ORIGINAL ARTICLE

Predictors of Occult Nodal Metastasis in Patients With Thin Melanoma

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Hypothesis: Thin primary lesions are largely responsible for the rapid increase in melanoma incidence, making identification of appropriate candidates for nodal staging in this group critically important. We hypothesized that common clinical variables may accurately estimate the risk of nodal metastasis after wide excision and determine the need for sentinel node biopsy.

Design: Review of prospectively acquired data in a large melanoma database.

Setting: A tertiary referral center.

Patients: A total of 2211 patients with thin melanoma treated by wide local excision alone were identified in the database between January 1, 1971, and December 31, 2005. Of those, 1732 met entry criteria.

Main Outcome Measures: We examined the rate of regional nodal recurrence and the impact of clinical and demographic variables by univariate and multivariate analyses.

Results: The overall nodal recurrence rate was 2.9%; median time to recurrence was 38.3 months. Univariate analysis of 1732 patients identified male sex ($P<.001$), increased Breslow thickness ($P<.001$), and increased Clark level ($P<.001$) as significant for nodal recurrence. Multivariate analysis identified male sex (hazard ratio, 3.5; 95% confidence interval, 1.8-7.0; $P<.001$), younger age (0.45; 0.24-0.86; $P=.001$), and increased Breslow thickness (2.5; 1.6-3.7; categorical $P<.001$) as significant for nodal recurrence. The Clark level was no longer significant ($P=.63$). Breslow thickness, age, and sex were used to develop a scoring system and nomogram for the risk of nodal involvement. Predictions ranged from 0.1% in the lowest-risk group to 17.4% in the highest-risk group.

Conclusions: Many patients with thin melanoma will have nodal recurrence after wide excision alone. Three simple clinical variables may be used to estimate recurrence risk and select patients for sentinel node biopsy.

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THE INCIDENCE OF MELANOMA has increased during the past several decades faster than virtually any other malignant tumor.[1] Approximately 70% of new cases of melanoma are thin lesions, less than 1 mm in thickness.[2,3] Patients with these lesions are generally considered to be at low risk for metastasis and melanoma-related death. However, it is well known that a portion of this group will eventually experience disease recurrence and risk death from melanoma. Because of the high number of cases, even a relatively small proportion of disease recurrence will lead to a large absolute number of recurrences in thin melanoma.

Sentinel lymph node dissection (SLND) is now a standard procedure for patients with intermediate-thickness melanoma.[4] The technique offers the most important piece of prognostic information for these patients, and we have recently confirmed this prognostic significance in thin melanoma.[5] Sentinel lymph node dissection allows selection of appropriate candidates for complete lymph node dissection; this upfront treatment of clinically occult nodal disease appears to reduce the risk of melanoma-related death.

However, the use of SLND in thin melanoma is more controversial. Universal application of the technique would be prohibitively expensive and would expose a large number of patients with an extremely low risk of nodal disease to the real, albeit low, risk of toxic effects related to the procedure. Several centers have examined their results with SLND in patients with thin melanoma, and some have suggested methods of selecting patients, but the selection factors have varied from series to series, and some of the selection criteria used may be difficult for nonspecialized centers to reproduce. In addition, the use of published SLND series to determine the appropriate candidates for future use of the procedure

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Table 1. Patient and Tumor Characteristics

Characteristic	No. (%) of 1732 Patients[a]
Sex	
Male	877 (50.6)
Female	855 (49.4)
Age, mean (median) [range], y	48.5 (47.2) [11-95]
Breslow thickness, mean (median) [range], mm	0.50 (0.50) [0.02-0.99]
Breslow thickness	
0.01-0.25	151 (8.7)
0.26-0.50	830 (47.9)
0.51-0.75	515 (29.7)
0.76-0.99	236 (13.6)
Clark level	
II	1163 (67.2)
III	463 (26.7)
IV	62 (3.6)
V	1 (0)
Unknown	43 (2.5)
Ulceration	
Yes	39 (2.2)
No	1243 (71.8)
Unknown	450 (26.0)
Site	
Trunk	746 (43.1)
Extremity	699 (40.4)
Head or neck	277 (16.0)
Follow-up, mean (median), y	13.2 (12.3)
Time to nodal recurrence, median, mo	38.3

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

is complicated by surgeon selection of patients with perceived higher risk and by relatively short follow-up duration.

To overcome these problems, we examined our prospective melanoma database to determine the incidence of nodal recurrence among patients with thin melanoma treated by wide local excision alone. We also used selection factors that were relatively straightforward to reproduce. We hypothesized that a small number of straightforward clinical characteristics could be used to determine the risk of harboring occult nodal metastasis in thin melanoma.

METHODS

We queried our prospectively maintained database of more than 13 000 patients with melanoma who were diagnosed as having thin (<1.00 mm) melanoma and treated with wide excision without immediate operative nodal staging (by elective node dissection or sentinel lymphadenectomy). Because of the potential for referral bias favoring recurrent cases in the database, analysis was limited to patients who were treated at our institution within 6 months of their diagnosis of melanoma. Patients who did not have clinical evidence of nodal disease at the time of initial treatment and patients with disease recurring within 3 months of diagnosis were excluded as well. Wide excisions were performed using excision margins following recommendations current during that treatment era. At present, 1-cm margins are used. Reconstruction was most often performed with local advancement flap, although skin grafting was used as necessary based on excision size and anatomical site.

Table 2. Univariate and Multivariate Predictors of Nodal Recurrence

Characteristic	Odds Ratio (95% Confidence Interval)	Univariate *P* Value	Multivariate *P* Value
Male sex	3.5 (1.8-7.0)	<.001	<.001
Breslow thickness by category[a]	2.5 (1.6-3.7)	<.001	<.001
Age <50 y	0.45 (0.24-0.86)	.08	.002
Clark level	0.7 (0.2-2.6)	<.001	.60
Primary site	NA	.13	NA

Abbreviation: NA, not applicable.
[a] Breslow categories were as follows: 0.01 through 0.25, 0.26 through 0.50, 0.51 through 0.75, and 0.76 through 0.99 mm.

Clinical follow-up recommendations consisted of complete dermatologic and physical examination every 3 months during the first 2 years, every 4 to 6 months for the next 3 years, and annually thereafter. Routine laboratory blood work, including complete blood cell count, comprehensive metabolic panel, and lactate dehydrogenase measurement, was performed annually. A chest x-ray examination was performed annually.

The primary end point was regional basin lymph node recurrence. Univariate analysis was performed for common prognostic variables, including Breslow thickness, Clark level, ulceration, age, sex, and primary tumor site. Breslow values were categorized into 4 groups (0.01-0.25, 0.26-0.50, 0.51-0.75, and 0.76-0.99 mm). Age was examined as a dichotomized variable and by decade. Two cutoff values previously established in the literature as significant for outcome and/or nodal recurrence were examined (50 and 60 years old). Ulceration, regression, and histologic subtype were also examined. A multivariate analysis was then undertaken by logistic regression to identify significant independent variables. Significant covariates were identified through the regression analysis, and predictors were selected for incorporation into the final nomogram based on statistical significance and clinical utility. The strongest predictor (Breslow thickness) was scaled for point values to 100, and other predictor values in the model were incorporated based on their predictive value relative to that of thickness. The overall predictive strength of the model (c-index) could then be calculated.

RESULTS

A total of 2211 patients with thin melanoma treated by wide local excision alone were identified in the database between January 1, 1971, and December 31, 2005. Of those, 1732 met entry criteria. The demographic and pathologic characteristics of this population are given in **Table 1**. With a median follow-up of 13.2 years, 51 patients (2.9%) experienced a nodal recurrence. Median time to nodal recurrence was 38.3 months. The overall population was fairly evenly divided by sex and had a mean tumor thickness of 0.50 mm. Two-thirds of the lesions were Clark level II.

By univariate analysis, sex ($P<.001$), Breslow thickness ($P<.001$), and Clark level ($P<.001$) were significant predictors of nodal recurrence (**Table 2**). Age (dichotomized at 50 years) was not statistically significant ($P=.08$). The nodal recurrence rate increased with Breslow thickness (<0.25 mm, 0%; 0.26-0.50 mm, 1.1%; 0.51-

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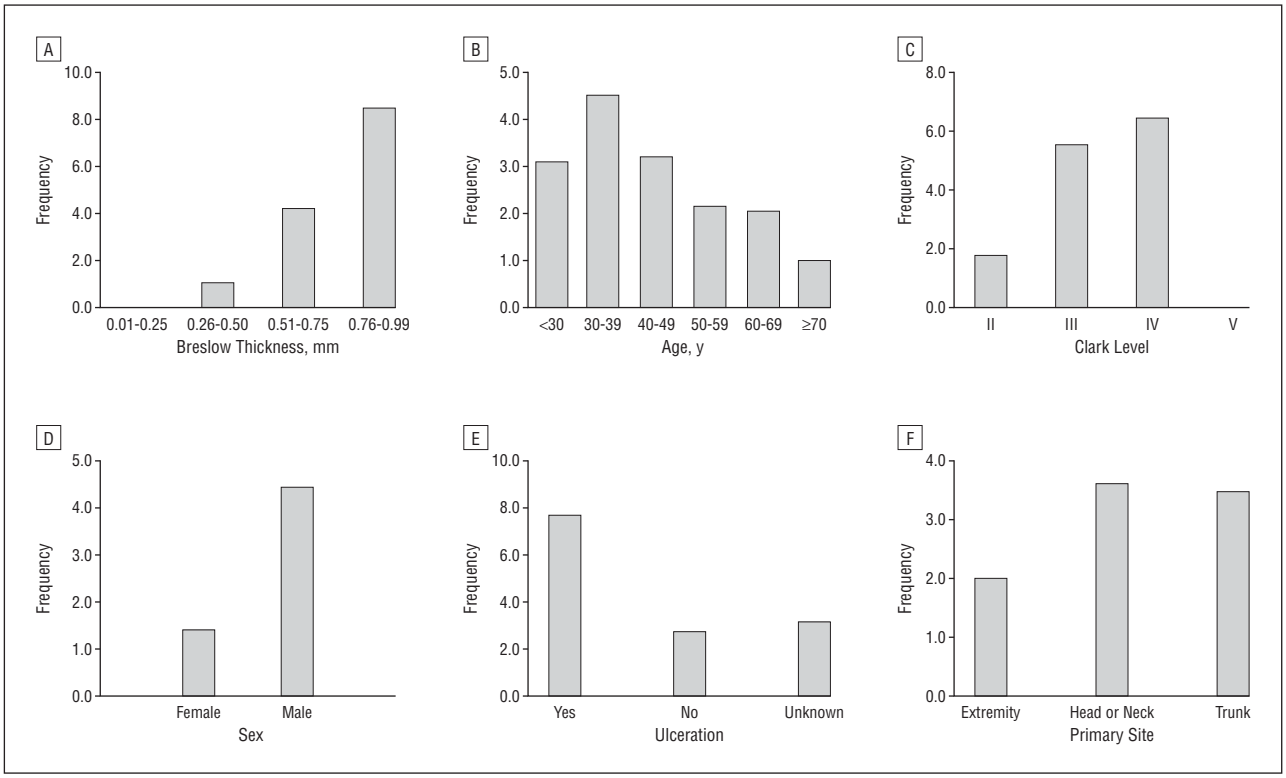

Figure 1. Frequency of regional nodal recurrence by several clinical and pathologic factors. A, Breslow thickness; B, age; C, Clark level; D, sex; E, ulceration; and F, primary melanoma site.

0.75 mm, 4.3%; and 0.76-0.99 mm, 8.5%) (**Figure 1**A). Nodal recurrence–free survival diminished most quickly in the thickest tumor category (**Figure 2**). No nodal recurrences were seen in the group with a Breslow thickness of up to 0.25 mm, but we observed several patients excluded from this study who had been previously treated at other institutions and presented to us after nodal recurrence of melanoma smaller than 0.25 mm (data not shown). The likelihood of nodal recurrence decreased with age (<30 years, 3.9%; 30-39 years, 4.5%; 40-49 years, 3.2%; 50-59 years, 2.2%; 60-69 years, 2.1%; and ≥70 years, 1.0%) (Figure 1B). Nodal recurrence increased directly with Clark level (Figure 1C). Because there was only 1 case rated as Clark level V, nodal risk assessment in this category is unreliable. Male patients were much more likely to develop nodal recurrence than were female patients (4.4% vs 1.4%; Figure 1D). Data regarding ulceration was present in 1282 patients (74.0%), among whom 39 (3.0%) had ulceration. Those with ulceration had a 7.7% nodal recurrence rate relative to 2.7% without ulceration (Figure 1E). Data for this field were more commonly missing earlier in the series, but because of the lack of data and the infrequency of this finding in thin melanoma, ulceration was not included in the final predictive modeling. Regression data were absent in most cases, so this variable was not investigated further in this study. Although there was a somewhat lower rate of nodal recurrence among patients with extremity melanoma, the association was not significant (P=.13; Figure 1F).

By multivariate analysis, sex, age, and Breslow thickness were significant; primary tumor site and Clark level were not. A scoring system using Breslow thickness, age, and sex was developed to predict nodal involvement (**Figure 3**). Because of the low risk of nodal metastasis for primary tumors smaller than 0.50 mm, these were grouped into 1 category. The inverse relationship between age and nodal recurrence decreased to a plateau between 50 and 70 years of age and then decreased again above that age. This led to the division of age into 3 categories (<50, 50-70, and >70 years). Predicted risk varied from 0.1% in the lowest-risk group to 17.4% in the highest-risk group.

COMMENT

Although thin melanoma is generally associated with favorable outcomes, there is clearly a subgroup of patients who will experience melanoma recurrence and subsequently die. Determination of which patients are at higher risk for relapse and death is important because of the large number of patients with a thin melanoma diagnosis. A number of series have examined factors that are associated with worse overall prognosis in thin melanoma, including large institutional database and population-based database analyses. These series confirm that a relatively small but consistent fraction of patients will have disease recurrence and suggest several potential risk factors.

McKinnon and colleagues[2] in Australia examined the New South Wales Cancer Registry and the Sydney Melanoma Unit database. For the Sydney Melanoma Unit group, the survival was 92.7% at 10 years, and for the New South Wales Cancer Registry group, it was 96.4%.

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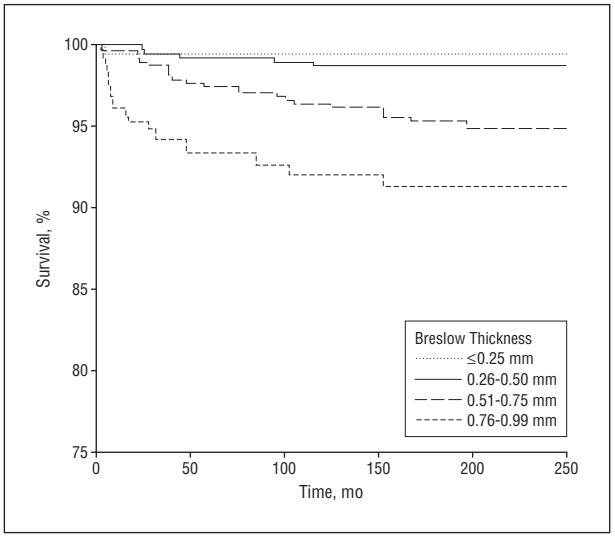

Figure 2. Regional nodal metastasis–free survival. Kaplan-Meier plot based on Breslow thickness categories: 0.01 through 0.25 mm (n=151), 0.26 through 0.50 mm (n=830), 0.51 through 0.75 mm (n=515), and 0.76 through 0.99 mm (n=236). $P<.01$ for overall comparison (3 groups) and $P<.01$ for <0.50 mm vs 0.51 to 0.75 mm or 0.76 to 0.99 mm by log-rank test.

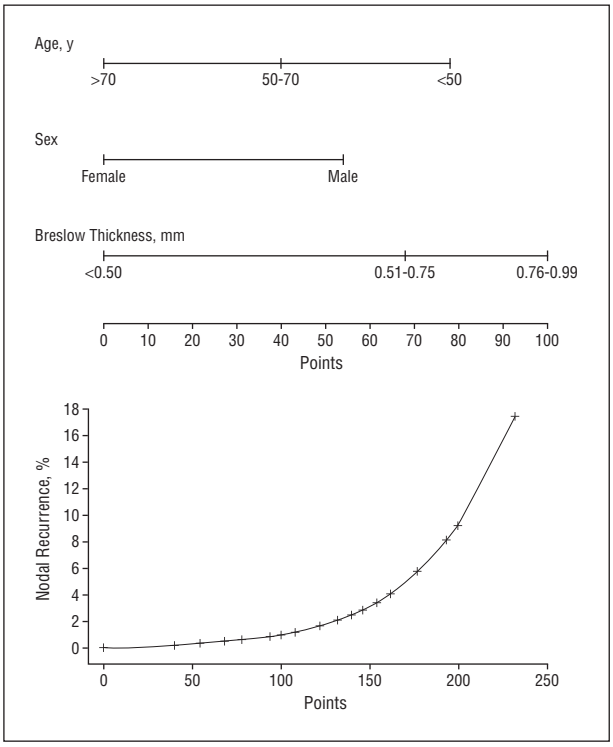

Figure 3. Nomogram predicting regional nodal recurrence in thin melanoma. Points are assigned based on patient and tumor characteristics. The total number of points is then used to determine the risk of nodal recurrence using the second plot. c-index=0.791.

The series noted a predilection toward late recurrence (median time to recurrence, 49.8 months) and the importance of long-term follow-up in accurately assessing melanoma risk. They also noted a steady decrease in 10-year survival with increasing Breslow thickness (<0.50 mm, 98%; 0.51-0.75 mm, 96.6%; and 0.76-1.00 mm, 91.5%). Gimotty et al[3] performed a similar study using the Surveillance, Epidemiology, and End Results and University of Pennsylvania Pigmented Lesion Group (PLG) databases. The 10-year survival for patients with thin melanoma in the Surveillance, Epidemiology, and End Results database was 95.1%. The PLG analysis found that Clark level (II vs III/IV), sex, and mitotic rate figured into a decision tree analysis. The Australian analysis reported a Clark level discrimination of II/III vs IV. Investigators at Duke University examined their database and found a 9.4% rate of recurrence after thin melanoma for patients followed up over time.[6] Male sex, older age, and Breslow thickness (>0.75 mm) were adverse prognostic factors in this analysis.

However, the predictors for worse overall or melanoma-related survival are not the same as those that predict nodal involvement. For example, increased age is a factor that is clearly related to worse overall and melanoma-specific survival, but paradoxically it is associated with a *lower* risk of nodal metastasis. It was recently reported that lymphatic function measured during a sentinel node (SN) biopsy diminishes with age, which may provide a biological mechanism to explain this paradox.[7] It is apparent that a prediction system specifically tailored to identify nodal risk is needed to select patients for additional nodal evaluation rather than an overall prognostic model.

It is now well established that the status of regional lymph nodes is the most important prognostic variable in clinically localized melanoma. Use of SLND allows assessment of the regional nodal basin with minimal morbidity, and multiple institutional series have confirmed the prognostic value of SN staging.[8] A recent prospective, multicenter clinical trial demonstrated that the SN status was the most powerful predictor of outcome in patients with clinically localized melanoma.[4] Because most new cases of melanoma are thin lesions, the absolute number of recurrences in this group is actually large. For example, of 100 patients with melanoma, approximately 70 will have thin lesions. If the overall SN metastasis rate is 3% for this group, 2 will have nodal metastases. Of the remaining 30 patients, approximately 23 will have intermediate-thickness lesions. With a 20% SN metastasis rate, 5 will be positive. So in absolute terms, because of the prevalence of thin lesions, metastases from thin lesions will account for more than one-quarter of positive nodes in these patients.

The prognostic importance of SN metastasis in thin melanoma has been questioned because of the low volume of disease often found in the SNs of these patients. Indeed, some small series have not found an independent value in the SN status.[9] However, our own series of SLND for thin melanoma, which includes a larger number of patients and enjoys longer follow-up, confirms a significant independent prognostic impact of SN status in thin melanoma.[5,10] The SN information is therefore important for the subgroup of patients with thin melanoma who harbor clinically occult metastases. However, it has also been shown that completely indiscriminate use of SN biopsy would be prohibitively cost-ineffective, with each detected SN metastasis costing $700 000 to $1 000 000.[11] It is, therefore, critically important to determine which patients are appropriate candidates for more aggressive intervention.

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Predictors of nodal disease have been sought largely through reviews of SN biopsy in thin melanoma. Several potential predictors of metastasis have been identified, including vertical growth phase, sex, mitotic rate, Breslow thickness, Clark level, age, and tumor-infiltrating lymphocytes.[12-18] However, not all series supported the same factors, and some suggested no factors correlated with SN status.[9,19]

These systems of SN prediction have several difficulties. Vertical growth phase, which is recommended as an indicator by the PLG, is not universally reported at many centers, and many pathologists are not well trained in distinguishing vertical growth phase from radial growth phase. Similar difficulties exist in determining the Clark level of invasion in a reproducible way.[20] In the present study, this lack of reproducibility may account for the loss of significance of Clark level when Breslow thickness subcategories (eg, 0.01-0.25 mm, 0.26-0.50 mm, and so on) were included.

The degree of tumor infiltration by host lymphocytes is also measured on a somewhat subjective scale that may be reported differently by different pathologists. Mitotic rate appears to be an extremely important variable in the assessment of melanoma risk.[21-23] This variable will be included in the updated American Joint Committee on Cancer staging system, but it has not been systematically collected in many centers for very long. A study[16] from the PLG found that this was a strong predictor of metastasis in thin melanoma, but in thin lesions the reported mitotic rate may vary with the proportion of the dermal component that is evaluated. Finally, ulceration is associated with both a worse outcome and greater propensity for nodal metastasis. However, this finding is infrequent in thin melanomas. In our own series, ulceration was only seen in 2.3% of patients. This is similar to the rate reported by Gimotty et al[3] of 1.2%. Although such ulcerated lesions clearly deserve greater concern and evaluation, the rarity of this finding decreases the utility of including it in a prediction scheme.

A more basic problem with prediction schemes derived from SN series is that the patients included in the series have already been selected by the surgeon to undergo the procedure. This selection bias may preclude sufficient evaluation of potential prognostic indicators. For example, if Clark level IV invasion is used as a consistent selection criterion for SN biopsy, it is highly unlikely to be found to be predictive of nodal metastasis. The present study examines a different population: those patients treated by wide local excision alone. This greatly reduces the impact of selection bias, making evaluation of multiple potential predictors possible.

In addition, the possibility of a false-negative SN biopsy result exists. At centers that are not experienced with the technique, this rate may be as high as 10% or greater.[24] This may be particularly true of thin lesions because the volume of disease in the node is often small. Using clinical nodal recurrence as an end point obviates that problem.

Other series have examined the rate of nodal recurrence among patients treated with wide local excision alone.[2,4,6,25-29] These rates have varied from 4.3% to 12.0% and appear higher than the reported rates of SN positivity for the same group. However, in many of these series, referral bias may have led to inclusion of patients that had been sent to a tertiary center only after disease recurrence, increasing the apparent rate of nodal metastasis. The series from the PLG-excluded patients referred for disease recurrence found an overall rate of 4.3% and a rate of 8.6% for lesions between 0.75 and 1.00 mm thick, which is similar to the present report. The PLG found that the risk of nodal recurrence was related to vertical growth phase, mitotic rate, and male sex in a decision tree analysis. Ulceration was also significant in a multivariate model.

Our predictive system for nodal metastasis in thin melanoma uses 3 simple and reproducible variables to determine the risk of harboring clinically occult nodal metastases. These variables should be easily available for all patients with melanoma. This risk assessment is not intended to mandate what risk level is appropriate for SN evaluation, but it allows for a better informed discussion with the patient newly diagnosed as having melanoma. Such information could be used to reassure extremely low-risk patients who may be anxious about the possibility of metastases or convince patients at higher risk of the need to consider SN biopsy.

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