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ORIGINAL ARTICLE – MELANOMA

# Validation of a Nomogram for Non-sentinel Node Positivity in Melanoma Patients, and Its Clinical Implications: A Brazilian–Dutch Study

**Eduardo Bertolli, MD, PhD[1,2], Viola Franke, MD[2], Vinicius Fernando Calsavara, PhD[3], Mariana Petaccia de Macedo, MD, PhD[4], Clovis Antonio Lopes Pinto, MD, PhD[4], Winan J. van Houdt, MD, PhD[2], Michel W. J. M. Wouters, MD, PhD[2], Joao Pedreira Duprat Neto, MD, PhD[1], and Alexander C. J. van Akkooi, MD, PhD[2]**

[1]Skin Cancer Department, AC Camargo Cancer Center, São Paulo, SP, Brazil; [2]Department of Surgical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [3]Epidemiology and Statistics Department, AC Camargo Cancer Center, São Paulo, SP, Brazil; [4]Department of Pathology, AC Camargo Cancer Center, São Paulo, SP, Brazil

## ABSTRACT

**Background.** Non-sentinel node (NSN) positivity impacts the prognosis of melanoma patients; however, the benefits of completion lymph node dissection in patients with positive sentinel nodes (SNs) are limited.

**Objective.** We aimed to present a predictive nomogram for NSN positivity in melanoma patients with a positive SN biopsy.

**Methods.** This retrospective analysis from patients who underwent SN biopsy in a Brazilian institution from 2000 to 2015 was used for the construction and internal validation of the nomogram. This nomogram was then externally validated in a cohort of Dutch patients.

**Results.** The Brazilian cohort comprised 1213 patients, with a mean follow-up of 5.11 years. Breslow thickness (odds ratio [OR] 1.170, 95% confidence interval [CI] 1.043–1.314]; $p = 0.008$), number of positive SNs (OR 1.092, 95% CI 1.034–1.153; $p = 0.001$), and largest diameter of the metastatic deposit (OR 3.217, 95% CI 1.551–6.674; $p = 0.002$) were statistically significant for NSN positivity. Internal validation was performed using a bootstrapping technique. A good performance was observed (Brier score 0.097) and an excellent power of discrimination was achieved (area under the curve [AUC] 0.822). The nomogram was then applied to the Dutch cohort, and its overall performance (Brier score 0.085), calibration (Hosmer–Lemeshow goodness-of-fit test; $p = 0.198$), and discriminatory power (AUC 0.752, 95% CI 0.615–0.890) were all adequate.

**Conclusions.** We presented a nomogram for assessing NSN probability that should not only be used for surgical considerations but also for risk stratification and clinical decisions. Internal validation has shown that this is an adequate model, while external validation increases the model's reliability and suggests that it can be globally incorporated.

Sentinel node biopsy (SNB) is the most important tool for nodal staging in melanoma patients without clinical disease.[1–4] Patients with a positive sentinel node (SN) are considered as stage III and further treatments should be discussed in this scenario.[4] In the last decades, it was accepted that these patients should undergo immediate completion lymph node dissection (CLND);[5] however, recent prospective, randomized studies, such as the German De-COG SLT trial[6] and the International MSLT-II,[7] have shown no benefits in overall survival (OS), distant metastases-free survival (DMFS), disease-free survival (DFS), recurrence-free survival (RFS), and melanoma-specific survival (MSS) from immediate CLND in comparison with observation, which led to considerations regarding changing practice.[8]



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E. Bertolli, MD, PhD
e-mail: ebertolli@hotmail.com

Nevertheless, these same studies have shown benefits from CLND regarding local control of the affected basin. In addition, some have suggested that there may be a few subgroups, such as those with neck dissection and larger-volume disease, that may have been underrepresented in the trials and may potentially benefit from CLND.[9] Furthermore, with the advent of showing benefit to adjuvant therapies for stage III patients,[10] CLND provides further staging information than SNB alone.

Using mathematical tools, such as nomograms, to identify patients who could benefit from surgery, or at least to stratify high-risk patients, has been a frequent practice for both melanoma and other malignancies such as breast cancer, colon cancer, and sarcomas.[11–18] Although most of the nomograms reported in the literature have been internally validated, external validation with an independent sample is more difficult but is the preferred method and should be utilised whenever possible.[18–21]

In this original research, we aimed to present a predictive nomogram for non-sentinel node (NSN) positivity in melanoma patients with positive SNB based on clinical and pathological characteristics from a Brazilian cohort of patients and externally validated in a Dutch cohort.

## METHODS

Two retrospective cohorts were used. The first analysis was performed using data records from the AC Camargo Cancer Center (ACCCC), Sao Paulo/SP, Brazil, and was used for constructing the nomogram. The external validation was then conducted using data records from the prospectively maintained database at the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, The Netherlands. Both cohorts comprised melanoma patients who underwent SNB from 2000 to 2015.

Single logistic regressions were used to identify variables that were associated with NSN positivity. All variables with a $p$ value $< 0.05$ were included in the multiple logistic regression models using the stepwise forward method for elimination. A $p$ value $< 0.05$ was also adopted as the threshold for retaining variables in the final model that were used in the nomogram. Overall performance, calibration, and the discriminatory power of the final multiple logistic regression model were assessed using the Brier score, the Hosmer–Lemeshow goodness-of-fit test, and the area under the receiver operating characteristic (ROC) curve (AUC), respectively.[22,23]

Internal validation of the multiple logistic regression model was performed via bootstrap analysis since this method has shown better performance than other methods of internal validation.[21,22,24] Performance of the internal validation model was assessed using the Brier score and AUC curve.

For external validation, the cohort from NKI-AVL was used. Comparisons between populations were performed using the Chi square test, Fisher's exact test, and T test. For each patient in the Dutch dataset, the Brazilian probability of NSN positivity was computed. The predictive ability of the nomogram was evaluated by comparing the AUC from both ROC curves and testing for the difference by using the DeLong method.[25] The final model was then compared with other nomograms, which can be found in literature using the Hanley and McNeil method.[26]

## RESULTS

The Brazilian cohort comprised 1213 patients, with a mean follow-up of 5.11 years, while the Dutch cohort comprised 1418 patients, with a mean follow-up of 4.88 years, as shown in Table 1.

It is important to mention two major differences in the routines of the two hospitals. The first relates to mitotic rate, which has been reported as a continuous scale of values at the ACCCC, and as a dichotomous variable at the NKI-AVL, as recommended in the 7th edition of the American Joint Committee on Cancer (AJCC) staging system.[27] Data were collected both ways from Brazilian patients, which led to two statistical models, which will be discussed below.

Second, the ACCCC's routine during the study period was to offer immediate CLND to every patient, whereas at the NKI-AVL, the practice of observation for patients with positive SNB was incorporated earlier, with participation of the institution in clinical trials such as the MSLT-II and EORTC 1208 MINITUB trials.

Regarding melanoma features, some differences were expected, as shown in Table 1. The incidence in the lower limbs was higher in the Brazilian cohort, as was the incidence of acral melanomas. This can be explained by a higher prevalence of Asian and African descendants living in Brazil, whereas more Caucasians live in The Netherlands.[28] In addition, the higher rate of head and neck cutaneous melanomas in the Dutch cohort can be attributable to the NKI-AVL being a national referral center.

Breslow thickness was also statistically different between the two populations; however, if we consider the thresholds for staging purposes, the mean value would be considered T3 in both groups. Ulceration and microsatellitosis, which are also used in the melanoma staging system for primary lesions,[2] were statistically similar between the

**TABLE 1** Clinical and pathological variables of patients who underwent sentinel node biopsy at The Netherlands Cancer Institute-Antoni van Leeuwenhoek and the AC Camargo Cancer Center between 2000 and 2015

| | NKI-AVL | | ACCCC | | *p* value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Sex | | | | | |
| Female | 682 | 48.1 | 603 | 49.7 | 0.183 |
| Male | 736 | 51.9 | 610 | 50.3 | |
| Total | 1418 | | 1213 | | |
| Topography | | | | | |
| Head and neck | 245 | 17.3 | 90 | 7.4 | < 0.0001 |
| Trunk | 551 | 38.9 | 456 | 37.7 | |
| Lower limbs | 194 | 13.7 | 264 | 21.8 | |
| Upper limbs | 428 | 30.2 | 400 | 33.1 | |
| Total | 1418 | | 1210 | | |
| Subtype | | | | | |
| Superficial spreading | 803 | 61.3 | 799 | 70.1 | < 0.0001 |
| Nodular | 394 | 30.1 | 117 | 10.3 | |
| Acral | 41 | 3.1 | 102 | 8.9 | |
| Lentigo maligna melanoma | 46 | 3.5 | 15 | 1.3 | |
| Other subtypes | 27 | 2.1 | 107 | 9.4 | |
| Total | 1311 | | 1140 | | |
| Ulceration | | | | | |
| Absent | 1032 | 74.2 | 845 | 74.2 | 1 |
| Present | 358 | 25.8 | 294 | 25.8 | |
| Total | 1390 | | 1139 | | |
| Regression | | | | | |
| Absent | 765 | 88.5 | 952 | 85.5 | 0.053 |
| Present | 99 | 11.5 | 162 | 14.5 | |
| Total | 864 | | 1114 | | |
| Mitotic rate | | | | | |
| Absent | 82 | 10.6 | 264 | 23.1 | < 0.0001 |
| Present | 690 | 89.4 | 880 | 76.9 | |
| Total | 772 | | 1144 | | |
| Clark | | | | | |
| I | 0 | 0.0 | 12 | 1.1 | < 0.0001 |
| II | 24 | 2.2 | 110 | 9.6 | |
| III | 333 | 30.0 | 629 | 55.1 | |
| IV | 668 | 60.2 | 329 | 28.8 | |
| V | 84 | 7.6 | 62 | 5.4 | |
| Total | 1109 | | 1142 | | |
| Lymphatic invasion | | | | | |
| Absent | 1001 | 96.1 | 1066 | 96.8 | 0.405 |
| Present | 41 | 3.9 | 35 | 3.2 | |
| Total | 1042 | | 1101 | | |
| Microsatellitosis | | | | | |
| Absent | 1081 | 95.8 | 1065 | 97.1 | 0.138 |

**TABLE 1** continued

| | NKI-AVL | | ACCCC | | *p* value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Present | 47 | 4.2 | 32 | 2.9 | |
| Total | 1128 | | 1097 | | |
| BRAF | | | | | |
| Wild-type | 46 | 41.8 | 27 | 45.0 | 0.812 |
| Mutation | 64 | 58.2 | 33 | 55.0 | |
| Total | 110 | | 60 | | |
| NRAS | | | | | |
| Wild-type | 34 | 54.8 | 54 | 90.0 | < 0.0001 |
| Mutation | 28 | 45.2 | 6 | 10.0 | |
| Total | 62 | | 60 | | |
| KIT | | | | | |
| Wild-type | 13 | 81.3 | 37 | 69.8 | 0.459 |
| Mutation | 3 | 18.8 | 16 | 30.2 | |
| Total | 16 | | 53 | | |
| Sentinel node biopsy | | | | | |
| Positive | 326 | 23.0 | 246 | 20.3 | 0.075 |
| Negative | 1092 | 77.0 | 967 | 79.7 | |
| Total | 1418 | | 1213 | | |
| Completion node dissection | | | | | |
| Performed | 204 | 62.6 | 242 | 98.4 | < 0.0001 |
| Not performed | 122 | 37.4 | 4 | 1.6 | |
| Total | 326 | | 246 | | |
| Positive NSN | | | | | |
| No | 177 | 86.8 | 205 | 84.7 | 0.635 |
| Yes | 27 | 13.2 | 37 | 15.3 | |
| Total | 204 | | 242 | | |

| | NKI-AVL | | | ACCCC | | | *p* value |
|---|---|---|---|---|---|---|---|
| | *n* | Median (min–max) | SD | *n* | Median (min–max) | SD | |
| Age, years | 1417 | 54.95 (11–100) | 15.07 | 1213 | 52.47 (5–89) | 15.73 | < 0.0001 |
| Breslow, mm | 1409 | 2.488 (0.2–25) | 2.01 | 1185 | 2.26 (0–29) | 2.57 | 0.014 |
| Number of positive SNs | 326 | 1.39 (1–5) | 0.698 | 244 | 1.21 (1–5) | 0.034 | < 0.0001 |
| Largest diameter | 274 | 2.32 (0.05–30) | 3.73 | 195 | 3.92 (0.05–55) | 8.4 | 0.013 |

*NKI-AVL* Netherlands Cancer Institute-Antoni van Leeuwenhoek, *ACCCC* AC Camargo Cancer Center, *NSN* non-sentinel node, *SD* standard deviation, *min* minimum, *max* maximum, *SNs* sentinel nodes

two populations. There was no difference in regression and lymphatic invasion, which also suggests that the prognosis of patients in the two groups is comparable.

Small samples of patients in both cohorts have been tested for genetic mutations, probably because they had become candidates for targeted therapies. BRAF and KIT status, two genes that have specific inhibitory agents when a mutation is found,[29] were also similar in the two groups. Although NRAS status was different between populations, it is unclear if it reflects genetic differences or is just related to the methodology of the genetic test that has been used. The small number of patients where genetic testing information is available limits any strong conclusions regarding potential similarities or differences between the groups.

After single and multiple logistic regressions, mitotic rate as a continuous variable (odds ratio [OR] 1.056, 95% confidence interval [CI] 1.014–1.100; $p = 0.009$), number of positive SNs (OR 12.243, 95% CI 1.857–80.702; $p = 0.009$), and largest diameter of the metastatic deposit

**TABLE 2** Comparison of the Brazilian/Dutch nomogram with other published models

| Author | NSN-negative patients | NSN-positive patients | % | AUC | *p* value[a] |
|---|---|---|---|---|---|
| Present study | 205 | 37 | 15.3 | 0.75 | |
| Rossi et al.[13] | 909 | 311 | 25.5 | 0.74 | 0.815 |
| Gershenwald et al.[11] | 295 | 48 | 14.0 | 0.65 | 0.125 |
| Murali et al.[12] | 356 | 53 | 13.0 | 0.65 | 0.116 |
| Lee et al.[17] | 145 | 46 | 24.1 | 0.65 | 0.137 |
| Kibrité et al.[14] | 171 | 33 | 16.2 | 0.65 | 0.166 |
| Sabel et al.[15] | 198 | 34 | 14.7 | 0.67 | 0.257 |

*NSN* non-sentinel node, *AUC* area under the curve

[a]Hanley and McNeil method

(OR 1.278, 95% CI 1.114–1.467; $p < 0.0001$) were statistically related to NSN positivity in the Brazilian cohort. The overall performance of this model was adequate (Brier score 0.069), as was its calibration (Hosmer–Lemeshow goodness-of-fit test; $p = 0.267$). In addition, the discriminatory power of the model was considered excellent, with an AUC of 0.863 (95% CI 0.728–0.999).

When analyzed as a dichotomous variable, as undertaken at the NKI-AVL, mitotic rate was no longer statistically significant in the Brazilian cohort. In this second model, Breslow thickness (OR 1.170, 95% CI 1.043–1.314; $p = 0.008$), number of positive SNs (OR 1.092, 95% CI 1.034–1.153; $p = 0.001$), and largest diameter of the metastatic deposit (OR 3.217, 95% CI 1.551–6.674; $p = 0.002$) were statistically significant for NSN positivity. Again, overall performance (Brier score 0.101), calibration (Hosmer–Lemeshow goodness-of-fit test; $p = 0.203$), and discriminatory power (AUC 0.817, 95% CI 0.732–0.901) of this second model were all adequate and were comparable with the first model ($p = 0.436$).

Variables from the second model were then used in the construction of the nomogram (Fig. 1). The first row corresponds to the general score. For each variable on the left, there is a corresponding row on the right that includes the possible values. In each row, after finding the adequate value, a perpendicular line towards the first row should be drawn to identify the value that will be attributed. This should be carried out for the three variables, resulting in a final score. This final score should be placed in the 'Total

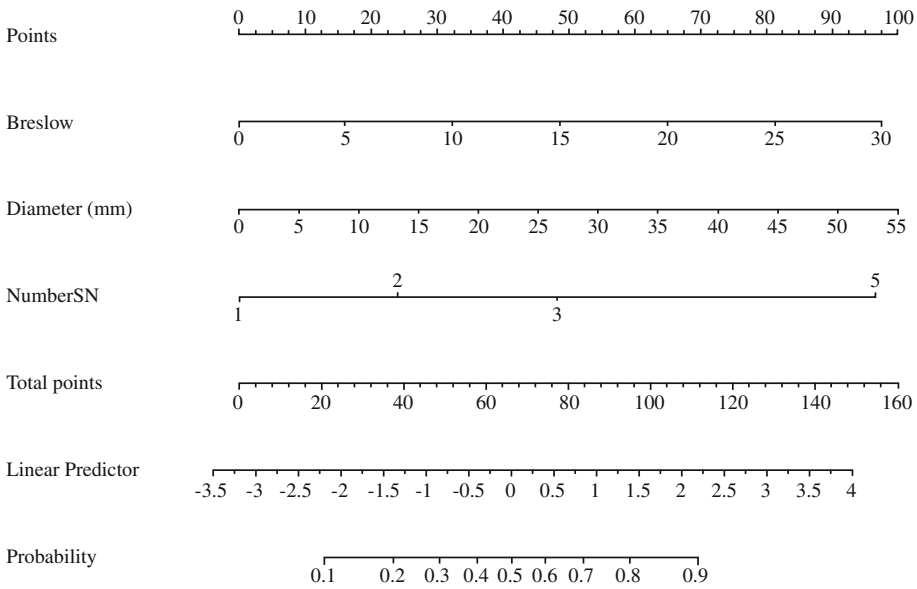


**FIG. 1** Nomogram for non-sentinel node positivity

points' row and then a perpendicular line should be drawn towards the last row, which corresponds to the probability of a positive NSN ("Appendix 1").

A total score of 28.6 points (14.3% probability) should be considered as the threshold value according to the ROC curve, to discriminate between positive and negative when using the nomogram (76.7% sensitivity, 78.8% specificity, and 78.5% accuracy). The negative predictive value (NPV) was 94.9%, and the positive predictive value (PPV) was 39.7%.

For internal validation of both models, 1000 replications were created by bootstrap analysis. A good performance was observed (Brier score 0.063 and 0.097 for the Brazilian and Dutch models, respectively), similar to the final model. In addition, an excellent power of discrimination was again observed (AUC 0.874 and 0.822 for the Dutch and Brazilian models, respectively).

The nomogram was then applied to the Dutch cohort (once it was not possible to use continuous measures for mitotic rate). When applying the model to NKI-AVL patients, its overall performance (Brier score 0.085), calibration (Hosmer–Lemeshow goodness-of-fit test; $p = 0.198$), and discriminatory power (AUC 0.752, 95% CI 0.615–0.890) were all adequate. Comparing AUC from the curves, they were also similar ($p = 0.437$) (Fig. 2a).

Calibration of the nomogram was evaluated graphically (Fig. 2b) by grouping patients according to their predicted probabilities in the nomogram, and plotting the actual proportions of patients with NSN positivity for each group. A dashed 45-degree line indicated where an ideal model, one that predicts perfectly, would lie. Our final model, after external validation, was then compared with other models presented in the literature (Table 2).

## DISCUSSION

Nomograms are graphic representations that allow fast computation of a specific or complex function. They have been widely adopted in oncology as they can be used during clinical encounters, giving both clinicians and patients more precise answers to their questions and better ability to make important decisions about their care.[19,20,30]

Even before the De-COG SLT and MSLT-II trials, some mathematical models were reported as predictors of NSN positivity after a positive SNB.[11,12,14–16] Some of these nomograms, such as the 'N-Snore', have also been validated in external and independent cohorts, but with some changes compared with the original study.[31,32]

The performance of a nomogram during the validation process is expected to be worse, or at least different, than the original.[18, 33] Most times, this happens due to differences in the populations. The previously cited validations of the N-Snore, for instance, have found clinical and pathological differences that should be related to NSN positivity, but this does not mean that the nomogram was invalid.

The main limitation of our nomogram was likely the low number of patients with positive NSNs in both cohorts, in contrast to an elevated number of negative cases, which reflects an elevated NPV (94.9%). The difference in mitotic rate assessment from both institutions was also a limitation, but we believe that different institutions that collect this data should, similarly, further investigate the role of the mitotic rate.

In our study, we expected to find differences when comparing the two cohorts. The Brazilian and Dutch populations have some very important epidemiologic differences, such as ancestry, miscegenation, and sun exposure, which can affect the presentation and outcomes of melanoma. In addition, since both cohorts comprised more than 1000 patients, there are some differences that can be clinically irrelevant yet statistically significant, such as age (Table 2); however, statistical analyses have shown that these differences did not affect the external validation of the nomogram.

There were no differences in the positivity of SNB. Although the number of positive nodes was statistically different, it was not clinically related to any differences in staging and prognosis of patients. The largest diameter of the metastatic deposit in the lymph node, which has been reported as a prognostic indicator,[34,35] was also different. One possible reason for this is the protocol for SN evaluation in Pathology Departments, which can lead to this kind of discordance among institutions.[36–39] In addition, the current AJCC staging system for melanoma does not use the size of metastatic deposits in lymph nodes to stratify patients into the N category.[2]

The practice of observation for patients with a positive SNB was incorporated earlier at the NKI-AVL than at the ACCCC. Although the surgeon's selection of patients undergoing CLND may have been biased, favoring higher-risk patients due to institution-specific practices, when analyzing data from the NKI-AVL, and comparing patients who underwent CLND and those who were observed, there were no differences in either RFS or MSS, corroborating the results from the De-COG SLT and MSLT-II trials [6, 7].

Nonetheless, the rate of patients with additional NSNs was similar between the two populations, as was the prognostic impact of NSN involvement, regardless of the difference in tumor burden between populations ("Appendix 2"). Based on current reports, there is evidence of limited benefit from CLND, but, on the other hand, patients with additional positive nodes will have worse outcomes. Identifying who these patients are, without them having to undergo surgery, can be attempted using the nomogram.

The Italian Melanoma Intergroup (IMI) has published the first nomogram on this topic after release of the MSLT-II results.[13] It is interesting to see that parameters considered not only in this nomogram but also in previous nomograms are very similar and are comparable with what we have also used in our model.

The largest diameter was used in both the Italian nomogram and the N-Snore. Although the MSLT-II trial did not show superiority in survival for any subgroup receiving CLND, including those with SLN tumor burdens $> 1$ mm, the trial did not include a large enough sample of patients fitting this criteria to be powered to make any assertions regarding this subgroup.[7] On the other hand, it is known that a higher tumor burden in the SN is associated with worse outcomes.[40–42]

The positive results of adjuvant treatment trials are promising.[43–45] Although some of these studies only included patients after CLND, it is also questionable whether surgery is really necessary for selecting patients to undergo adjuvant treatments.[46] A retrospective analysis from the European Organization for Research and Treatment of Cancer (EORTC) has shown that ulceration in primary tumors, and tumor burden in SNs, performed as well as CLND for risk stratification, and could also be used to guide adjuvant therapy.[47] We believe that using this nomogram will help to better identify patients to undergo adjuvant treatments, even without CLND, since, according to the nomogram, patients who are considered stage IIIA can have relevant probability of NSN involvement.

Moreover, there are certain groups of patients who should still be considered for CLND, based on several factors, such as regional relapse risk, inability to follow patients as proposed in the trials,[6, 7] or those who are not able to receive adjuvant therapy (e.g. BRAF-negative or receiving immunosuppressive treatments). Using our nomogram can help with the selection of these patients, especially those with a high risk for additional nodal involvement.

In our nomogram, we did not include ulceration, but did include mitotic rate, in the first model, which has not been used in any other previously reported nomogram. As previously mentioned, a different approach was used for mitotic rate between institutions during the period of the study. However, the 8th edition of the AJCC has demonstrated the association between increasing mitotic rate and decreasing MSS.[2] The staging system also considers that mitotic rate will be an important parameter of prognostic models in the future, which reinforces its use in daily practice.

Looking towards the future, more precise tumor genetic profiling has the potential to offer more personalized patient risk assessment.[48, 49] In addition, a better understanding of immunology and cancer-immune system interactions will also help guide treatment choice, as proposed by the 'cancer immunogram'.[50] However, until it becomes widely used, we believe that clinically-based tools will continue to help in daily practice. We have presented a nomogram for assessing NSN probability that should not only be used for surgical considerations but also for risk stratification and clinical decisions, such as adjuvant treatments. Internal validation has shown that it is an adequate model, and external validation increases its reliability and suggests that it can be globally incorporated for those who deal with melanoma patients, once it had been evaluated in two demographically different populations, with similar results.

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## APPENDIX 1

See Table 3.

**TABLE 3** Points for each variable used in the Nomogram and the probability of non-sentinel node positivity according to general score

| | |
|---|---|
| Points per unit of linear predictor: 20.68041 | |
| Linear predictor units per point: 0.04835493 | |
| *Breslow (mm)* | Points |
| 0 | 0 |
| 5 | 16 |
| 10 | 33 |
| 15 | 49 |
| 20 | 65 |
| 25 | 81 |
| 30 | 98 |
| *Largest diameter (mm)* | |
| 0 | 0 |
| 5 | 9 |
| 10 | 18 |
| 15 | 27 |
| 20 | 36 |
| 25 | 45 |
| 30 | 55 |
| 35 | 64 |
| 40 | 73 |
| 45 | 82 |
| 50 | 91 |
| 55 | 100 |
| *Number of positive sentinel node(s)* | |
| 1 | 0 |
| 2 | 24 |
| 3 | 48 |
| 5 | 97 |
| Total score | Probability |
| 5 | 0.05 |
| 21 | 0.10 |
| 30 | 0.15 |
| 37 | 0.20 |
| 43 | 0.25 |
| 49 | 0.30 |
| 53 | 0.35 |
| 58 | 0.40 |
| 62 | 0.45 |
| 66 | 0.50 |
| 70 | 0.55 |
| 75 | 0.60 |
| 79 | 0.65 |
| 84 | 0.70 |
| 89 | 0.75 |
| 95 | 0.80 |
| 102 | 0.85 |
| 112 | 0.90 |
| 127 | 0.95 |

## APPENDIX 2

See Figs. 3, 4 and 5.

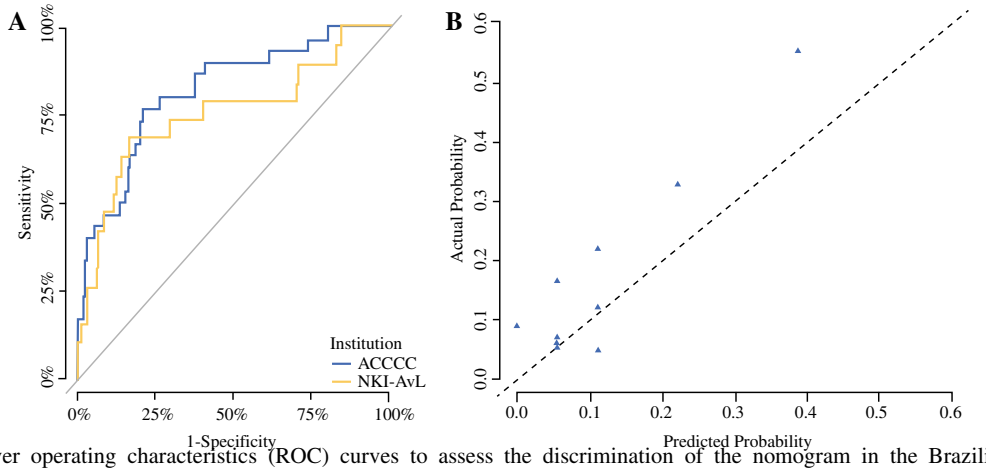


**FIG. 2** **A** Receiver operating characteristics (ROC) curves to assess the discrimination of the nomogram in the Brazilian and in Dutch populations (Area under curve 0.816 and 0.752, respectively. DeLong's test for two ROC-Curves, $p$ 0.4377); **b** Calibration plot for external validation

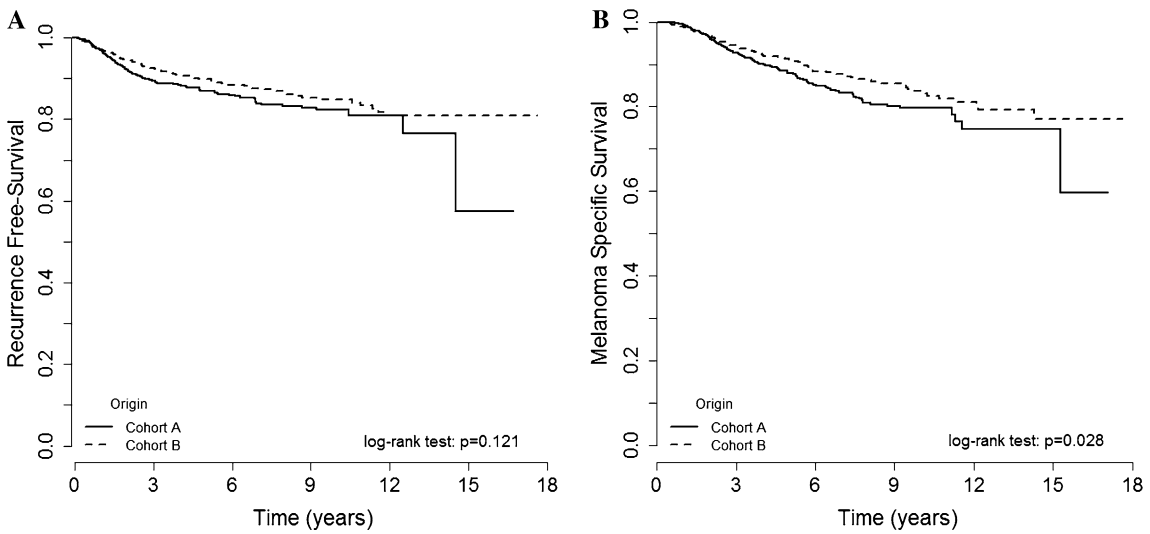


**FIG. 3** Kaplan–Meier curves for melanoma patients who underwent sentinel node biopsy from 2000 to 2015 at the AC Camargo Cancer Center and The Netherlands Cancer Institute-Antoni van Leeuwenhoek, for **a** recurrence-free survival (log-rank 0.130) and **b** melanoma-specific survival (log-rank 0.027)

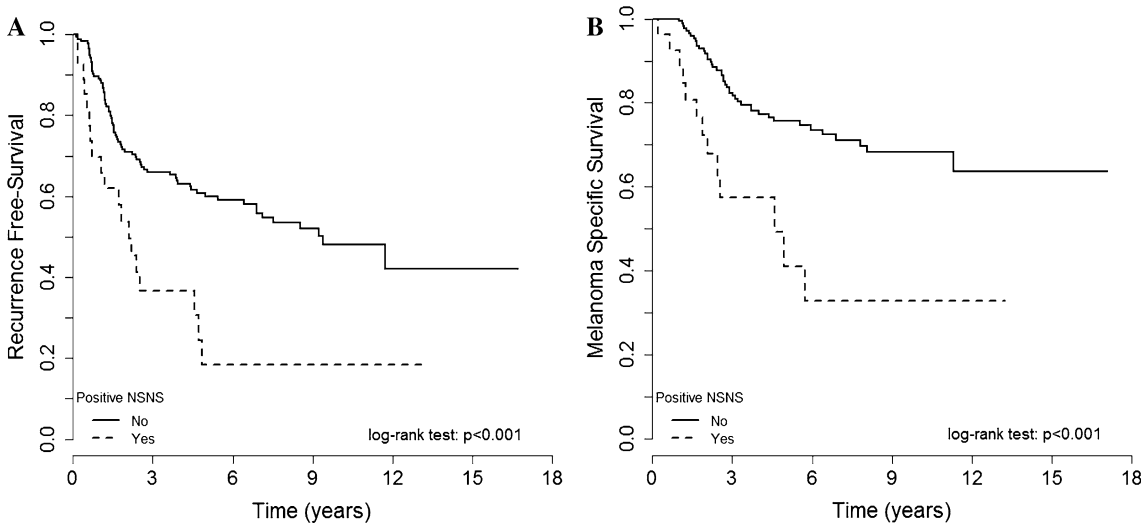


**FIG. 4** Kaplan–Meier curves for melanoma patients with positive non-sentinel nodes from 2000 to 2015 at The Netherlands Cancer Institute-Antoni van Leeuwenhoek, for **a** recurrence-free survival (log-rank $< 0.0001$) and **b** melanoma-specific survival (log-rank $< 0.0001$)

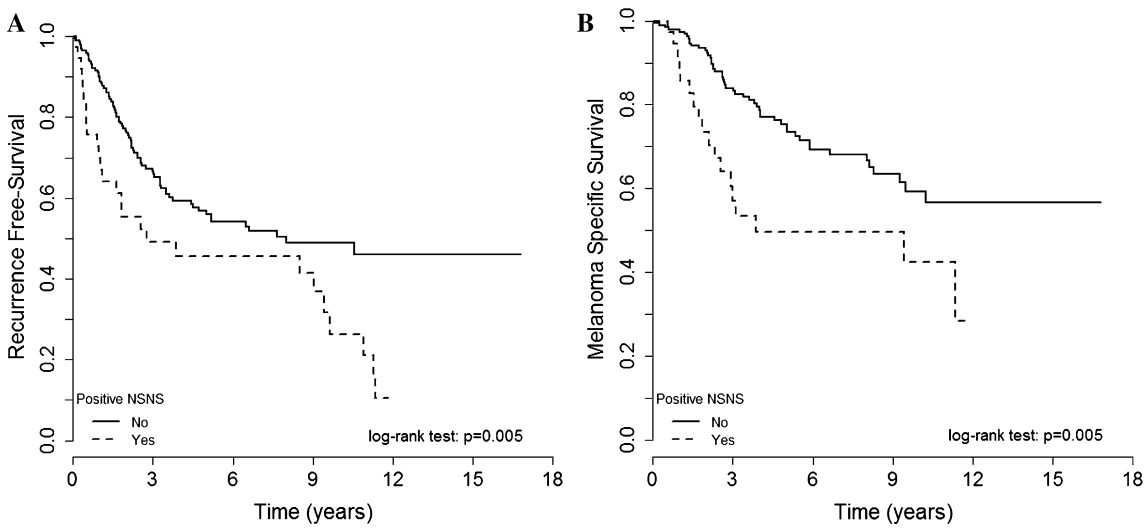


**FIG. 5** Kaplan–Meier Curves for melanoma patients with positive non-sentinel nodes from 2000 to 2015 at the AC Camargo Cancer Center, for **a** recurrence-free survival (log-rank 0.005) and **b** melanoma-specific survival (log-rank 0.005)

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