A nomogram to identify high-risk melanoma patients with a negative sentinel lymph node biopsy

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Background: Melanoma patients with negative nodes after sentinel lymph node biopsy are a heterogeneous group. Current guidelines fail to adequately stratify surveillance and treatment for this group. Also, there is scarce data on adjuvant treatments for these patients.

Objective: To create a nomogram including clinical and pathologic characteristics capable of evaluating the risk for recurrence of primary melanoma patients with negative sentinel lymph node biopsies (SLNBs).

Methods: We used a retrospective cohort of patients who underwent SLNB during 2000-2015 at a single institution.

Results: Our cohort comprised 1213 patients. Among these patients, 967 (79.7%) had a negative SLNB, and mean follow-up was 59.67 months. There were 133 recurrences (13.8%); 45 (33.8%) presented with nodal recurrence, and 35 (26.3%) recurred where a SLNB was performed. Breslow thickness, ulceration, and microsatellitosis were found to be predictive of risk for recurrence at 1, 2, 5, and 10 years.

Limitation: Single center analysis.

Conclusion: We created a predictive nomogram for melanoma patients with negative SLNBs. This nomogram is easy to use and identifies high-risk patients who should have more strict surveillance and be considered for adjuvant treatment. (J Am Acad Dermatol 2019;80:722-6.)

Key words: melanoma; nomograms; recurrence; sentinel lymph node biopsy.

Sentinel lymph node biopsy (SLNB) is considered the main tool for nodal staging in melanoma patients without clinical disease.[1-3] Patients with a positive SLNB are considered as stage III, and this is important for prognosis as shown in the survival curves of the 8th edition of the American Joint Committee on Cancer staging system.[2] In this scenario, complete lymph node dissection and adjuvant treatments should be discussed.[4,5]

However, ~80% of patients who undergo this procedure will have a negative sentinel lymph node.[6,7] Even though this might initially represent a better outcome, these patients can also recur and even die from melanoma.

Guidelines are unclear on how to follow these patients. There is no consensus on how often these patients should be evaluated. Neither is there

Abbreviation used:

SLNB: sentinel lymph node biopsy

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consensus on the role of imaging or on how long these patients should remain under surveillance.[8,9] Also, recent studies of adjuvant treatments included only stage III and IV patients.[10-12] There is scarce data on adjuvant treatments with either immunotherapies or targeted therapies for stage II patients. Our primary objective is to create a nomogram that includes the clinical features and pathologic characteristics of primary melanoma to evaluate the risk for recurrence in melanoma patients who have negative SLNBs.

CAPSULE SUMMARY

- Melanoma might recur even after a negative sentinel lymph node biopsy.
- A nomogram identifies patients without nodal disease who are at a higher risk for recurrent melanoma and need more strict surveillance and adjuvant treatments.

PATIENTS AND METHODS

We performed a retrospective analysis of patients who underwent SLNB at our institution (the Skin Cancer Department, AC Camargo Cancer Center, São Paulo, Brazil) during 2000-2015. Our routine has been previously reported,[6,13] and our local ethics committee approved this research.

Data was assessed from both clinical and pathology reports, which are reported in accordance with what is suggested in the literature.[3,14] Statistical analysis was performed with the IBM SPSS software for Mac version 24.0 and R software (www.r-project.org).

Patients with a negative SLNB were included. Cox regression models were used to evaluate which features were related to melanoma recurrence in follow-up with the stepwise forward method. These features were used to create the nomogram. Schoenfeld residuals tests were performed to test the proportional hazard assumption in Cox model.[15,16]

Internal validation of the final model was performed via bootstrap analysis with 200 replications because this method has shown better performance than other methods of internal validation.[17] The model discriminatory power, or the capacity of the model to discriminate between events and nonevents, was assessed by the C-index. The calibration process of the model for predicting probabilities reflected adequately the event occurrence.

RESULTS

Our cohort comprised 1213 patients who underwent SLNB during 2000-2015. There was a slight predominance of male patients (50.3%), and mean age was 52.5 (range 5-89) years. Regarding pathologic aspects, superficial spreading was the most common subtype (65.9%), and mean Breslow thickness was 1.4 mm (standard deviation 2.57); 24.2% presented ulcerated tumors, and 2.6% presented microsatellitosis in primary tumors.

Among these patients, 967 (79.7%) had a negative SLNB after a mean follow-up of 59.7 months. The clinical and pathologic features used for staging these patients according to the 8th edition of the American Joint Committee on Cancer staging system for melanoma[2] are summarized in Table I.

In addition to clinical and pathologic features used for staging purposes, other characteristics were analyzed. Clinical and pathologic features that were statistically related to recurrence both in simple and multiple Cox regression models are summarized in Table II.

Although the mean recurrence-free survival for these patients was not achieved, 133 recurrences (13.8%) occurred during follow-up. Among these patients, 45 (33.8%) presented with nodal recurrence, of which 35 (26.3%) recurred where the SLNB was performed.

With the variables in Table II, it was possible to create a nomogram to predict the probability of recurrence-free survival at 1, 2, 5, and 10 years for melanoma patients with a negative SLNB (Fig 1). The top row of the nomogram corresponds to the general score. For each variable listed on the left (microsatellitosis, Breslow thickness, and ulceration), there is a corresponding row on the right indicating possible descriptors. After characterizing the patient for each variable, a perpendicular line toward the first row should be drawn to identify that value. This action should be performed for all 3 variables, and a final score tallied. This final score should be identified in the total points row and then a perpendicular line drawn crossing the 4 lines below that correspond to the probability of recurrence-free survival in 1, 2, 5, and 10 years.

For instance, consider a hypothetical patient with a primary tumor of Breslow thickness 2 mm with ulceration and without microsatellitosis. This patient will have 0 points for microsatellitosis, 10 points for Breslow thickness, and 61 points for ulceration, which represents a score of 71 points. This patient has a 90% probability to be free of recurrence after 1 year of follow-up, 77% after 2 years, 64% after 5 years, and 50% after 10 years.

After internal validation with the bootstrap technique, the C-index was 0.749, which represents an adequate discriminatory power.

DISCUSSION

Melanoma patients with positive SLNBs are considered stage III patients, and despite any other characteristic, their 5-year survival will be 77%.[2] In these patients, there is the discussion of whether or not to offer complete lymph node dissection[4,18,19] and adjuvant treatments.[5,20]

However, most melanoma patients will have a negative SLNB, and it is unclear whether they need further treatments and how long they should be followed.[3,8,9] One of the reasons for this uncertainty is the heterogeneity of this group of patients.[7] In our cohort, although the great majority of patients were stage I and II, there were 17 stage III patients, 11 stage IIIB, 4 stage IIIC, and 2 stage IIID. The prognosis of these patients can be as bad as—or even worse than—patients with a positive SLNB.[2]

The nomogram we created can identify these high-risk patients; this nomogram is easy to use and incorporate into daily practice without extra resources.[21] There are several nomograms for melanoma patients in the literature, but to our knowledge, all these are based on patients with positive SLNBs.[22-24]

For instance, consider the hypothetical patient we previously mentioned. According to the current staging system, this patient would be considered stage IIA (pT2bN0M0) with a 5 and 10 year overall survival of 94% and 88%, respectively.[2] However, according to our nomogram, this patient has a 36% risk for recurrence in 5 years and 50% in 10 years. The contrast between these rates and the prognosis according to the staging system should be used to reinforce the importance of strict surveillance during the follow-up of this patient.

Pathologists must routinely report the variables that were used in the nomogram: Breslow thickness, ulceration, and microsatellitosis.[6,7,14] It is also important to mention that Ki67 expression was also significant in our analysis. However, due to the small number of patients with Ki67 expression data, its inclusion in the nomogram was statistically difficult. Although we decided not to include Ki67 expression in the nomogram, we do believe this parameter is an important factor and should be part of pathology reports for melanoma patients.

Most guidelines suggest that these patients should be followed with 1 or 2 visits each year for 5 years, and there is no clear direction on whether patients should undergo radiologic examination, which tests should be performed, and how often they should be done. We believe these decisions should be based on the individual risk for each patient by using the nomogram, as we have shown with the hypothetical patient.

Patients with a low risk for recurrence in short-term and long-term follow-up could be seen by a melanoma specialist once a year for 5 years without further examination and then be advised to self-examine and continue follow-up with a general dermatologist or surgeon. However, patients with a high risk for recurrence should undergo a more strict surveillance and imaging should be more liberal. Because around a quarter of recurrences happen in the same nodal basin of the SLNB, we believe that routine nodal ultrasound would be helpful. Around two thirds of recurrences are systemic, which should justify the use of tomographies or positron emission tomography scans according to the score achieved in our nomogram. Also, a melanoma specialist should follow these patients for >5 years for clinical examination and imaging evaluation. This should all be explained to the patient soon after the SLNB so that the patient will know the importance of surveillance even with a negative SLNB.

In addition to follow-up, these patients should also be considered for adjuvant treatments. In recent studies of immunotherapy or targeted therapies[10-12] in the adjuvant setting, only stage III and IV patients were included. Identifying other high-risk patients for recurrence, even stage II patients, might be useful in further studies.

Table I. Clinical and pathologic features for staging patients with negative sentinel lymph node biopsy at AC Camargo Cancer Center, 2000-2015

		Ulceration, n (%)		
Microsatellitosis	**T category**	**Absent**	**Present**	**Total**
Absent	T1	332 (39.6)	18 (2.1)	350
	T2	217 (25.9)	49 (5.8)	266
	T3	94 (11.2)	57 (6.8)	151
	T4	23 (2.7)	49 (5.8)	72
	Total	666 (79.4)	173 (20.6)	839
Present	T1	4 (23.5)	0 (0)	4
	T2	1 (5.9)	1 (5.9)	2
	T3	5 (29.4)	1 (5.9)	6
	T4	3 (17.6)	2 (11.8)	5
	Total	13 (76.4)	4 (23.5)	17
Total	T1	336 (39.2)	18 (2.1)	354
	T2	218 (25.4)	50 (5.8)	268
	T3	99 (11.56)	58 (6.8)	157
	T4	26 (3.0)	51 (5.9)	77
	Total	679 (79.3)	177 (20.7)	856

Table II. Clinical and pathological features related to melanoma recurrence in patients with negative sentinel node biopsy at AC Camargo Cancer Center, 2000-2015

	Simple Cox regression			Multiple Cox regression		
Feature	***P***	**HR**	**CI 95%**	***P***	**HR**	**CI 95%**
Age at diagnosis, y	.017	1.014	1.003-1.026			
Topography*						
Trunk	.004	0.435	0.245-0.771			
Upper limbs	.003	0.379	0.201-0.715			
Histology†						
Nodular	<.0001	3.781	2.384-5.997			
Acral	.002	2.478	1.386-4.432			
Desmoplastic	.049	3.208	1.005-10.243			
Other/Unclassified	.001	2.963	1.516-5.791			
Growth phase‡	.021	5.159	1.275-20.875			
Breslow thickness, mm	<.0001	1.175	1.126-1.225	<.0001	1.109	1.048-1.174
Mitotic index, HPF	<.0001	1.040	1.028-1.052			
Mitotic index, mm^2	<.0001	1.063	1.030-1.096			
Clark level IV and V	<.0001	2.122	1.471-3.062			
Ulceration	<.0001	3.729	2.611-5.327	<.0001	3.431	2.294-5.131
Perineural invasion	.034	2.644	1.078-6.483			
Microsatellitosis	.004	3.388	1.487-7.716	.003	3.551	1.543-8.170
Ki67	<.0001	1.027	1.013-1.041	.02	1.029	1.005-1.055

CI, Confidence interval; *HPF*, high-power field; *HR*, hazard ratio.
*Lower limbs was the reference.
†Superficial spreading was the reference.
‡Radial was the reference.

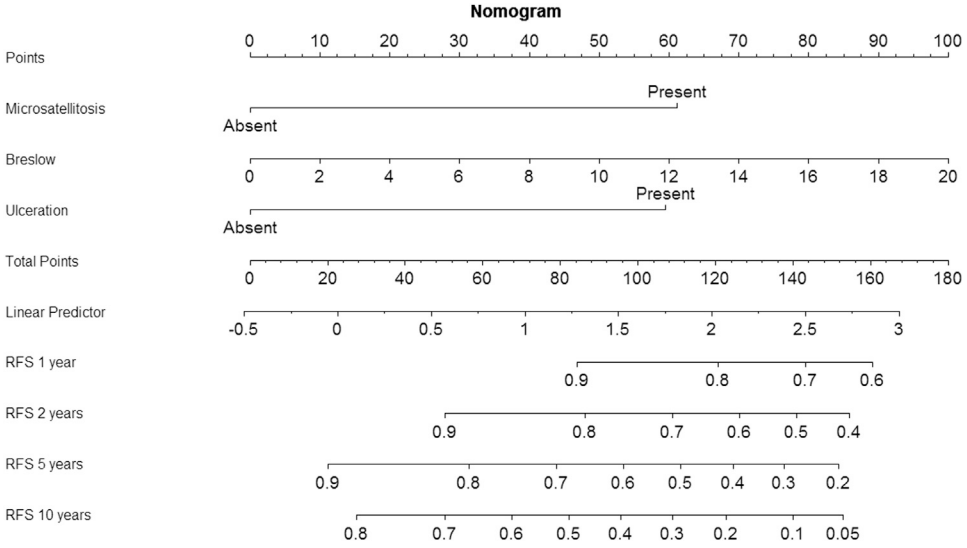

Fig 1. Predictive nomogram for recurrence in melanoma patients with a negative sentinel lymph node biopsy. *RFS*, Recurrence-free survival.

Genetic profiles will probably soon be incorporated into these predictive tools, enabling even more personalized risk evaluation.[25,26] Immunology and the interactions between the cancer and immune system will also be used, especially for treatment decisions.[27] However, clinical tools such as the nomogram presented in this paper will still be helpful in daily routine until these new biomarkers become available.

In summary, we created a predictive nomogram for SLNB-negative melanoma patients. This nomogram is easy to use and can help clinicians

provide an individualized follow-up program for patients, as well as identify high-risk patients who should be considered for adjuvant treatments.

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