasion, particularly if the melanoma was greater than 0.75 mm, whereas some said they would use thickness greater than 0.75 mm as the sole criterion. Ulceration, mitotic rate, and Clark level are especially relevant in patients without significant comorbidity, who are younger than 40 to 45 years, or whose primary tumor depth is uncertain because of tumor-positive deep margins in the biopsy specimen. The panel concurred that it was not necessary to show a survival advantage for SLN biopsy before recommending this procedure, that it represents standard care and should be discussed with all appropriate patients with clinically node-negative melanoma who will undergo wide excision of a primary melanoma.

Despite current real challenges in determining predictors of SLN metastasis in patients with thin melanoma, a minority of patients with thin melanoma clearly harbor occult regional lymph node metastasis at initial diagnosis. In summary, based on detailed findings of this review and the fact that SLN biopsy is included in the AJCC staging guidelines, NCCN treatment guidelines, and practice plans of most specialty surgeons who treat melanoma in the United States, Australia, and Western Europe, thoughtful dialogue between patients and clinicians about SLN biopsy, including the rationale for the procedure and the potential benefits, risks, and alternatives in light of the patient’s known clinico-pathologic factors, is warranted for all patients with thin melanoma.

References
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