

Nomograms for predicting sentinel lymph node metastasis in melanoma in a Southern Brazilian population: an accuracy study

Nomogramas de predição de metástase no linfonodo sentinela em melanoma em uma população do sul do Brasil: um estudo de acurácia

AMARILDO FRANCISCO CANDIAGO JÚNIOR AsCBC-SC¹ ; JEFFERSON TRAEBERT^{2,3} ; EDUARDO ZANELLA CORDEIRO TCBC-SC¹ .

ABSTRACT

Introduction: Sentinel lymph node biopsy is fundamental for staging and prognostication of cutaneous melanoma when indicated. However, it still yields a high rate of negative results. To reduce the rate of true negatives, oncology centers have developed nomograms to better stratify patients for whom the procedure is recommended. **Objective:** To study the accuracy of two nomograms developed by the Memorial Sloan-Kettering Cancer Center (MSKCC) and the Melanoma Institute Australia (MIA) for calculating the probability of sentinel lymph node positivity in a population of patients from southern Brazil. **Methods:** An accuracy study was conducted, including data from 320 patients diagnosed with melanoma at a referral oncology institution in Santa Catarina, Brazil. The risk of sentinel lymph node positivity was calculated for each patient using the studied nomograms and compared to the results of histopathological examination. Discrimination was assessed by calculating the area under the Receiver Operating Characteristic (ROC) curve, thereby determining the accuracy of each nomogram. **Results:** The MSKCC nomogram demonstrated an overall accuracy of 69.05%, while the MIA nomogram showed an accuracy of 68.38%. **Conclusion:** The nomograms did not exhibit acceptable levels of accuracy for application in the studied population.

Keywords: Melanoma. Lymphatic Metastasis. Sentinel Lymph Node Biopsy.

INTRODUCTION

Melanoma is a skin neoplasm that has been widely studied and has a well-defined staging. Sentinel lymph node biopsy (SLNB) is widely accepted as a way of staging the lymph node chains of patients with cutaneous melanoma¹⁻⁴. Studies such as the Multicenter Selective Lymphadenectomy Trial (MSLT-I) have ratified the SLNB prognostic value, as well as the technique to be applied for its performance⁵. Its indications are clear, and the prognosis of the disease is in the editions of the American Joint Committee on Cancer (AJCC) Staging System for Melanoma⁶.

Data from studies on SLNB currently show sentinel lymph node positivity ranging from 15% to 20%, with lower and self-limited complication rates, such as infections, seroma, and lymphedema^{7,8}. Due to the high rates of sentinel lymph node negativity, predictive nomograms were created to better select patients who should undergo the procedure. The

Memorial Sloan-Kettering Cancer Center (MSKCC) created its mathematical model in 2005⁹, which is currently very well established, based on 158 patients with sentinel lymph node positivity in a total population of 604 patients in the Sunbelt Melanoma Trial¹⁰. The methodology used to validate the nomograms was similar to the methods of the nomograms for prostate or breast cancer^{11,12}.

More recently, in 2020, the Melanoma Institute Australia (MIA) created its tool with different variables, obtaining sensitivity and specificity indices higher than those of the MSKCC. These results were obtained after adding other variables considered more predictive of sentinel lymph node positivity. This study had a larger population of 3,477 patients and was later internationally validated with a population of 3,496 patients from the MD Anderson Cancer Center¹³.

The accuracy of these tools is the best attribute for the benefit of the patient when indicating the procedure¹⁴⁻¹⁷. However, both nomograms were

1 - Centro de Pesquisas Oncológicas (CEPON), Serviço de Cirurgia Oncológica Cutânea - Florianópolis - SC - Brasil 2 - Centro de Pesquisas Oncológicas (CEPON), Departamento de Ensino e Pesquisa - Florianópolis - SC - Brasil. 3 - Universidade do Sul de Santa Catarina, Programa de Pós-Graduação em Ciências da Saúde, Curso de Medicina - Palhoça SC - Brasil

based on populations of developed countries, with characteristics potentially different from the Brazilian one, which could, hypothetically, alter their accuracy. Thus, it is essential to validate the use of these nomograms in order to be used in the Brazilian population, especially in a state where the incidence of melanoma is high, such as Santa Catarina¹⁸.

Thus, our goal was to study the accuracy of the MSKCC and MIA nomograms for detecting the risk of sentinel node positivity in a population of patients from an oncology referral institution in Santa Catarina.

METHODS

We conducted an accuracy study in which we included data from 320 patients diagnosed with melanoma at a referral institution in oncology in the Southern Brazilian State of Santa Catarina.

Data were collected from the medical records of patients diagnosed with cutaneous melanoma from January 2013 to July 2022, confirmed by anatomopathological examination, and treated at the institution itself. The medical records were analyzed directly from the hospital's computer system.

The indication to perform sentinel lymph node research varied, as the AJCC has undergone changes over the years. However, the indication was given to all patients with a Breslow index of one millimeter or more. In patients with lower depth, the indication was due to lesion ulceration.

Patients undergoing SLNB were previously exposed to the technetium isotope in their scars or directly in the lesion. Subsequently, they underwent the surgical procedure of sentinel lymph node research guided by the gamma-probe.

Patients who underwent sentinel lymph node screening and who had the necessary information recorded in their medical records to meet the inclusion criteria for each of the nomograms had their data entered into both online tools – available free of charge on the websites of the Memorial Sloan-Kettering Cancer Center (<https://www.mskcc.org/nomograms>) and the Melanoma Institute Australia (<https://melanoma.org.au/for-clinicians/risk-calculators/>) – for the calculation of the risk of sentinel lymph node positivity.

After data collection, we compared the positive groups in the sentinel lymph node screening for each of the nomograms, using the Student's t-test to compare means.

The accuracy of the nomograms was measured by the area under the Receiver Operator Curve with the Hanley and McNeil method¹⁹. The data were analyzed using the R software (version 4.1.0).

The project of this study was submitted to, and approved by, the Ethics in Research Committee under CAAE number 74920223.3.0000.5355 and opinion number 6.524.588.

RESULTS

We included data from 320 patients, of which 160 (50.0%) underwent sentinel lymph node biopsy (SLNB). In 17 (5.3%) medical records, data lacked that would have made it possible to ascertain whether SLNB had been performed. A total of 143 (44.7%) individuals did not undergo SLNB. Of these, 128 (89.5%) had no indication (92 were T1a and 36 were metastatic at diagnosis); in seven (4.9%), there was not enough information in the medical records, and in eight (5.6%), there was loss to follow-up.

We found positive SLNB results in 28.12% (95% CI 21.16-35.08), which corresponds to 46 patients. The epidemiological profile of the study population can be seen in Table 1.

Table 1 - Demographic and clinical characteristics of the population studied..

Variable	n	%
Sex		
Male	150	46.87
Female	170	53.13
Age group (years)		
16-30	13	4.06
31-40	47	14.69
41-50	62	19.38
51-60	61	19.06
61 and over	137	42.81
Lesion site		
Head and neck	45	14.06
Trunk	153	47.81
Extremity	113	35.31
No information	9	2.81
Type of injury		

Variable	n	%
Superficial extensive	126	39.38
Nodular	71	22.19
Acral	25	7.81
Lentigo maligna	8	2.50
Other	12	3.75
No information	78	24.37
Ulceration		
Present	91	28.44
Absent	145	45.31
No information	84	26.25
Breslow Index		
Less than 1mm	89	27.81
1.1-2mm	61	19.06
2.1-4mm	58	18.13
Greater than 4mm	56	17.50
No information	56	17.50
Sentinel lymph node positivity (n=160)		
Absent	103	64.37
Present	45	28.12
No information	12	7.51

Among the eligible patients in the study period, 84 medical records had sufficient data to be included in the MSKCC nomogram and 127 in the MIA one. Table 2 presents the comparative analysis between the metastasis groups (absent/present) considering the data obtained by the MSKCC and MIA nomograms. The difference in the mean values obtained by the MSKCC between the groups with present and absent metastasis was not statistically significant ($p=0.14$). The difference between the groups measured by the MIA was significant ($p=0.005$).

Table 3 presents the performance indicators of MSKCC and MIA nomograms for the detection of metastases. The former displayed an overall accuracy of 69.05% (95% CI 58.02-78.69), sensitivity of 55.56%, and specificity of 72.73%. The latter presented an overall accuracy of 68.38% (95% CI 59.13-76.66), sensitivity of 48.98%, and specificity of 82.35%.

The MSKCC nomogram showed an area under the ROC curve (AUC) of 0.578 (Figure 1), while the MIA nomogram showed an AUC of 0.695 (Figure 2).

Table 2 - Comparative analysis between the occurrence of metastasis and nomograms.

Nomogram	Metastasis	n	Minimum	Maximum	Average	SD	Median	p-value
MSKCC	Absent	56	1	42	17,95	10,73	16	0,140
	Present	28	3	42	22,39	13,70	20	
MIA	Absent	83	5	79	22,83	18,88	19	0,005
	Present	35	9	72	33,47	18,29	31	

Table 3 - Comparison of indicators between the MSKCC and MIA nomograms.

Indicators	MSKCC	MIA
Accuracy (%) (95% CI)	69.05 (58.02-78.69)	68.38 (59.13-76.66)
p-value (McNemar)	0.077	0.048
Youden Index	29.5	24.5
Sensitivity (%)	55.56	48.98
Specificity (%)	72.73	82.45
Positive predictive value	35.71	66.67
Negative predictive value	85.71	69.14
Kappa	0.2353	0.3254

DISCUSSION

Nomograms are suitable tools to be used, since they have been externally validated. The present study used

the area under the ROC curve (AUC-ROC) as the method of choice to identify affected from unaffected patients among individuals positive for a condition. It is considered acceptable when values above 0.7 are reached¹⁹.

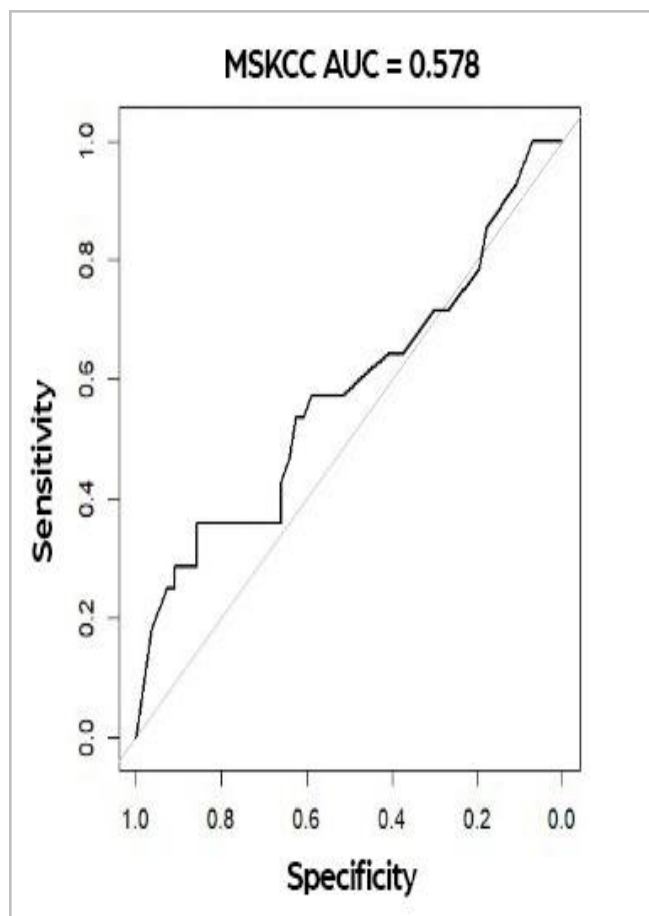


Figure 1. ROC curve for the MSKCC nomogram and the area under the curve (AUC) value.

In the present study, the MSKCC nomogram had an AUC accuracy of 69.05% and a Youden index of 29.5 ($p=0.077$), which indicates a poor performance¹⁹. The AUC had a low sensitivity and a high specificity, which means that the nomogram had difficulty in correctly identifying positive cases. The curve also showed a low-grade slope, meaning that the nomogram was not sensitive to changes in the threshold. In more detail, a low-grade slope means that the curve is almost parallel to the diagonal line that represents mere chance. This implies that the nomogram cannot discriminate well between positive and negative cases.

The MIA nomogram had an overall accuracy of 68.38% and a Youden index of 24.5 ($p=0.048$), which implies a reasonable performance¹⁹. The curve presented variable sensitivity and specificity, depending on the threshold chosen. These results highlight a superior specificity of the MIA nomogram in the identification of negative cases, but with a lower sensitivity.

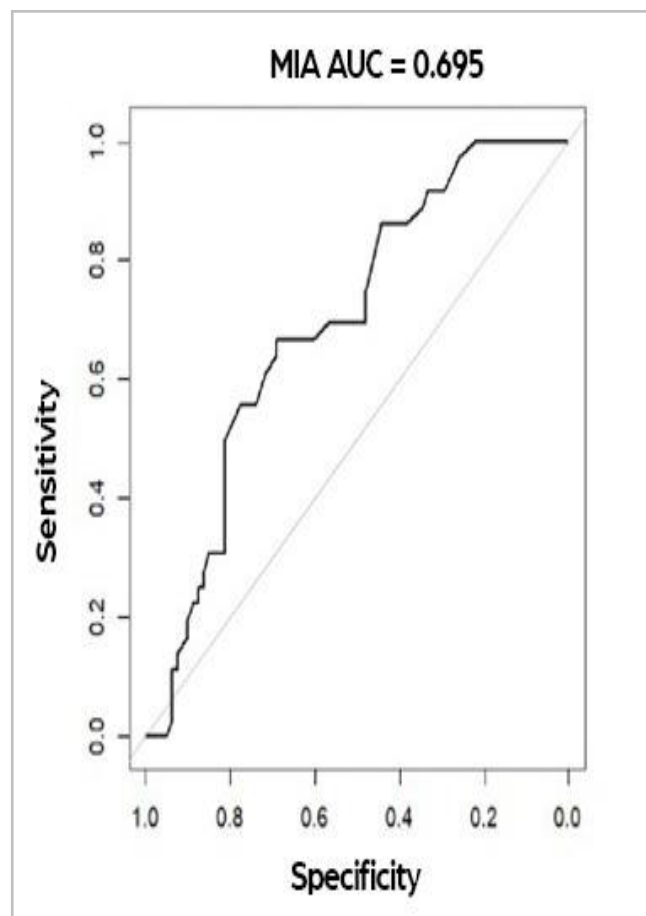


Figure 2. ROC curve for the MIA nomogram and the area under the curve (AUC) value.

SLNB has improved in recent decades, becoming minimally aggressive to the patient. However, it is not free of complications, and the morbidity associated with it is known and well established. Associated with the risks, there is a high rate of true negative results. It is thus notorious the need to stratify patients who must undergo the procedure. To this end, the largest oncology centers have created tools to better indicate the procedure to their population^{8,9,13}, to identify the best tool to meet their needs.

Both centers where the MSKCC and MIA nomograms were developed are large-volume cancer centers, located in developed countries, and with populations with different characteristics from the Brazilian one. On the other hand, the service where we conducted the present study is a state-owned referral oncology center in a developing country, which is why our results are relevant. Another important aspect refers to the fact that Santa Catarina went through strong

colonization of European origin, especially German and Italian, and had a low rate of miscegenation compared with other Brazilian states. This could, however, be considered a relative similarity to the populations where the cancer centers developed the nomograms under study, regarding the profile of patients with the neoplasm. It is necessary, in turn, to note the difference of a higher Breslow index of less than one millimeter in the present study. Hypothetically, this fact could be explained by the greater awareness of the population due to prevention campaigns for early diagnosis of the disease.

The applicability and usefulness of both nomograms is not a question, since both have already been tested and validated in different populations around the world¹⁴⁻¹⁷. The variables are also easy to access and with simple applicability. However, in the study population, we observed low accuracy indicators in both nomograms. The differences could be due to the characteristics of the population studied, which would necessarily imply new studies, including other variables, to propose a more specific nomogram for the population of Santa Catarina.

Some limitations warrant caution in the interpretation of our results. A retrospective study is not as reliable as a prospective study, since it may generate selection bias in a cohort with an established diagnosis. In addition, the patients were operated on by several surgeons and the lymph nodes were evaluated by different pathologists. Moreover, gamma-probes of different brands, with different radiopharmaceuticals, were possibly used. It is also essential to note that the medical records of a large proportion of the population studied did not have necessary information to fill the tool and thus generate the risk estimates, reducing the sample size and, consequently, reducing the accuracy of the study.

CONCLUSION

The nomograms studied did not reach acceptable degrees of accuracy for their applicability in the population of Santa Catarina in the present study. However, it is recommended that further studies be conducted with larger samples, preferably with a prospective design.

R E S U M O

Objetivo: A biópsia do linfonodo sentinela é fundamental no estadiamento e prognóstico do melanoma cutâneo quando há indicação de ser realizado. Porém, ainda se obtém alto índice de resultados negativos. Para diminuir a taxa de verdadeiros negativos, centros oncológicos têm desenvolvido nomogramas para melhor estratificar o paciente a ser indicado o procedimento. **Objetivo:** Estudar a acurácia de dois nomogramas para o cálculo de probabilidade de positividade do linfonodo sentinela criados pelo Memorial Sloan-Kettering Cancer Center (MSKCC) e pelo Melanoma Institute Australia (MIA) em uma população de pacientes do sul do Brasil. **Métodos:** Foi realizado um estudo de acurácia em que foram incluídos dados de 320 pacientes com diagnóstico de melanoma em uma instituição de referência em oncologia de Santa Catarina. Foi calculado o risco de cada paciente submetido à biópsia do linfonodo sentinela pelos nomogramas estudados e comparados com os resultados do exame anatomopatológico. A discriminação dos valores foi feita pelo cálculo da área abaixo da curva da Receiver Operator Curve e assim obtido o valor da acurácia de cada nomograma. **Resultados:** O nomograma do MSKCC apresentou acurácia global de 69,05% e o nomograma do MIA de 68,38%. **Conclusão:** Os nomogramas não apresentaram graus de acurácia aceitáveis para sua aplicabilidade na população estudada.

Palavras-chave: Melanoma. Metástase de Linfonodo. Biópsia de Linfonodo Sentinela.

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Mailing address:

Amarildo Francisco Candiago Júnior

E-mail: amarildocandiago@hotmail.com

