The Impact of Factors Beyond Breslow Depth on Predicting Sentinel Lymph Node Positivity in Melanoma

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Received July 10, 2006; revision received October 4, 2006; accepted October 10, 2006.

BACKGROUND. In addition to Breslow depth, the authors previously described how increasing mitotic rate and decreasing age predicted sentinel lymph node (SLN) metastases in patients with melanoma. The objectives of the current study were to verify those previous results and to create a prediction model for the better selection of which patients with melanoma should undergo SLN biopsy.

METHODS. The authors reviewed 1130 consecutive patients with melanoma in a prospective database who underwent successful SLN biopsy. After eliminating patients aged <16 years and patients who had melanomas that measured <1 mm, 910 remaining patients were reviewed for clinical and pathologic features and positive SLN status. Univariate association of patient and tumor characteristics with positive SLN status was explored by using standard logistic regression techniques, and the best multivariate model that predicted lymph node metastases was constructed by using a backward stepwise-elimination technique.

RESULTS. The characteristics that were associated significantly with lymph node metastasis were angiolymphatic invasion, the absence of regression, increasing mitotic rate, satellitosis, ulceration, increasing Breslow depth, decreasing age, and location (trunk or lower extremity compared with upper extremity or head/neck). Previously reported interactions between mitotic rate and age and between Breslow depth and age were confirmed. The best multivariate model included patient age (linear), angiolymphatic invasion, the number of mitoses (linear), the interaction between patient age and the number of mitoses, Breslow depth (linear), the interaction between patient age and Breslow depth, and primary tumor location.

CONCLUSIONS. Younger age, increasing mitotic rate (especially in younger patients), increasing Breslow depth (especially in older patients), angiolymphatic invasion, and trunk or lower extremity location of the primary tumor were associated with a greater likelihood of positive SLN status. The current results support the use of factors beyond Breslow depth to determine the risk of positive SLN status in patients with cutaneous melanoma. ***Cancer*** **2007:109:100–8.** © *2006 American Cancer Society.*

KEYWORDS: melanoma, sentinel lymph node positivity, age, mitotic rate.

Sentinel lymph node (SLN) biopsy has become an important and widely employed technique for detecting subclinical metastases to lymph nodes in patients with cutaneous melanoma. Identifying lymph node micrometastases facilitates more accurate staging and identifies patients who may benefit from an early, complete lymph node dissection and adjuvant therapy or clinical trial consideration.[1–4] For this reason, a number of investigators have sought to identify factors that may predict patients at higher or lower risk of having a positive SLN to identify higher risk patients while potentially sparing lower risk patients from undergoing the procedure. Several clinical and histologic characteristics of the primary melanoma have been examined with regard to their potential role in predicting SLN positiv-

DOI 10.1002/cncr.22382
Published online 4 December 2006 in Wiley InterScience (www.interscience.wiley.com).

ity. Breslow depth has been a consistently reported characteristic that predicts positive SLN status.[2,3] Other factors that have been examined variably include patient age, anatomic location, mitotic rate, ulceration, angiolymphatic invasion, lymphangiogenesis, Clark level, vertical growth phase, tumor-infiltrating lymphocytes, regression, and satellitosis.[5–10] Differences in study design and data collected no doubt explain some of the variation in factors that reportedly are associated significantly with positive SLN status.

We previously reported that, in a multivariate analysis of 419 patients, Breslow depth, younger age, and higher mitotic rate, especially in younger patients, were associated significantly with a positive SLN and that there was a complex relation between these factors.[6] In an attempt to validate and expand those results, we studied a larger series of patients who underwent SLN biopsy for cutaneous melanoma. Our objectives were to explore the clinical and histologic characteristics of a primary melanoma that correlate with the probability of a positive SLN and to assess the interactions among these factors with the goal of identifying a better method of selecting melanoma patients for sentinel lymph node biopsy beyond Breslow depth alone.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board at the University of Michigan. Our prospective melanoma database was queried for patients with cutaneous melanoma who underwent SLN biopsy at the University of Michigan between August 1997 and March 2004. This included a relatively small partial overlap of patients previously analyzed and reported from January 1996 to August 1999 who cannot be identified completely, because their link between clinical and research records were broken intentionally after the publication of that study (see Results, below).[6] Patients aged <16 years at the time of surgery were excluded from the current analysis to avoid the issues of atypical Spitz-like lesions of uncertain biologic behavior and the potentially different biology of pediatric melanomas. Patients with thin melanomas that measured <1 mm in Breslow depth also were excluded from statistical analysis to avoid biasing the data, because we do not offer SLN routinely to patients with thin melanomas; our practice is to offer the procedure for thin melanomas based on the presence of adverse features. Finally, patients with multiple primary melanomas draining to the same lymph node basin and excised concurrently were excluded, because it is believed that these patients are have a greater likelihood of SLN positivity. Patients were categorized by the presence or absence of metastatic melanoma in ≥ 1 SLN. Our SLN biopsy technique and our method of SLN evaluation have been described previously.[6,11]

Statistical Analysis

Clinical variables analyzed included patient age, gender, site of the primary melanoma (categorized into 4 anatomic locations: head and neck, trunk, upper extremity, or lower extremity), the number of lymph node basins investigated during SLN biopsy, and the number of SLNs resected. Histologic features evaluated were Breslow depth, the number of mitoses per square millimeter (with 1 mm^2 approximately equal to 4 or 5 high-power [$\times 40$] microscopic fields, starting in the fields with the most mitoses), histologic subtype, and the presence or absence of the following features: ulceration, angiolymphatic invasion, regression, neurotropism, microsatellitosis, and periadnexal extension. All primary lesion and SLN biopsy slides were reviewed by 1 of 4 pathologists in the University of Michigan Melanoma Pathology Group, who generated a 14-point melanoma profile for the primary lesion that included the histologic factors described above.

The event of interest was defined as the presence of ≥ 1 positive SLN. To determine a univariate association between any clinical or pathologic factor and the event of interest, a logistic regression model was fit with each factor by itself and adjusted for age (continuous term) and gender. The parameter estimates from those models, the P value from the Wald chi-square test for the significance of the parameter, the odds ratio (OR), and a 95% Wald-based confidence interval (95% CI) for the OR were reported.

To appropriately account for potential correlation and confounding between the many clinical and pathologic characteristics when explaining lymph node metastases, multivariate logistic regression was used. All characteristics were modeled simultaneously in the same logistic model, with estimates compared with the univariate models for evidence of confounding. When no confounding was identified, nonsignificant covariates were removed from the model by using an iterative, stepwise variable selection procedure. The covariate with the highest P value was removed, the model was reestimated, and the process was repeated until only significant ($P < .05$) covariates remained in the model. Interaction between significant characteristics was reported in our group's earlier work.[6] All 2-way interactions between significant covariates were constructed and considered in the logistic regression model. Only significant 2-way interactions were retained, and this model was considered our *best* multivariate model. All analyses for this research were performed using SAS

TABLE 1
Sentinel Lymph Node Biopsy Results for Each of the Clinical and Histologic Characteristic Considered

Characteristic	Total sample No.	Total sample % SLN positive
Sex		
Men	526	25.7
Women	384	28.1
Age		
<20 y	15	53.3
20–29 y	72	37.5
30–39 y	135	31.1
40–49 y	173	32.4
50–59 y	201	23.4
60–69 y	181	16.6
≥70 y	133	24.8
Primary tumor site		
Head and neck	176	17.6
Trunk	360	31.4
Upper extremity	180	20.0
Lower extremity	194	32.5
Histologic subtype		
Acral lentiginous	33	33.3
Desmoplastic	31	12.9
Epitheloid	14	42.9
Lentigo maligna	20	15.0
Nodular	186	31.2
Polypoid	13	53.9
Spitz-like	33	27.3
Superficial spreading	457	25.2
All others/not classified	123	24.4
Breslow depth		
1.01–2 mm	490	19.4
2.01–3.99 mm	301	31.6
≥4 mm	119	44.5
Mitotic rate		
<1//mm^2	424	19.1
1–5//mm^2	299	32.1
>5	137	43.1
Unknown	50	14.0
Ulceration		
Absent	659	24.1
Present	245	33.5
Unknown	6	33.3
Angiolymphatic invasion		
Absent	836	24.4
Present	63	52.4
Unknown	11	54.6
Regression		
Absent	771	28.2
Present	130	17.7
Unknown	9	33.3
Neurotropism		
Absent	860	26.3
Present	39	33.3
Unknown	11	36.4
Microsatellitosis		
Absent	881	26.1
Present	23	47.8
Unknown	6	33.3
Periadnexal extension		
Absent/unknown	886	26.3
Present	24	41.7
No. of lymph node basins		
1	742	26.7
2	168	26.8
No. of SLNs resected		
1	272	22.1
2	244	26.2
3	154	28.6
≥4	240	31.3

SLN indicates sentinel lymph node.

software (version 9.1; SAS Institute, Cary, NC). For modeling purposes, missing data were assumed to be missing completely at random.

RESULTS

One thousand one hundred thirty-five unique melanoma patients who underwent SLN biopsy were identified in our database in the 6.5-year study period from August 1997 to March 2004. One thousand one hundred thirty patients (99.6%) had ≥1 SLN identified and resected. Seventeen patients were excluded, because they had 2 primaries draining to the same lymph node basin that were excised concurrently. Of the remaining 1096 patients, 910 had melanoma ≥1 mm in Breslow depth and were aged ≥ 16 years at the time of surgery. These 910 patients constituted our study sample for statistical analysis. Table 1 lists the distribution of patient and tumor characteristics along with the percentage of patients with ≥1 positive SLN for each characteristic considered. Complete information for all characteristics considered was available in 93.4% of patients. Patients ranged in age from 16 years to 87 years (median, 52 years). Overall, ≥1 positive SLNs were identified in 243 of 910 patients (26.7%). SLN positivity rates range from 13% to 31%,[2,12–18] placing our results at the upper range of reported series. This probably was caused by several factors that limited the current study primarily to patients with melanoma ≥1 mm in Breslow depth. van Akkooi et al[18] reported a 29% SLN-positivity rate for the European Organization for Research and Treatment of Cancer melanoma Group protocol with a mean Breslow depth of 2.76 mm. In the current study, the mean Breslow depth was 2.57 mm.

TABLE 2
Univariate Analyses of the Relations Between the Clinical and Histologic Characteristics Considered and Positive Sentinel Lymph Node Status

	Univariate analysis		
Characteristic	***P***	**OR**	**95% CI**
Men	.4076	0.88	0.66–1.19
Age, linear	<.0001	0.98	0.97–0.99
No. of SLNs resected, linear	.0006	1.11	1.05–1.18
1		1.00	
2	.2689	1.23	0.84–1.88
3	.1337	1.36	0.90–2.22
≥4	.0190	1.41	1.08–2.39
Angiolymphatic invasion	<.0001	3.41	2.03–5.73
Regression	.0137	0.55	0.34–0.88
No. of mitoses/mm^2, linear	<.0001	1.10	1.06–1.14
Low mitotic rate, <1//mm^2		1.00	
Moderate mitotic rate, 1–5/mm^2	.0001	1.97	1.42–2.82
High mitotic rate, >5/mm^2	<.0001	3.20	2.11–4.85
Satellitosis	.0247	2.59	1.13–5.96
Ulceration	.0049	1.58	1.15–2.18
Neurotropism	.3313	1.40	0.71–2.78
Periadnexal extension present	.0989	2.00	0.88–4.57
Breslow depth, linear	<.0001	1.22	1.13–1.31
1.01–2 mm		1.00	
2.01–4 mm	<.0001	1.92	1.38–2.67
≥4.01 mm	<.0001	3.34	2.18–5.11
Head and neck location*	.0027	0.53	0.35–0.80
Trunk location*	.0099	1.48	1.10–1.99
Upper extremity location*	.0242	0.63	0.42–0.94
Lower extremity location*	.0411	1.43	1.02–2.02

OR indicates odds ratio; 95% CI, 95% confidence interval; SLN, sentinel lymph node.
* Comparing this body site with all other sites.

TABLE 3
Best Multivariate Model of the Relations Between Important Histologic and Clinical Characteristics and Positive Sentinel Lymph Node Status

Characteristic	***P***	**Estimate**	**OR**	**95% CI**
Age, linear*	<.0001	−0.0405	0.96	0.94–0.98
Angiolymphatic invasion	.0001	1.1549	3.17	1.77–5.68
No. of mitoses/mm^2, linear	<.0001	0.1124	1.12	1.07–1.17
Interaction: Mitoses by age*	.0097	−0.00376	0.996	0.993–0.999
Breslow depth, linear	.0025	0.1252	1.13	1.05–1.23
Interaction: Breslow depth by age*	.0028	0.00952	1.01	1.003–1.016
Head/neck or upper extremity		0	1.00	
Trunk or lower extremity	.0003	0.6533	1.92	1.35–2.74

OR indicates odds ratio; 95% CI, 95% confidence interval.
* Age of the patient at surgery was centered at 50 years.

Univariate Analysis

Results from the univariate analyses of patient and tumor characteristics with SLN positivity are summarized in Table 2. The following characteristics were associated significantly with a positive SLN: decreasing age ($P <$ .0001), increasing mitotic rate ($P <$ .0001), increasing Breslow depth ($P <$.0001), presence of angiolymphatic invasion ($P <$ .0001), satellitosis ($P =$.025), ulceration ($P =$.005), absence of regression ($P =$.014), and location on the trunk ($P =$.010) and lower extremity ($P =$.041) compared with tumors on the head/neck ($P =$.003) or upper extremity ($P =$.024). Periadnexal extension and neurotropism were not associated significantly with SLN positivity.

Multivariate Analysis

Results of the multivariate analyses are summarized in Table 3. The best multivariate model included the following single variables: patient age ($P <$.0001), Breslow depth ($P =$.003), the presence of angiolymphatic invasion ($P =$.0001), the number of mitoses ($P <$.0001), and body site location of the melanoma ($P =$.0003). For the purposes of the model, patients who had head and neck melanomas were grouped with patients who had upper extremity melanomas, because they both had an OR $<$ 1; and patients who had trunk and lower extremity melanomas were grouped together, because they both had an OR $>$ 1. In the model, the patient age at surgery was centered at 50 years, which was chosen because it was close to the median age (52 years) of our patient population. The estimate for age was negative, indicating that younger age was associated with greater SLN positivity. Age as a single variable had a major impact on the likelihood of SLN positivity: For a 10-year decrease in age, the OR was 1.5; for a 20-year decrease in age, the OR was 2.25; and, for a 30-year decrease in age, the OR was 3.37 (as calculated from the estimate). Thus, for example, a patient aged 20 years had >3 times the odds of SLN positivity as a patient aged 50 years, all other factors being equal. The presence of angiolymphatic invasion tripled the odds of SLN positivity (OR, 3.04). Location on the trunk and lower extremity, as opposed to the upper extremity or head and neck, almost doubled the odds of SLN positivity (OR, 1.92). The estimates for the number of mitoses and for Breslow depth were positive, indicating that increasing number of mitoses and increasing Breslow depth were associated with greater SLN positivity.

Although ulceration is used often as a determinate for performing SLN biopsy in patients with thin melanomas, it did not appear in our multivariate analysis when mitotic rate and angiolymphatic invasion were included. Ulceration was associated significantly with both of these factors in our population. The patients with ulceration had a mean mitotic rate of 4.97 compared with patients without ulceration, who had a mean mitotic rate of 2.13 ($P <$ .0001). Of the patients who had ulceration, 11.9% had angiolymphatic inva-

sion compared with patients who did not have ulceration (4.9%; $P < .0002$).

Two-way Interactions

Analysis of all 2-way interactions of the variables in our multivariate model revealed that the interaction between patient age and the number of mitoses ($P = .01$) and the interaction between patient age and Breslow depth ($P = .003$) were statistically significant. For the interaction between mitoses and age, the estimate was negative, indicating that for a given number of mitoses (and ignoring all other factors), the younger patient was more likely to have a positive SLN than the older patient. In other words, mitotic rate was a more important predictor of SLN positivity in the younger patient. For the interaction between Breslow depth and age, the estimate was positive, indicating that, for a given Breslow depth (and ignoring all other factors), the younger patient was less likely to have a positive SLN than an older patient. However, the magnitude of this interaction estimate was small (0.00959) compared with the magnitude of the estimates for Breslow depth (0.1348) and age (−0.0406), which diluted its effect in the overall model. Still, Breslow depth was a more important predictor of SLN positivity in the older patient. We previously reported the interactions between Breslow depth and age, mitotic rate and age, and Breslow depth and mitotic rate.[6] Our results confirmed the significant association between patient age and mitotic rate and between age and Breslow depth, but the significant interaction between mitotic rate and Breslow thickness previously reported was not observed in this expanded patient series.

Body Site Location Analyses

The emergence of body site location as a potential predictor of SLN positivity, namely, that melanoma located on the head/neck or upper extremity had a lower probability of lymph node metastases than melanoma on the trunk or lower extremity, led to further analysis of the possible associations between body site and the other clinical and histologic characteristics of melanoma. There was no significant association between body site and Breslow depth ($P = .2427$), mitotic rate ($P = .4741$), ulceration ($P = .2366$), angiolymphatic invasion ($P = .5616$), satellitosis ($P = .2012$), or periadnexal extension ($P = .8861$). However, age ($P = .0010$), gender ($P < .0001$), regression ($P < .0001$), neurotropism ($P = .0260$), and histologic subtype ($P < .0001$) differed significantly by body site location. Because sex, regression, and neurotropism were not associated independently with SLN positivity, it is doubtful that they contributed in a substantial way to the association between SLN positivity and body site location. When age was analyzed by body site, we observed that patients with either head/neck or upper extremity melanoma were significantly ($P < .05$) older than patients with either trunk or lower extremity melanoma. In this series, we demonstrated that increasing decreased the likelihood of SLN positivity (Table 2); however, age also was present in the multivariate model (Table 3), and no significant 2-way interaction was observed; thus, the association of body site location appears to be independent of age.

Histologic subtype also was analyzed further for its potential contribution to body site location as a variable in our multivariate model. A greater proportion of patients with head/neck melanoma had desmoplastic or lentigo maligna subtypes, both of which had lower percentages metastases compared with the other subtypes, as shown in Table 1 and as reported previously.[19–21] Therefore, the analysis was repeated without the 51 patients who had either lentigo maligna or desmoplastic melanoma. This had no effect on the end results (data not shown), and the same factors were significant on multivariate analysis, including anatomic location of the primary melanoma. Hence, the significance of body site location as a predictor of positive SLN status appears to be independent of the histologic subtype.

Generating Predicted Probability Graphs for SLN Positivity

Using calculations directly from our multivariate model, we generated graphs of the predicted probabilities of ≥ 1 positive SLN using the variables in our model. We analyzed the predicted probabilities in patients with melanomas that measured from 1 mm to 2 mm in Breslow depth. This range of Breslow depth was chosen to reflect a population of melanoma patients with a high likelihood of having a subset of patients who may not need SLN biopsy. Figure 1 demonstrates the predicted probabilities of a positive SLN for melanomas between 1 mm and 2 mm in depth on the trunk or lower extremity with angiolymphatic invasion (Fig. 1B) and without angiolymphatic invasion (Fig. 1A). Figure 2A,B shows the equivalent graphs for melanomas on the upper extremity or head/neck. In all figures, separate lines were calculated for a patient aged 35 years, 50 years, 65 years, and 80 years. Age was a linear variable in our multivariate model, but we chose these particular ages to divide our age range roughly into quartiles. The width of each line represents the predicted probabilities of a positive SLN if the Breslow depth were varied from 1 mm to 2 mm (correlating with the lower to the upper border of the line), and the slope of each line represents the impact of mitotic rate on SLN positivity. In all of the figures, the width of the lines was greatest for the patient aged 80 years, indicating that the impact of Breslow depth was greater the

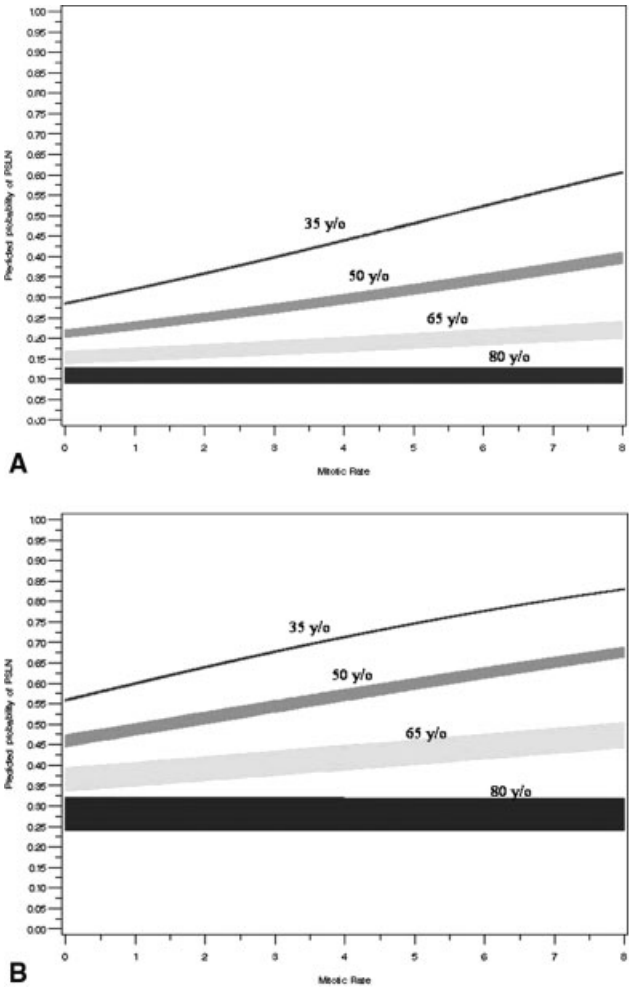

FIGURE 1. Predicted probability of ≥1 positive sentinel lymph node (PSLN) by age and mitotic rate for melanoma that measured between 1 mm and 2 mm in Breslow depth located on the trunk or lower extremity without angiolymphatic invasion (A) and with angiolymphatic invasion (B). Separate lines were calculated for a patient aged 35 years, 50 years, 65 years, and 80 years. The width of each line represents the variation between 1 mm (the lower border of the line) and 2 mm (the upper border of the line). The slope of each line represents the impact of mitotic rate. The width of the lines increases with increasing age, indicating that the impact of Breslow depth was greater for older patients. The slope of the line is greatest for younger patients, indicating that the impact of mitotic rate was greater for younger patients.

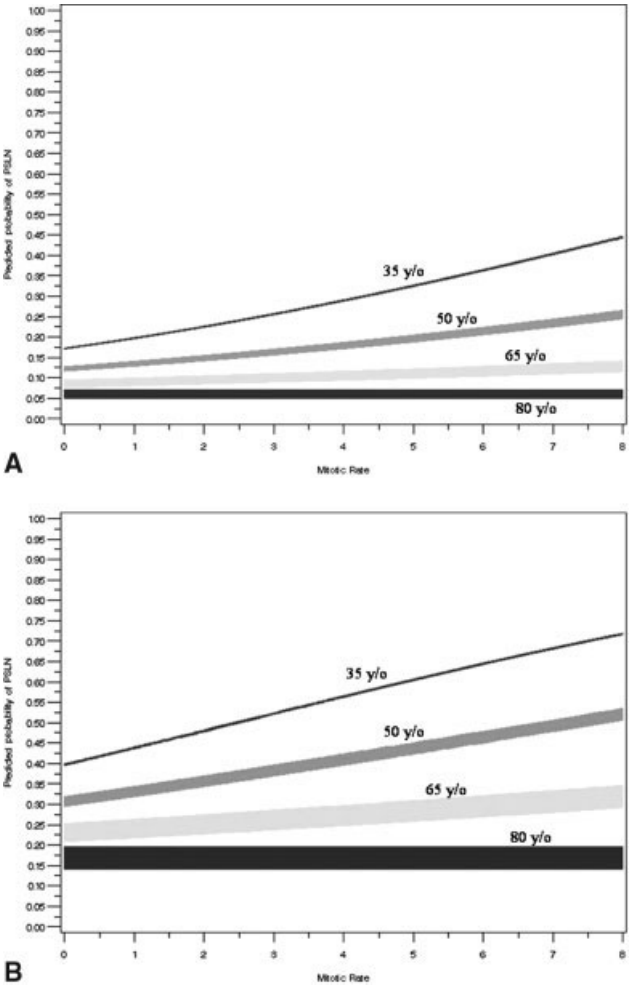

FIGURE 2. Predicted probability of ≥1 positive sentinel lymph node (PSLN) by age and mitotic rate for melanoma that measured between 1 mm and 2 mm in Breslow depth located on the head and neck or the upper extremity without angiolymphatic invasion (A) and with angiolymphatic invasion (B). For constant body site location, angiolymphatic invasion status, and mitotic rate, younger patients had a much greater risk of having a positive SLN than older patients, regardless of the variation of Breslow depth from 1 mm to 2 mm. For all age groups, patients who had melanoma on the head/neck or upper extremity without angiolymphatic invasion had the lowest rates of SLN positivity.

older the patient. In addition, in all of the figures, the slope of the lines was greatest for the patient aged 35 years, indicating that the impact of mitotic rate was greater the younger the patient. In each figure, the line that represents the patient aged 35 years is located above the line that represents the patient aged 50 years, and so on; in other words, for constant body site location, angiolymphatic invasion status, and mitotic rate, younger patients had a much greater risk of finding a positive SLN than older patients, regardless of the variation in Breslow depth from 1 mm to 2 mm. For all age groups, melanoma on the head/neck or upper extremity without angiolymphatic invasion had the lowest rates of SLN positivity.

DISCUSSION

Numerous clinical and histologic characteristics have been reported as being predictive of SLN positivity. In our multivariate model, using comprehensive data from 910 patients, we observed that increasing Breslow depth, younger patient age, higher mitotic rates, the presence of angiolymphatic invasion, and location of

the primary melanoma on the trunk or lower extremities were significant predictors of SLN positivity.

Our current results confirm previous studies, which showed that younger age is a predictor of SLN positivity.[6,22–24] What is remarkable is just how large an effect age had on predicting SLN positivity in our model. All other factors being equal, a 10-year decrease in age increased the odds of SLN positivity by 50%; a 20-year decrease in age more than doubled the odds of SLN positivity, and a 30-year decrease in age more than tripled the odds of SLN positivity. Not only did age affect the probability of SLN positivity as an independent variable, it also interacted with mitotic rate and Breslow depth, validating our previous findings about these interactions.[6] Higher mitotic rate was an important predictor of SLN positivity in younger patients, but that importance decreased in older patients. Conversely, increasing Breslow depth played a greater role in predicting SLN positivity in older patients.

In our model, the impact of mitotic rate in predicting SLN positivity was affected by patient age. In general, higher mitotic rates were associated with SLN positivity, but the effect was greater in younger patients. Using Figure 1A as a visual example, we can see that the top red line, which represents the patient aged 35 years, has the steepest slope, indicating that, even a small change of 1 in the mitotic rate has a significant impact on SLN positivity. With all other variables constant, a mitotic rate of 8 approximately doubles the likelihood of SLN positivity compared with a mitotic rate of 0 in a patient aged 35 years with melanoma on the trunk or lower extremities without angiolymphatic invasion. However, the green line, which represents the patient aged 80 years, has a nearly horizontal line, indicating that a mitotic rate of 0 has approximately the same likelihood of SLN positivity as a mitotic rate of 8.

We observed that the presence of angiolymphatic invasion was a very significant predictor of SLN positivity. In both univariate and multivariate analyses, angiolymphatic invasion had a high OR of SLN positivity at 3.46 (95% CI, 2.09–5.73) and 3.04 (95% CI, 1.72–5.35), respectively, (Tables 2, 3). The presence of angiolymphatic invasion tripled the odds of SLN positivity, with all other factors in our multivariate model being constant. Angiolymphatic invasion has been reported as an adverse indicator for both SLN positivity and overall survival in patients with melanoma.[7,8,25,26]

Body site location also was a significant predictor of SLN positivity in our model. Location of the primary melanoma on the trunk or lower extremities doubled the odds of SLN positivity (OR, 1.92) compared with location on the head/neck or upper extremities. The emergence of body site location as a predictor of SLN positivity in our study led to additional analyses to examine associations that may contribute to the significance of body site location, although we did not observe any, including histologic type of melanoma. It is noteworthy that our data on anatomic location were divided into the trunk and lower extremities (with greater SLN positivity) versus the head/neck and upper extremities. This breakdown may reflect the greater technical ease of performing SLN biopsies in the inguinal basins versus cervical and axillary basins rather than reflecting the biologic behavior of melanoma in the different anatomic locations. Body location has been reported quite variably and infrequently as a risk factor for melanoma in the literature.[27,28] Differences in the data collected explain some of the discordant conclusions. For example, the large database analyzed to produce the 2001 American Joint Committee on Cancer melanoma staging system categorized location into either head/neck/trunk or extremities.[27] Other studies have differentiated the upper arm from the lower arm and the breast from the lower trunk.

Breslow depth is a validated, reproducible factor that is predictive of SLN status, and it currently is the primary criterion used to determine whether or not SLN biopsy is considered. At National Comprehensive Cancer Network institutions, SLN biopsy is considered generally for melanomas that measure $\geq$1 mm and is considered selectively for melanomas that measure $<$1 mm based on the presence of other adverse factors. To explore this criteria, we generated predicted probabilities for patients with melanomas between 1 mm and 2 mm in Breslow depth. Breslow depth played a greater role in predicting SLN positivity in older patients than in younger patients. This is illustrated visually in the figures (Figs. 1A,B, 2A,B), in which the greater width of the lines represents older patients. What is remarkably clear is that variation in Breslow depth from 1 mm to 2 mm had a nominal impact on the likelihood of SLN positivity in younger patients, with the other factors being equal. This is even more apparent in Figure 3A,B, in which Breslow depth varies from 2 mm to 4 mm. Mitotic rate and the presence of angiolymphatic invasion had a greater effect on predicting SLN positivity in younger patients. Especially for younger patients, our data support the use of patient age, mitotic rate, angiolymphatic invasion, and anatomic location, in addition to Breslow depth, when determining whether or not to consider SLN biopsy. The formula derived from our multivariate model, which may be used to determine an individual patient's risk of harboring micrometastases in the SLN, is available online (http://www.cancer.med.umich.edu/clinic/melclinic.htm).

If adverse factors can identify patients with melanomas $<$1 mm for SLN biopsy, then, in theory, the ab-

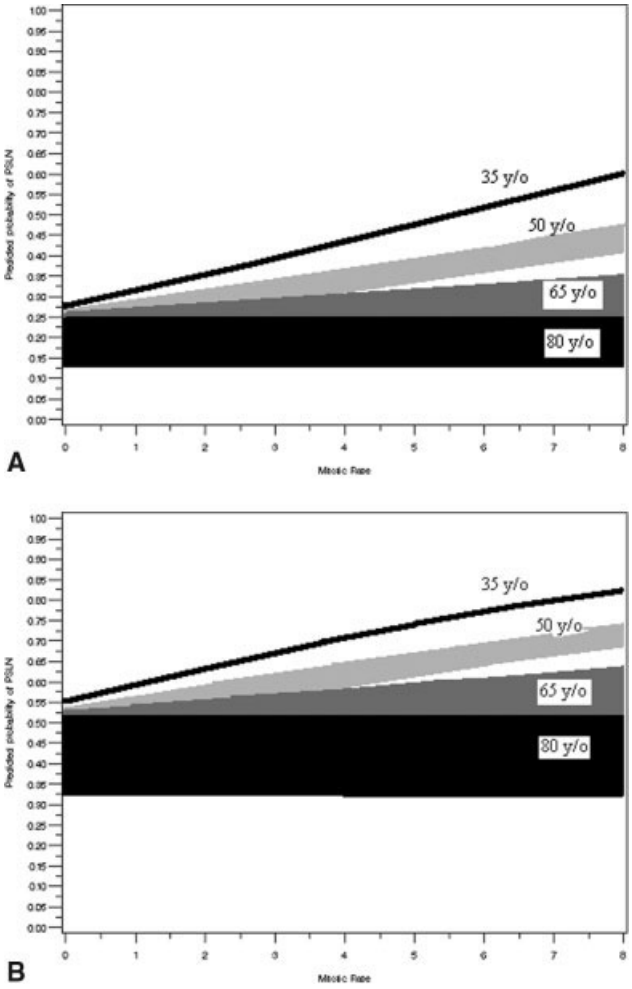

FIGURE 3. Predicted probability of ≥1 positive sentinel lymph node (PSLN) by age and mitotic rate for melanoma that measured between 2 mm and 4 mm in Breslow depth without angiolymphatic invasion (A) and with angiolymphatic invasion (B). All body site locations are included. The width of each line represents the variation between 2 mm (the lower border of the line) and 4 mm (the upper border of the line).

sence of those factors should select patients with melanomas ≥1 mm who may not require SLN biopsy. In this analysis, the patient at lowest risk for metastatic spread of melanoma to the SLN was the older patient with melanoma just greater than 1 mm, without angiolymphatic invasion, located on the head/neck or upper extremities. Mitotic rate had less impact on the older patient. In the older patient with multiple medical comorbidities, consideration of these other variables may provide valuable information in risk assessment. Whether these factors should be used routinely to determine which patients undergo SLN biopsy depends on the threshold for finding a positive SLN that justifies the procedure. For example, if the clinician believes that SLN biopsy is justified only if there is at least a 10% chance of finding a positive SLN, then observation alone would be warranted for patients aged >65 years who have melanomas <2 mm located on the head/neck or upper extremity without angiolymphatic invasion (Fig. 2A). Identifying the most appropriate threshold is a complex issue and depends on the impact of SLN biopsy on outcome, which still is being explored.

Beyond the implications of these data on clinical practice, our findings raise an interesting biologic question. Although younger patients have a significantly greater risk of positive SLN status, and a positive SLN clearly is associated with a poor outcome, older patients typically have a worse prognosis. This suggests a difference in the biology of the disease in younger patients compared with older patients. Whether this represents differences in the primary melanoma (such as a greater proclivity for hematogenous spread in older patients) or the patient's response (such as a diminished capability of the immune system to eradicate systemic disease in older patients) is unclear and begs further exploration.

In conclusion, younger age, increasing mitotic rate (especially in younger patients), increasing Breslow depth (especially in older patients), the presence of angiolymphatic invasion, and location of the primary tumor on the trunk or lower extremities are associated with higher likelihood of positive SLN status. The current results support the use of factors beyond Breslow depth to determine the risk of SLN positivity in patients with cutaneous melanoma and provide a better model for determining which patients should undergo SLN biopsy and which patients may undergo wide local excision alone. In addition, further research into the variations of behavior of melanoma in younger and older populations warrants further investigation.

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