original reports

Factors Affecting Sentinel Node Metastasis in Thin (T1) Cutaneous Melanomas: Development and External Validation of a Predictive Nomogram

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abstract

PURPOSE Thin melanomas (T1; ≤ 1 mm) constitute 70% of newly diagnosed cutaneous melanomas. Regional node metastasis determined by sentinel node biopsy (SNB) is an important prognostic factor for T1 melanoma. However, current melanoma guidelines do not provide clear indications on when to perform SNB in T1 disease and stress an individualized approach to SNB that considers all clinicopathologic risk factors. We aimed to identify determinants of sentinel node (SN) status for incorporation into an externally validated nomogram to better select patients with T1 disease for SNB.

PATIENTS AND METHODS The development cohort comprised 3,666 patients with T1 disease consecutively treated at the Istituto Nazionale Tumori (Milan, Italy) between 2001 and 2018; 4,227 patients with T1 disease treated at 13 other European centers over the same period formed the validation cohort. A random forest procedure was applied to the development data set to select characteristics associated with SN status for inclusion in a multiple binary logistic model from which a nomogram was elaborated. Decision curve analyses assessed the clinical utility of the nomogram.

RESULTS Of patients in the development cohort, 1,635 underwent SNB; 108 patients (6.6%) were SN positive. By univariable analysis, age, growth phase, Breslow thickness, ulceration, mitotic rate, regression, and lymphovascular invasion were significantly associated with SN status. The random forest procedure selected 6 variables (not growth phase) for inclusion in the logistic model and nomogram. The nomogram proved well calibrated and had good discriminative ability in both cohorts. Decision curve analyses revealed the superior net benefit of the nomogram compared with each individual variable included in it as well as with variables suggested by current guidelines.

CONCLUSION We propose the nomogram as a decision aid in all patients with T1 melanoma being considered for SNB.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Thin melanomas (T1; Breslow thickness ≤ 1 mm) constitute nearly 70% of newly diagnosed cutaneous melanomas and generally have favorable prognoses,[1] although a recent study reported that 20-year melanoma-specific survival for patients with melanoma thickness of 0.9 to 1.0 mm was as low as 71.4%.[2] Thus, some patients develop metastases, and because of the large number of T1 cases, there is a large absolute number of recurrences.[3]

Sentinel node biopsy (SNB) is the standard procedure for staging and obtaining prognostic information in intermediate or thick melanomas,[4] but for patients with T1 disease, the probability of sentinel node (SN) involvement is low (< 0.8 mm [< 5%]; 0.8-1 mm [5%-12%])[5] and SNB often constitutes overtreatment. The eighth (2017) edition of the American Joint Committee on Cancer (AJCC) Staging Manual revised the definitions of T1 disease: T1a is now < 0.8 mm without ulceration, and T1b is 0.8 to 1.0 mm with or without ulceration or < 0.8 mm with ulceration.[6] These revisions prompted changes in the recommendations of the American Society of Clinical Oncology

(ASCO)/Society of Surgical Oncology (SSO)[7] and National Comprehensive Cancer Network (NCCN)[8] for performing SNB—SNB is generally not recommended for T1a but can be considered for T1b melanomas after discussion of the potential benefits and harms with the patient.[7,8] However, 2 recent reports have suggested that these recommendations carry the risk of overtreatment or undertreatment in many patients with T1 disease.[9,10]

Until recently, most SN-positive patients were offered completion lymph node dissection (CLND), because there was evidence that it could improve prognosis.[11] However, the Multicenter Selective Lymphadenectomy Trial II showed that immediate CLND did not improve survival.[12] As a result, the standard of care for SN-positive patients, including those with thin melanomas, has been changing rapidly, particularly because recent trials[13,14] have suggested that adjuvant therapy may become curative in the near future.

Nevertheless, SNB remains important for prognosis and staging.[7,8] SN status identifies low- and high-risk groups, informing decisions on follow-up frequency in low-risk and adjuvant therapy in high-risk patients. At the same time, it is important to avoid unnecessary SNB in view of its morbidity and cost.

We addressed these issues by analyzing 2 large retrospective cohorts (development and validation cohorts) of patients with T1 disease. We aimed to develop, externally validate, and assess the performance of a nomogram to predict SN status.

PATIENTS AND METHODS

Development Cohort

A total of 4,327 consecutive patients age ≥ 18 years diagnosed with T1 melanoma between 2001 and 2018 at the Istituto Nazionale Tumori (Milan, Italy) were considered for inclusion; 310 (7.2%) had missing data and were excluded; 351 initially treated at other hospitals with a diagnostic excision, found to have ≥ 1 risk factors, and sent to us for definitive treatment were also excluded, because in these cases, histologic material for reassessment was incompletely available. Therefore, 3,666 patients formed the development cohort (Appendix Fig A1, online only). These patients received an initial diagnostic biopsy followed by wide (1-cm) excision; 1,635 underwent SNB because they were considered at high risk of occult nodal metastasis according to then-current guidelines.[11,15,16] Criteria for SNB did not change over the study period in either the development or validation cohort, and SNB was performed after discussing benefits and harms with the patient and obtaining informed consent. In the development cohort, 185 patients eligible for SNB declined the procedure or had comorbidities contraindicating it or were not offered it. SNB was not offered to the remaining 1,846 patients at low risk of occult nodal metastasis according to the guidelines.[11,15,16]

The following data were retrieved from the database prospectively maintained by the institute: age, sex, tumor site, deep margin status at diagnostic biopsy (clear *v* involved), growth phase (radial *v* vertical), Breslow thickness, ulceration (present *v* absent), mitotic rate (mitoses per mm^2), Clark level, tumor-infiltrating lymphocytes (absent, nonbrisk, or brisk), lymphovascular invasion (presence *v* absence of melanoma cells in lymphatic or blood vessels), and regression (absent, partial [< 75% of entire primary], or extensive [≥ 75%]).[17] All slides were reviewed by pathologists according to a common protocol,[17] with diagnosis and staging revised according to the AJCC 2017 criteria.[6] The study was approved by the ethics committee of the Istituto Nazionale Tumori.

Validation Cohort

A total of 5,188 consecutive patients age ≥ 18 years diagnosed with T1 melanoma from 2001 to 2018 were considered; 449 (8.7%) had missing data and were excluded; 512 initially treated at other hospitals with a diagnostic excision were also excluded for incomplete availability of histologic material for reassessment, leaving 4,227 to form the validation cohort (Appendix Fig A1). These patients were treated at the Regional Cancer Center (Stockholm, Sweden; n = 672, 15.9%); University of Leeds, Queen Mary University of London, or Royal Marsden National Health Service Trust (London, United Kingdom; n = 623; 14.7%); Istituto Oncologico Svizzera Italiana (Bellinzona, Switzerland; n = 16, 0.4%); University Hospital of Heraklion (Heraklion, Greece; n = 346, 8.2%); and University Hospitals of Brescia, Florence, Genoa, Modena, Pavia, Reggio Emilia, or Turin (Italy; n = 2,570; 60.8%).

Validation cohort patients were treated according to the protocol applied to the development cohort. Of the 4,227 patients, 1,767 underwent SNB. Two hundred forty-nine at high risk of SN involvement according to then-current guidelines[11,15,16] were not offered SNB or were offered it but declined or had contraindicating comorbidities. SNB was not offered to the other 2,211 patients, because they were at low risk of SN involvement.[11,15,16] There were too many cases for central histopathologic revision to be feasible, but all slides were reviewed at each center according to the criteria used for the development cohort.[17] Ethics committees at all the hospitals approved the study.

Statistical Methods

The Wilcoxon-Mann-Whitney test or Fisher's exact test was used to assess differences in the distribution of variables within the development cohort and between the development and validation cohorts.

Details of the methods used to develop and test the nomogram to predict SN positivity are provided in the Data Supplement (online only). Briefly, a random forest procedure[18] was applied to select development cohort variables for inclusion in a multiple binary logistic model to estimate the probability of SN positivity[19]; the nomogram

TABLE 1. Clinicopathologic Characteristics of Development and Validation Cohort Patients Undergoing SNB

Characteristic	No. (%)		P^a
	Development Cohort (n = 1,635)	Validation Cohort (n = 1,767)	
Sex			.8937
Female	778 (47.6)	852 (48.2)	
Male	857 (52.4)	915 (51.8)	
Age, years			.8419
Median	51	53	
Range	18-80	18-81	
IQR	41-57	43-59	
< 50	796 (48.7)	838 (47.4)	
≥ 50	839 (51.3)	929 (52.6)	
Site			.0036
Head and neck	304 (18.6)	249 (14.1)	
Trunk	580 (35.5)	684 (38.7)	
Upper or lower limbs	751 (45.9)	834 (47.2)	
Deep margin status			.8257
Clear	1,517 (92.8)	1,610 (91.1)	
Involved	118 (7.2)	157 (8.9)	
Growth phase			.7322
Radial	348 (21.3)	327 (18.5)	
Vertical	1,287 (78.7)	1,440 (81.5)	
Breslow thickness, mm			< .0001
Median	0.8	0.9	
Range	0.1-1	0.1-1	
IQR	0.7-0.8	0.8-0.9	
≥ 0.8	1,123 (68.7)	1,327 (75.1)	
< 0.8	512 (31.3)	440 (24.9)	
Mitoses per mm^2			.7841
≤ 1	1,244 (76.1)	1,382 (78.2)	
> 1	391 (23.9)	385 (21.8)	
Ulceration			.8652
Absent	1,547 (94.6)	1,687 (95.5)	
Present	88 (5.4)	80 (4.5)	
LVI			.9463
Absent	1,614 (98.7)	1,749 (99.0)	
Present	21 (1.3)	18 (1.0)	
Clark level			< .0001
< IV	690 (42.2)	846 (47.9)	
≥ IV	945 (57.8)	921 (52.1)	
TILs			< .0001
Absent	530 (32.4)	485 (27.4)	
Nonbrisk	739 (45.2)	777 (44.0)	
Brisk	366 (22.4)	505 (28.6)	

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TABLE 1. Clinicopathologic Characteristics of Development and Validation Cohort Patients Undergoing SNB (continued)

Characteristic	No. (%) Development Cohort (n = 1,635)	Validation Cohort (n = 1,767)	P[a]
Regression, %			< .0001
Absent	1,203 (73.6)	1,396 (79.0)	
Partial (< 75)	260 (15.9)	226 (12.8)	
Extensive (≥ 75)	172 (10.5)	145 (8.2)	
SN status			.8134
Negative	1,527 (93.4)	1,673 (94.7)	
Positive	108 (6.6)	94 (5.3)	
CLND			.0024
Performed	93 (86.1)	76 (80.9)	
Not performed	15 (13.9)	18 (19.1)	

Abbreviations: CLND, completion lymph node dissection; IQR, interquartile range; LVI, lymphovascular invasion; SN, sentinel node; SNB, sentinel node biopsy; TIL, tumor-infiltrating lymphocyte.

[a]Wilcoxon-Mann-Whitney (age, Breslow thickness, and mitoses; all continuous) or Fisher's exact test (other categorical variables).

was elaborated from this model. Nomogram performance was assessed in the development cohort by a calibration plot as indicator of internal calibration, the Hosmer-Lemeshow test to evaluate goodness of fit, and Harrell's C statistic as a measure of discriminative ability.[20] Nomogram performance was assessed in the validation cohort using the same methods as the development cohort, overall and in each country. The 16 patients from Bellinzona (Italian-speaking Switzerland) were grouped with Italian patients.

Decision curve analyses were then applied to the development cohort to assess nomogram performance in comparison with other methods of selecting patients for SNB.[21] The analyses were performed with SAS (version 9.2)[22] and R software.[23]

RESULTS

Characteristics of Development and Validation Cohorts

The characteristics of patients undergoing SNB in the development and validation cohorts are listed in Table 1. The cohorts were similar in sex ratio, age, deep margin status, growth phase, mitotic rate, ulceration, lymphovascular invasion, and SN positivity (n = 108; 6.6% *v* n = 94; 5.3%). Site of primary, thickness, Clark level, tumor-infiltrating lymphocytes, regression, and number of patients undergoing CLND differed.

Median follow-up in the development cohort was 114 months (interquartile range [IQR], 90-148 months); 10-year overall survival (OS) was 89.5% (95% CI, 87.5% to 91.2%). Median follow-up in the validation cohort was 108 months (IQR, 84-139 months); 10-year OS was 90% (95% CI, 88.1% to 92.3%).

Appendix Table A1 (online only) lists the characteristics of development and validation cohort patients not undergoing SNB. Sex ratio, age, deep margin status, growth phase, thickness, ulceration, lymphovascular invasion, and tumor-infiltrating lymphocytes were similar in the 2 cohorts. Median follow-up in the no-SNB development cohort was 110 months (IQR, 85-138 months); 10-year OS was 97.4% (95% CI, 95.5% to 99.4%). Median follow-up in the no-SNB validation cohort was 106 months (IQR, 83-136 months); 10-year OS 97.8% (95% CI, 95.8% to 99.6%). During follow-up, 16 patients (0.8%) in the no-SNB development cohort and 17 (0.7%) in the no-SNB validation cohort developed regional node metastases.

Table 2 summarizes univariable analyses of SN status in relation to characteristics in development cohort patients undergoing SNB. Young age, site of primary on head or neck, vertical growth phase, Breslow thickness ≥ 0.8 mm, mitotic rate > 1, ulceration, lymphovascular invasion, Clark level ≥ IV, and extensive regression were significantly associated with SN positivity. Univariable analyses of SN status in relation to characteristics of validation cohort patients undergoing SNB are summarized in Appendix Table A2 (online only).

Factors Predicting SN Status

Random forest selection showed that 6 variables were significant predictors of SN status (Table 3): age (P = .0092), Breslow thickness (P = .0065), mitotic rate (P = .0038), ulceration (P = .0054), lymphovascular invasion (P = .0089), and regression (P = .0079).

The 6 factors found significant with the random forest procedure were included in the binary logistic model used to construct the nomogram; all factors were significant predictors of SN status in the logistic model (Fig 1). Nomogram weightings for each factor (Appendix Table A3, online only) were derived from the β coefficients. Factors associated with SN positivity contributed points, so

TABLE 2. Univariable Analysis of SN Status in Relation to Clinicopathologic Characteristics in Development Cohort Patients Undergoing SNB

Characteristic	SN Status			All Patients (N = 1,635)	
	No. (%) Negative (n = 1,527)	No. (%) Positive (n = 108)	P[a]	No. (%)	SN Positive, %
Sex			.9714		
Female	727 (47.6)	51 (47.2)		778 (47.6)	6.6
Male	800 (52.4)	57 (52.8)		857 (52.4)	6.7
Age, years			.0018		
Median	51	47		51	
Range	18-80	18-71		18-80	
IQR	41-57	37-51		41-57	
< 50	738 (48.3)	58 (53.7)		796 (48.7)	7.3
≥ 50	789 (51.7)	50 (46.3)		839 (51.3)	6.0
Site			.0034		
Head and neck	279 (18.3)	25 (23.1)		304 (18.6)	8.2
Trunk	546 (35.7)	34 (31.5)		580 (35.5)	5.9
Upper or lower limbs	702 (46.0)	49 (45.4)		751 (45.9)	6.5
Deep margin status			.5430		
Clear	1,420 (93.0)	97 (89.8)		1,517 (92.8)	6.4
Involved	107 (7.0)	11 (10.2)		118 (7.2)	9.3
Growth phase			< .0001		
Radial	340 (22.3)	8 (7.4)		348 (21.3)	2.3
Vertical	1,187 (77.7)	100 (92.6)		1,287 (78.7)	7.8
Breslow thickness, mm			< .0001		
Median	0.8	0.9		0.8	
Range	0.1-1	0.1-1		0.1-1	
IQR	0.7-0.8	0.8-0.9		0.7-0.8	
≥ 0.8	1,034 (67.7)	89 (82.4)		1,123 (68.7)	7.9
< 0.8	493 (32.3)	19 (17.6)		512 (31.3)	3.7
Mitoses per mm^2			< .0001		
≤ 1	1,168 (76.5)	76 (70.4)		1,244 (76.1)	6.1
> 1	359 (23.5)	32 (29.6)		391 (23.9)	8.2
Ulceration			< .0001		
Absent	1,449 (94.9)	98 (90.7)		1,547 (94.6)	6.3
Present	78 (5.1)	10 (9.3)		88 (5.4)	11.4
LVI			< .0001		
Absent	1,508 (98.8)	106 (98.1)		1,614 (98.7)	6.6
Present	19 (1.2)	2 (1.9)		21 (1.3)	9.5
Clark level			< .0001		
< IV	651 (42.6)	39 (36.1)		690 (42.2)	5.7
≥ IV	876 (57.4)	69 (63.9)		945 (57.8)	7.3
TILs			.8217		
Absent	496 (32.5)	34 (31.5)		530 (32.4)	6.4
Nonbrisk	691 (45.2)	48 (44.4)		739 (45.2)	6.5
Brisk	340 (22.3)	26 (24.1)		366 (22.4)	7.1

(continued on following page)

TABLE 2. Univariable Analysis of SN Status in Relation to Clinicopathologic Characteristics in Development Cohort Patients Undergoing SNB (continued)

Characteristic	SN Status			All Patients (N = 1,635)	
	No. (%) Negative (n = 1,527)	No. (%) Positive (n = 108)	P[a]	No. (%)	SN Positive, %
Regression			< .0001		
Absent	1,126 (73.8)	77 (71.3)		1,203 (73.6)	6.4
Partial (< 75)	246 (16.1)	14 (13.0)		260 (15.9)	5.4
Extensive (≥ 75)	155 (10.1)	17 (15.7)		172 (10.5)	9.9

Abbreviations: IQR, interquartile range; LVI, lymphovascular invasion; SN, sentinel node; SNB, sentinel node biopsy; TIL, tumor-infiltrating lymphocyte.

[a]Wilcoxon-Mann-Whitney (age, Breslow thickness, and mitoses; continuous variables) or Fisher's exact test (other categorical variables).

increasing total points were associated with an increasingly greater probability of a positive SN. A detailed description of nomogram use is provided in the legend of Figure 1.

The nomogram calibration plot (Appendix Fig A2A, online only) indicates that the nomogram was well calibrated, with mean predicted probabilities for each subgroup close to observed probabilities. This is further supported by a *P* value of .806 for the Hosmer-Lemeshow test, indicating no reason to reject the null hypothesis of no difference between predicted and observed SN positivity probabilities in each subgroup.

A C index of 95.8% was obtained. This high value indicates that the nomogram has excellent discriminative ability with respect to the C indices of the univariable models incorporating each of the individual variables used to construct the nomogram (mitotic rate > 1 *v* ≤ 1/mm^2, C index of 85.6%; presence of ulceration *v* absence, C index of 83.9%; extensive regression *v* no regression, C index of 78.7%; Breslow thickness ≥ 0.8 *v* < 0.8 mm, C index of 83.2%; presence of lymphovascular invasion *v* absence, C index of 74.7%; and age < 50 *v* ≥ 50 years, C index of 73.1%).

TABLE 3. Results of Random Forest Variable Selection Procedure

Variable	Unadjusted P[a]	FDR-Adjusted P[b]
Sex	.7905	.8412
Age	.0076	.0092
Site	.0565	.0637
Deep margin status	.6812	.7653
Growth phase	.0508	.0641
Breslow thickness	.0053	.0065
Mitotic rate	.0026	.0038
Ulceration	.0042	.0054
LVI	.0074	.0089
Clark level	.0642	.0771
TILs	.8125	.8917
Regression	.0068	.0079

Abbreviations: FDR, false discovery rate; LVI, lymphovascular invasion; TIL, tumor-infiltrating lymphocyte.

[a]Permutation test *P* value.

[b]FDR-adjusted permutation test *P* value.

The nomogram was also well calibrated in the validation cohort (Appendix Fig A2B), with a *P* value of .827 for the Hosmer-Lemeshow test and a C index of 96.5%, again indicating excellent discriminative ability. Similar results were obtained for all countries assessed separately (data not shown).

The results of decision curve analyses to compare the performance of the nomogram (nomogram model) with the performance of univariable models representing each of the variables selected by the random forest procedure are shown in Figure 2. Figure 2A shows that performing an SNB based on the indications of the nomogram has greater net benefit than performing biopsy in all patients with at least 1 unfavorable variable as well as adhering to policies based on each of the 6 individual variables over all threshold probabilities. This finding is supported by the C indices of the models of the individual variables, all of which were lower than the C index of the nomogram. Figure 2B shows net reduction of SNBs in relation to threshold probability and indicates that decisions to perform SNB based on the nomogram would reduce the number of unnecessary SNBs compared with decisions based on each of the 6 individual variables.

The results of decision curve analyses to compare nomogram performance (nomogram model) with models derived from SNB guidelines[7,8] are shown in Figure 3. For ASCO/SSO guidelines,[7] the first model was univariable with a single dichotomous covariable to compare high-risk (thickness ≥ 0.8 mm and presence of ulceration) with low-risk patients. The second model was multivariable and included thickness (< 0.8 *v* ≥ 0.8 mm) and ulceration (absent *v* present).

For NCCN guidelines,[8] we used 3 models. The first 2 were univariable with a single dichotomous covariable to compare high-risk with low-risk patients. In the first univariable

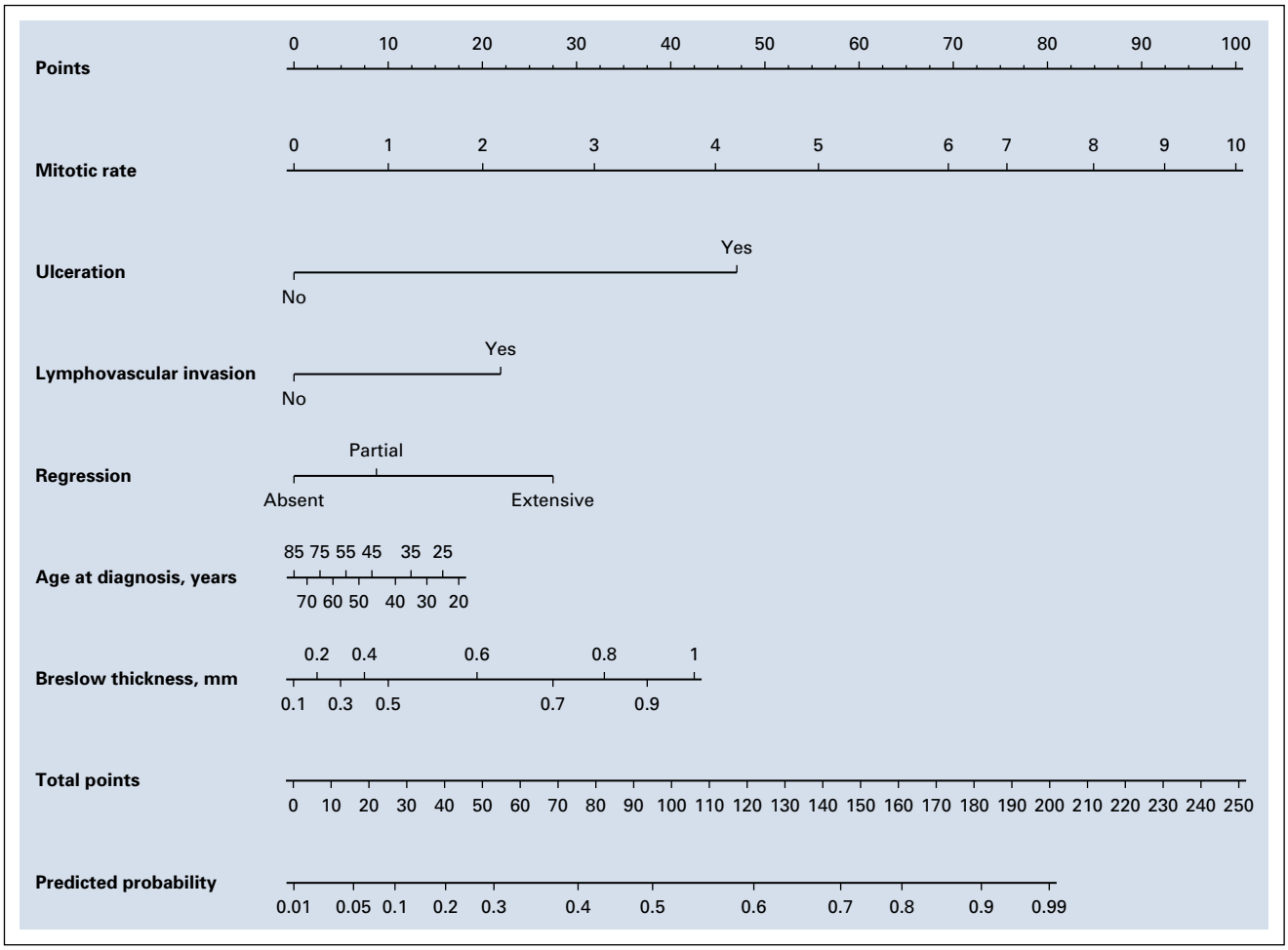

FIG 1. Nomogram to predict sentinel node (SN) positivity in thin cutaneous melanoma. To estimate the probability of SN positivity for a given patient, locate the number of mitoses per mm^2 and draw a line straight up to the Points axis to determine the score associated with that number. Repeat the process for ulceration, lymphovascular invasion, regression, age, and Breslow thickness; sum the scores and locate this sum on the Total Points axis. Then, draw a vertical line down to the Probability axis and read off the probability.

model (with age; Figs 3C and 3D), high-risk patients were those, irrespective of Breslow thickness, with at least 1 of the following: ulceration, mitotic rate ≥ 2 in patients age < 40 years, and lymphovascular invasion. In the second univariable model (without age; Figs 3C and 3D), age was not included (young age is not clearly defined in NCCN guidelines). In both univariable models, the low-risk group was composed of patients with thickness < 0.8 mm, no ulceration, no lymphovascular invasion, and mitotic rate < 2. The third model was multivariable and included Breslow thickness, ulceration, mitotic rate, lymphovascular invasion, and age. The nomogram performed better than all guideline models both for net benefit (Figs 3A and 3C) and reduction in SNBs (Figs 3B and 3D) at all threshold probabilities.

DISCUSSION

Our nomogram proved well calibrated in both cohorts, indicating excellent discriminative ability and suggesting general applicability. Decision curve analyses showed that the nomogram had greater net benefit and was able to reduce the number of unnecessary SNBs compared with use of current guidelines to select patients for SNB at all threshold probabilities. The method used to develop the nomogram adhered essentially to all AJCC criteria for model acceptability, except that SNB status rather than survival was the end point.[24]

In 2005, Wong et al[25] published a nomogram to predict SN status and select patients for SNB. The training set consisted of 979 melanomas, 19% of which were thin. However, it examined only a limited number of clinicopathologic characteristics and was not specifically designed for T1 melanomas.

In 2010, Faries et al[26] developed a scoring system to predict nodal recurrence by retrospective analysis of 1,732 T1 melanomas on which wide local excision alone was performed. Sex, age, and Breslow thickness were included as significant predictors of nodal recurrence; however, mitotic

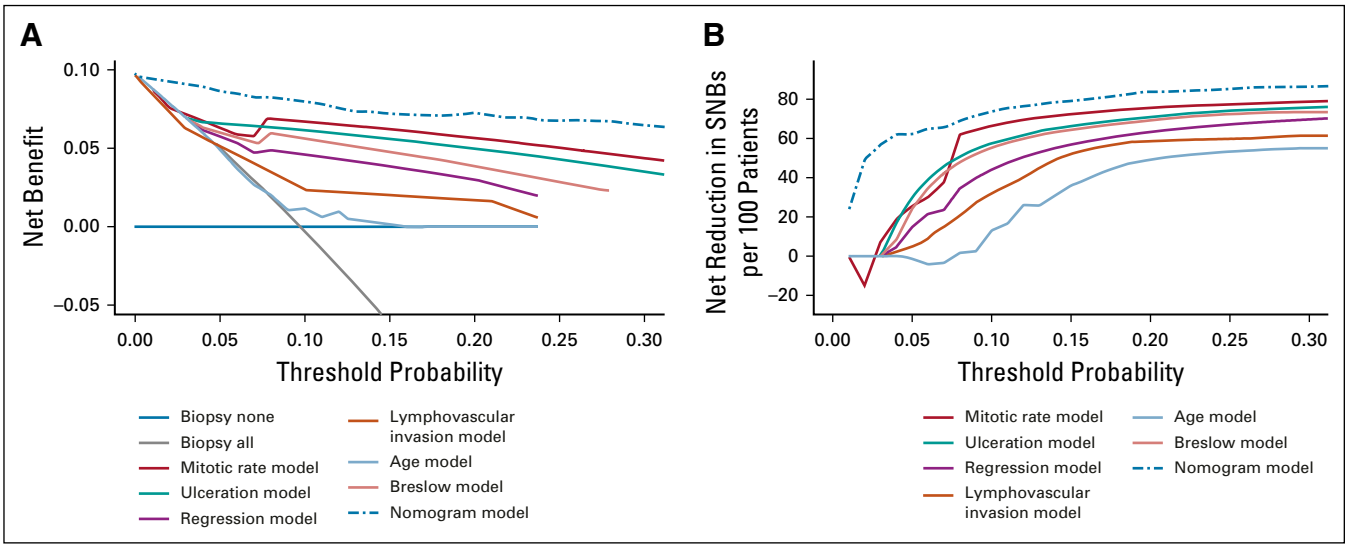

FIG 2. Results of decision curve analysis. Decision curve analysis was performed to compare the policy of not performing sentinel node biopsy (SNB) for any patient in the cohort (biopsy none) with other policies: performing SNB for all, performing SNB based on the nomogram-predicted probability, and performing SNB based on the probability predicted by each of the 6 univariable logistic models that modeled 1 of the nomogram variables. (A) Net benefit in relation to threshold probability. (B) Net reduction of SNBs in relation to threshold probability.

rate, lymphovascular invasion, and regression could not be investigated, which may limit the generalizability of the system.

Two recent studies[9,10] indicate that performing SNB based on T1a versus T1b status is problematic. Egger et al[9] showed that not all patients with nonulcerated T1b melanomas should undergo SNB, because age and mitotic rate can identify patients with a $< 5\%$ risk of a positive SN, in whom SNB can reasonably be omitted. Piazzalunga et al[10] found that, despite a reduction in the proportion of patients with a positive SN in the newly defined pT1a category compared with the old pT1a, 10.71% of those with pT1a disease had a positive SN. These studies indicate that performing SNB based on T1a versus T1b status risks overtreatment or undertreatment in a considerable proportion of patients. The NCCN guidelines[8] recommended that SNB be considered in T1a melanomas when deep margin status is uncertain, when mitotic rate $\geq 2/mm^2$ (particularly in young patients), or when lymphovascular invasion is present. However, these guidelines do not systematically consider all variables (particularly tumor regression) that may determine whether a T1a case is likely to be SN positive.

The current ASCO/SSO guidelines emphasize the importance of an individualized approach to SNB, suggesting that all clinicopathologic risk factors should be assessed in prognostic models so as to optimize risk prediction for individual patients.[7] In this context, our nomogram provides an important additional indication as to whether SNB is advisable.

As regards the variables included in our nomogram, all except regression are considered to affect SN positivity in current guidelines.[7,8] However, extensive regression emerged as an important predictor of SN positivity in our nomogram, as indicated by the length of the axis representing this variable (Fig 1). In their retrospective analysis of 287 melanomas ≤ 1.5 mm thick, Massi et al[27] found that only the presence of peritumoral or intratumoral inflammatory infiltrate and the combined variable of tumor thickness and regression were independent predictors of metastases; the authors suggested that regression probably masked thickness to a greater extent in thin lesions. This hypothesis is supported by data from the College of American Pathologists indicating that regression $> 75\%$ has a negative impact on prognosis.[17] Nevertheless, the findings of a review that analyzed the prognostic role of regression were conflicting, perhaps in part because of the use of varying criteria to define regression.[28]

A strength of our nomogram is that it was built from histopathologic variables widely used in melanoma staging. It can therefore be used in resource-limited settings, where clinicians and pathologists are still likely to have all the data required to use it effectively. Another strength is that the nomogram was validated on a large, independent, heterogeneous cohort of patients from wide-ranging parts of Europe, and it is thus likely to be useful in a wide variety of clinical settings. Furthermore, decision curve analyses showed the nomogram had greater net benefit and was able to reduce the number of unnecessary SNBs compared with use of current guidelines. In view of the inability of T1a versus T1b status to define regional node status,[9,10] our nomogram presents as an important additional source of information to guide the decision as to whether to perform SNB. We recommend its use in all cases where the multidisciplinary team is considering proposing SNB to the

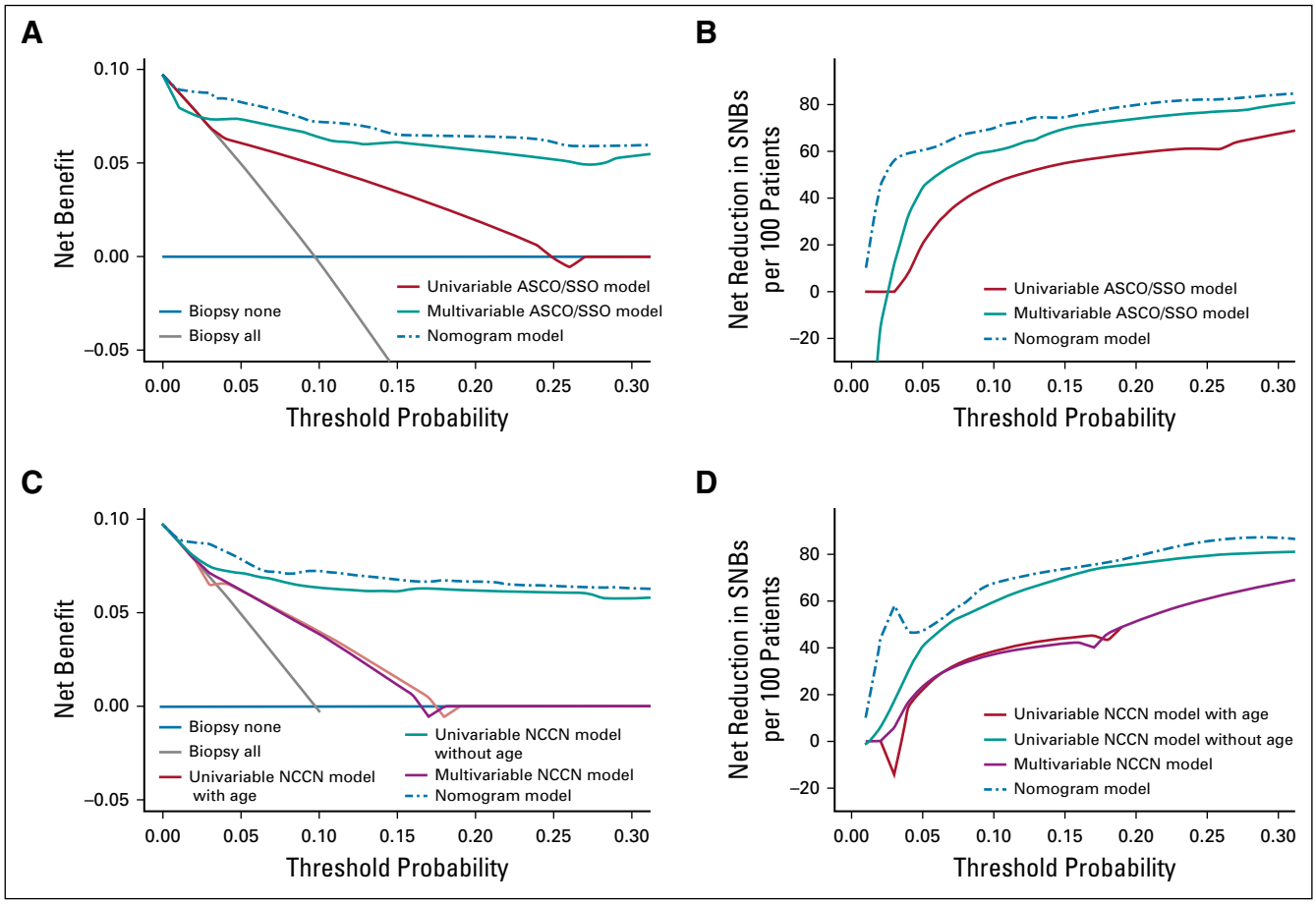

FIG 3. Results of decision curve analysis. Decision curve analysis was performed to compare the policy of not performing sentinel node biopsy (SNB; biopsy none) with other policies: performing SNB for all, performing SNB based on nomogram-predicted probability, and performing SNB based on probabilities of SNB involvement predicted by univariable and multivariable logistic models based on American Society of Clinical Oncology (ASCO)/Society of Surgical Oncology (SSO) and National Comprehensive Cancer Network (NCCN) guidelines.[7,8] (A, C) Net benefit in relation to threshold probability. (B, D) Net reduction of SNBs in relation to threshold probability.

patient; if the nomogram indicates a high probability of SN involvement, this supports proposing SNB.

A limitation of our study is that genetic signatures were not available for much of the study period and could not be investigated as predictors of SN status.[29] If prospective studies confirm the predictive value of genetic signatures, they may be used in next-generation nomograms. It is also likely that biomarkers to better select SN-positive patients will become available in the future to improve the selection of patients for SNB and perhaps render our nomogram obsolete. In the meantime, we propose ongoing assessment of the validity of our nomogram.

Another limitation is that 7.2% and 8.6% of patients, respectively, were excluded from the development and validation cohorts because of missing data; this is a possible source of bias. Furthermore, large proportions of the development and validation cohorts did not undergo SNB because of low risk, comorbidities, or refusal, and their SNB status is unknown. Regional failure rates in these patient cases were reassuringly low (0.8% and 0.7%, respectively), indicating that any bias resulting from the impossibility of including them in the analyses is likely to be negligible.

To conclude, in the context of rapidly evolving surgical and systemic approaches to melanoma, our nomogram is able to refine the prediction of SN status in T1 melanomas and indicates more accurately than current guidelines whether SNB should be performed. We recommend its use in all patient cases where SNB is being considered.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Factors Affecting Sentinel Node Metastasis in Thin (T1) Cutaneous Melanomas: Development and External Validation of a Predictive Nomogram

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APPENDIX

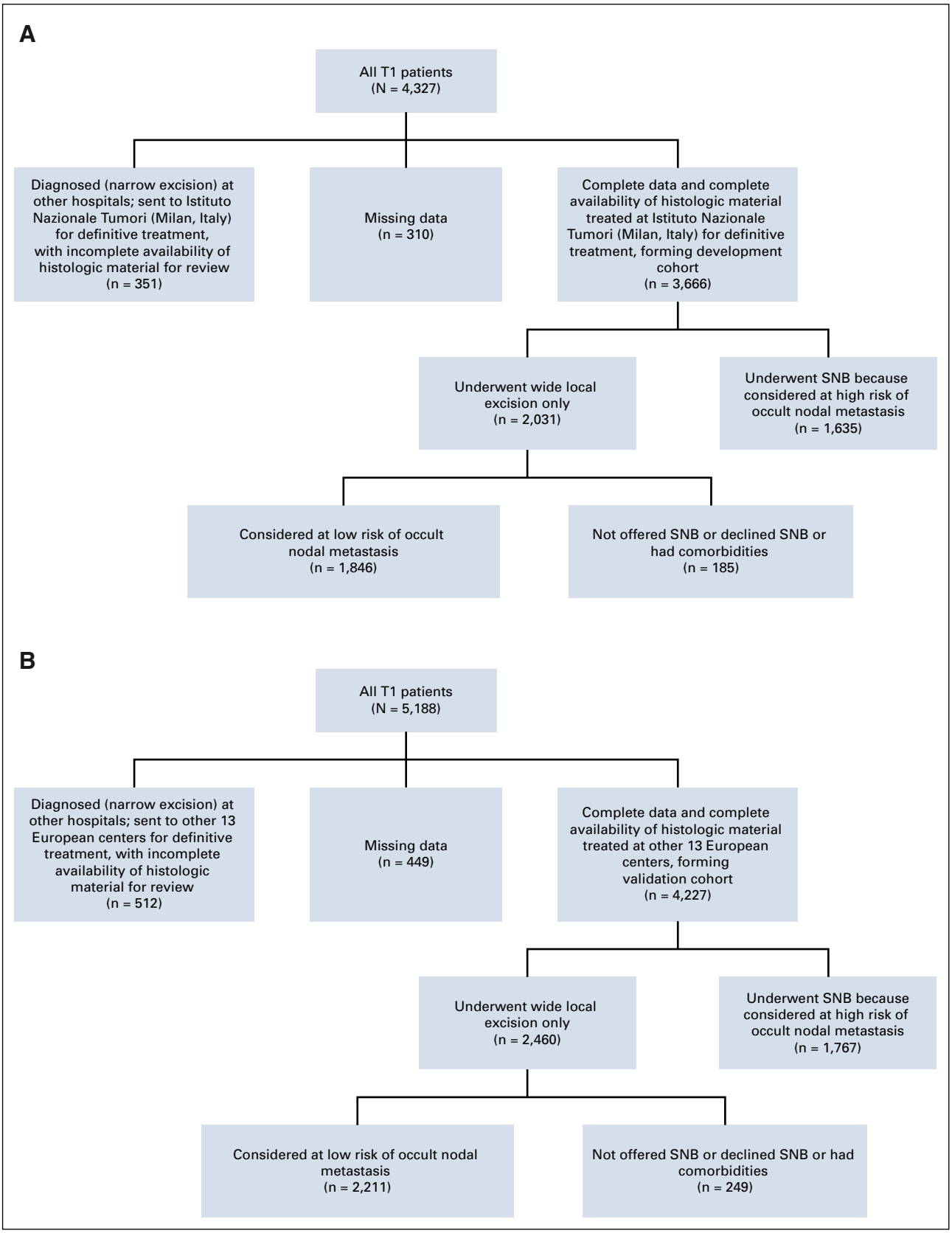

FIG A1. CONSORT diagram showing (A) development and (B) validation cohort (2001-2018) patients considered, eliminated, and selected for inclusion in the study.

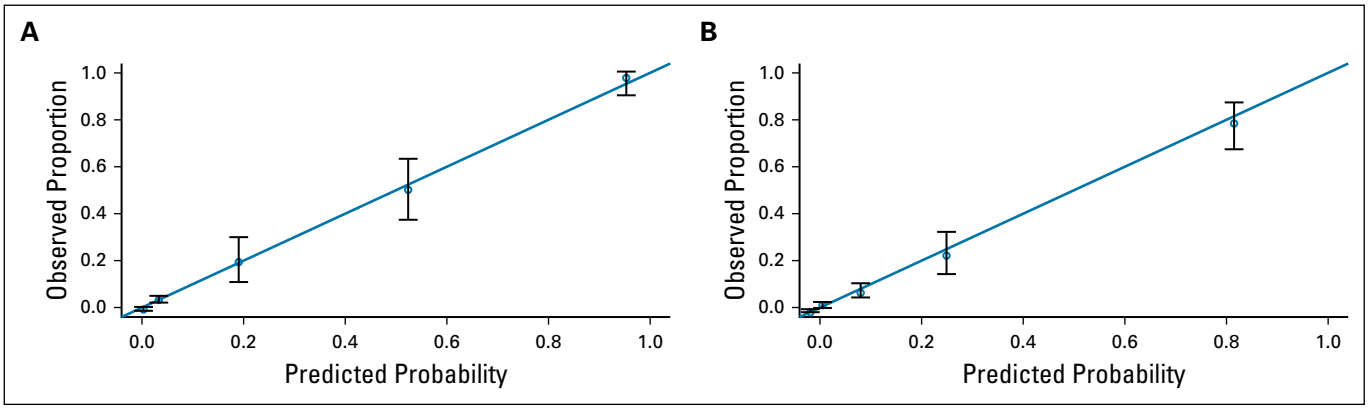

FIG A2. Nomogram-predicted probabilities were stratified into subgroups as described in the text. For each subgroup, the probability (observed proportion of sentinel node–positive patient cases/total patient cases in each subgroup) was plotted (*y*-axis) against the average predicted probability (*x*-axis). The error bars are Clopper-Pearson 95% CIs. The solid diagonal line is the reference line, indicating the probability of an ideal nomogram.

TABLE A1. Clinicopathologic Characteristics of Development and Validation Cohort Patients Not Undergoing SNB

Characteristic	No. (%)		P[a]
	Development Cohort (n = 2,031)	Validation Cohort (n = 2,460)	
Sex			.8824
Female	959 (47.2)	1,181 (48.0)	
Male	1,072 (52.8)	1,279 (52.0)	
Age, years			.8528
Median	52	54	
Range	19-81	18-79	
IQR	42-58	44-60	
< 50	967 (47.6)	1,141 (46.4)	
≥ 50	1,064 (52.4)	1,319 (53.6)	
Site			.0018
Head and neck	299 (14.7)	275 (11.2)	
Trunk	881 (43.4)	1,033 (42.0)	
Upper or lower limbs	851 (41.9)	1,152 (46.8)	
Deep margin status			.9215
Clear	1,964 (96.7)	2,362 (96.0)	
Involved	67 (3.3)	98 (4.0)	
Growth phase			.7931
Radial	784 (38.6)	893 (36.3)	
Vertical	1,247 (61.4)	1,567 (63.7)	
Breslow thickness, mm			.9227
Median	0.5	0.6	
Range	0.1-1	0.1-1	
IQR	0.5-0.6	0.6-0.7	
< 0.8	1,867 (91.9)	2,273 (92.4)	
≥ 0.8	164 (8.1)	187 (7.6)	
Mitoses per mm^2			.0042
≤ 1	1,824 (89.8)	2,320 (94.3)	
> 1	207 (10.2)	140 (5.7)	
Ulceration			.9246
Absent	2,007 (98.8)	2,440 (99.2)	
Present	24 (1.2)	20 (0.8)	
LVI			.9548
Absent	2,021 (99.5)	2,453 (99.7)	
Present	10 (0.5)	7 (0.3)	
Clark level			.0038
< IV	1,765 (86.9)	2,253 (91.6)	
≥ IV	266 (13.1)	207 (8.4)	
TILs			.7639
Absent	1,505 (74.1)	1,887 (76.7)	
Nonbrisk	414 (20.4)	455 (18.5)	
Brisk	112 (5.5)	118 (4.8)	

(continued on following page)

TABLE A1. Clinicopathologic Characteristics of Development and Validation Cohort Patients Not Undergoing SNB (continued)

Characteristic	No. (%)		
	Development Cohort (n = 2,031)	Validation Cohort (n = 2,460)	*P*[a]
Regression			< .0001
Absent	1,708 (84.1)	2,207 (89.7)	
Partial (< 75)	272 (13.4)	224 (9.1)	
Extensive (≥ 75)	51 (2.5)	29 (1.2)	

Abbreviations: IQR, interquartile range; LVI, lymphovascular invasion; SNB, sentinel node biopsy; TIL, tumor-infiltrating lymphocyte.

[a]Wilcoxon-Mann-Whitney (age, Breslow thickness, and mitoses; all continuous) or Fisher's exact test (other categorical variables).

TABLE A2. Univariable Analysis of SN Status in Relation to Clinicopathologic Characteristics in Validation Cohort Patients Undergoing SNB

	SN Status			All Patients (N = 1,767)	
Characteristic	No. (%) Negative (n = 1,673)	No. (%) Positive (n = 94)	P[a]	No. (%)	SN Positive, %
Sex			.8163		
Female	808 (48.3)	44 (46.8)		852 (48.2)	5.2
Male	865 (51.7)	50 (53.2)		915 (51.8)	5.5
Age, years			.0134		
Median	53	49		53	
Range	18-81	18-73		18-81	
IQR	43-59	39-54		43-59	
< 50	789 (47.2)	49 (52.1)		838 (47.4)	5.8
≥ 50	884 (52.8)	45 (47.9)		929 (52.6)	4.8
Site			< .0001		
Head and neck	230 (13.8)	19 (20.2)		249 (14.1)	7.6
Trunk	651 (38.9)	33 (35.1)		684 (38.7)	4.8
Upper or lower limbs	792 (47.3)	42 (44.7)		834 (47.2)	5.0
Deep margin status			.8478		
Clear	1,525 (91.2)	85 (90.4)		1,610 (91.1)	5.3
Involved	148 (8.8)	9 (9.6)		157 (8.9)	5.7
Growth phase			< .0001		
Radial	321 (19.2)	6 (6.4)		327 (18.5)	1.8
Vertical	1,352 (80.8)	88 (93.6)		1,440 (81.5)	6.1
Breslow thickness, mm			< .0001		
Median	0.9	1.0		0.9	
Range	0.1-1	0.1-1		0.1-1	
IQR	0.8-0.9	0.9-1.0		0.8-0.9	
≥ 0.8	1,246 (74.5)	81 (86.2)		1,327 (75.1)	6.1
< 0.8	427 (25.5)	13 (13.8)		440 (24.9)	3.0
Mitoses per mm^2			< .0001		
≤ 1	1,314 (78.5)	68 (72.3)		1,382 (78.2)	4.9
> 1	359 (21.5)	26 (27.7)		385 (21.8)	6.8
Ulceration			< .0001		
Absent	1,601 (95.7)	86 (91.5)		1,687 (95.5)	5.1
Present	72 (4.3)	8 (8.5)		80 (4.5)	10.0
LVI			< .0001		
Absent	1,657 (99.0)	92 (97.9)		1,749 (99.0)	5.3
Present	16 (1.0)	2 (2.1)		18 (1.0)	11.1
Clark level			< .0001		
< IV	810 (48.4)	36 (38.3)		846 (47.9)	4.3
≥ IV	863 (51.6)	58 (61.7)		921 (52.1)	6.3
TILs			.7147		
Absent	461 (27.6)	24 (25.5)		485 (27.4)	4.9
Nonbrisk	737 (44.0)	40 (42.6)		777 (44.0)	5.1
Brisk	475 (28.4)	30 (31.9)		505 (28.6)	5.9

(continued on following page)

TABLE A2. Univariable Analysis of SN Status in Relation to Clinicopathologic Characteristics in Validation Cohort Patients Undergoing SNB (continued)

Characteristic	SN Status			All Patients (N = 1,767)	
	No. (%) Negative (n = 1,673)	No. (%) Positive (n = 94)	*P*[a]	No. (%)	SN Positive, %
Regression			< .0001		
Absent	1,324 (79.1)	72 (76.6)		1,396 (79.0)	5.2
Partial (< 75)	217 (13.0)	9 (9.6)		226 (12.8)	4.0
Extensive (≥ 75)	132 (7.9)	13 (13.8)		145 (8.2)	9.0

Abbreviations: IQR, interquartile range; LVI, lymphovascular invasion; SN, sentinel node; SNB, sentinel node biopsy; TIL, tumor-infiltrating lymphocyte.

[a]Wilcoxon-Mann-Whitney (age, Breslow thickness, and mitoses; continuous variables) or Fisher's exact test (other categorical variables).

TABLE A3. Results of Multiple Binary Logistic Model to Predict SN Positivity in Development Cohort

Variable	OR (β coefficient)	95% CI	*P*
Age (< 50 *v* ≥ 50 years)	1.96 (0.673)	0.84 to 3.22	.0632
Breslow thickness (≥ 0.8 *v* < 0.8 mm)	3.68 (1.303)	2.41 to 5.48	< .0001
Mitotic rate (> 1*v* ≤ 1/mm^2)	3.95 (1.374)	2.64 to 5.97	< .0001
Ulceration (present *v* absent)	3.83 (1.343)	2.56 to 5.62	< .0001
Regression			
Partial (< 75) *v* absent	1.34 (0.293)	0.52 to 3.16	.0968
Extensive (≥ 75) *v* absent	3.28 (1.188)	2.02 to 4.64	.0003
LVI (present *v* absent)	2.84 (1.044)	1.56 to 4.58	.0134

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: LVI, lymphovascular invasion; OR, odds ratio; SN, sentinel node.