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ORIGINAL REPORT

Prediction of Survival in Patients With Thin Melanoma: Results From a Multi-Institution Study

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ABSTRACT

Purpose
Cutaneous melanoma incidence is increasing. Most new cases are thin (≤ 1 mm) with favorable prognoses, but survival is nonetheless variable. Our aim was to investigate new prognostic factors and construct a nomogram for predicting survival in individual patients.

Patients and Methods
Data from 2,243 patients with thin melanoma were retrieved from prospectively maintained databases at six centers. Kaplan-Meier survival and crude cumulative incidences of recurrence were estimated, and competing risks were taken into account. Multivariable Cox regression was used to investigate survival predictors.

Results
Median follow-up was 124 months (interquartile range, 106 to 157 months); 12-year overall survival was 85.3% (95% CI, 83.4% to 87.2%). Median times to local, regional, and distant recurrence were 79, 78, and 107 months, respectively. Relapse was significantly related to age, Breslow thickness, mitotic rate (MR), ulceration, lymphovascular invasion (LVI), and regression; incidence was lower and subgroup differences were less marked for distant metastasis than for regional relapse. The worst prognosis categories were age older than 60 years, Breslow thickness more than 0.75 mm, MR ≥ 1, presence of ulceration, presence of LVI, and regression ≥ 50%. Breslow thickness more than 0.75 mm, MR ≥ 1, presence of ulceration, and LVI (all $P = .001$) were significantly associated with sentinel node positivity. Age, MR, ulceration, LVI, regression, and sentinel node status were independent predictors of survival and were used to construct a nomogram to predict 12-year overall survival. The nomogram was well calibrated and had good discriminative ability (adjusted Harrell C statistic, 0.88).

Conclusion
Our findings suggest including LVI and regression as new prognostic factors in the melanoma staging system. The nomogram appears useful for risk stratification in clinical management and for recruiting patients to clinical trials.

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INTRODUCTION

The incidence of cutaneous melanoma is increasing.[1] Most new cases are diagnosed when thin (Breslow thickness ≤ 1 mm)[2] and have favorable prognoses. However, the 2009 American Joint Committee on Cancer (AJCC) emphasized the variability (85% to 99%) of 10-year survival for thin melanoma.[3] It is important therefore to identify factors that influence prognosis.

Although thickness has long been recognized as an important prognostic factor for primary localized melanoma,[4] various other factors have been proposed as prognostic and suggested as stage indicators.[5] The current AJCC classification[3] recognizes two tumor-associated factors for thin melanomas: mitotic rate (MR) and ulceration. Low-risk (T1a) melanomas are nonulcerated, with an MR of less than one mitosis per square millimeter; higher-risk (T1b) melanomas have an MR of one or more mitoses per square millimeter, ulceration, or both. The Committee noted that regional node metastasis was also an important prognostic factor in early-stage melanoma and recommended sentinel node biopsy (SNB) in selected T1b patients[3] but did not have sufficient data to assess the risk of occult nodal micrometastases in T1 patients.

Several studies have attempted to define the role of SNB in thin melanoma and identify predictors of sentinel node (SN) positivity, but findings have been discordant.[6-8] Recent guidelines,[9,10] also

noting the lack of evidence to support routine SNB in T1 patients, state that SNB should be considered for selected high-risk patients.

These considerations highlight the variable risks associated with T1 melanomas and the need to identify characteristics for reliable risk stratification. The aim of this study was to identify determinants of survival and predictors of SN status in a large multicentric series of patients with thin melanoma and construct a nomogram predicting survival.

PATIENTS AND METHODS

All patients diagnosed and treated for a single thin (Breslow thickness 1.00 mm or less) primary melanoma from 1996 through 2004 at six European centers were considered. Clinicopathologic data were retrieved from prospectively maintained databases. Patients with satellites or metastases at diagnosis or history of other cancer were excluded. Information retrieved comprised age, sex, site (head and neck, trunk, limbs), Breslow thickness, MR, ulceration, Clark level, presence or absence of lymphovascular invasion (LVI), regression, and tumor-infiltrating lymphocytes (TILs). MR was expressed as number of mitoses per square millimeter. TILs were classified as brisk, nonbrisk, or absent. Regression was characterized as absent, partial ($<$ 50% of the entire primary lesion), or extensive ($\geq$ 50%). LVI was defined as the presence of melanoma cells within lymphatic or blood vessels.

After excluding 86 patients lost immediately after discharge and 42 patients with missing data, 2,243 patients were included. All slides were reviewed independently by three pathologists (G.T., B.V., and C.L.) with disagreements resolved by discussion.

Treatment consisted of diagnostic excision with 1-to 2-mm margins followed by wider excision to achieve histologically confirmed 1-cm margins in healthy tissue. SNB was offered to high-risk patients, for which criteria were Breslow thickness 0.75 to 1.00 mm, MR one or more mitoses per square millimeter, presence of ulceration, presence of LVI, Clark level IV or V, and extensive regression. The benefits and risks of SNB were discussed with patients. Some patients asked for and received SNB, although the risk of occult nodal metastasis was low. All patients with a positive SN were urged to undergo node dissection.

Recurrences subsequent to definitive surgery were classified as local if they developed within the primary scar, regional if they were in-transit dermal or subcutaneous metastases or in lymph nodes, and distant if they were nonregional skin, nodal, or visceral metastases. All skin and node recurrences were confirmed histologically.

The χ^2 or Wilcoxon-Mann-Whitney test was used to determine significant differences between stage T1a and T1b. Multivariable binary logistic modeling was used to explore propensity to perform SNB according to year of diagnosis, sex, age, tumor site, Breslow thickness, MR, ulceration, LVI, Clark level, TILs, and regression. The response variable was zero if SNB was not performed and 1 if it was performed.

In patients receiving SNB, the Wilcoxon-Mann-Whitney test (year of diagnosis, age, Breslow thickness) or χ^2 test (other variables) assessed differences in the distribution of these variables between SN-negative and SN-positive groups.

The main study end point was overall survival (OS) calculated from date of surgery for primary melanoma to date of death as a result of all causes or censored at date of last follow-up in living patients. OS curves were estimated by using the Kaplan-Meier method, and the log-rank test was used to compare subgroups. Additional end points were (crude cumulative incidences of) regional relapse and distant metastasis, analyzed in a competing risks framework[11]; time was calculated from date of definitive surgery to event date and was censored at date of last follow-up in event-free patients. For regional relapse, competing events were distant metastasis, death as a result of an unrelated cause, local relapse, or second malignancy, whichever occurred first. For distant metastasis, competing events were regional relapse, death as a result of an unrelated cause, local relapse, and second malignancy.[12] Because cumulative incidences did not reach 50%, we noted values at maximum observation time and halved them: times at which half the maximum cumulative incidence occurred were considered median times to events.

Multivariable Cox modeling was used to analyze OS. The proportional hazards assumption was checked by using tests based on scaled Schoenfeld residuals.[13] The covariates age, Breslow thickness, MR, ulceration, LVI, regression, SNB status, and SN status were investigated as prognostic factors. SNB and SN status were initially represented by a three-level covariate (SNB not done, SNB done/SN negative, SNB done/SN positive). However, the proportional hazards assumption did not hold in that the hazard ratio for SNB not done versus SNB done/SN negative tended to increase after 8 years. Use of SNB was therefore modeled as a stratification factor, and its interaction with SN status was included as a covariate; the latter made it possible to estimate the prognostic effect of SN-positive versus SN-negative disease, conditional on SNB. SNB use did not interact significantly with other prognostic factors, so no other interaction terms were included. A backward procedure based on the Akaike information criterion[14] was used to select covariates.

The nomogram to predict 12-year OS probability was developed from the final Cox model. Nomogram performance was assessed by calibration plot as an indicator of internal calibration and by the Harrell C statistic as a measure of discriminative ability.[15] The Harrell C statistic corresponds to the area under the receiver operating characteristic curve; values 0.5 and 1, respectively, indicate lack of discriminative ability and perfect discriminative ability. A bootstrap procedure[16] was adopted to adjust the C statistic estimate for the optimism implicit in the use of sample data for model fitting and variable selection.

In the multivariable models, year of diagnosis, age, and Breslow thickness were continuous variables using three-knot restricted cubic splines.[17] Restricted cubic spline modeling has the advantage of avoiding categorization and use of cutoffs (necessary to estimate Kaplan-Meier and crude cumulative incidence curves) and of obtaining a flexible fit allowing the effects of continuous variables not to be the same in every part of the range. Thus, the covariate values presented in the Cox model tables do not define categories but are exact values (quartiles of the variable distribution). All categorical covariates were modeled by using dummy variables. The analyses were carried out with SAS (SAS Institute, Cary, NC) and R software (http://www.r-project.org/).

RESULTS

Patient and Disease Characteristics

Characteristics of the 2,243 patients, by stage, are summarized in Table 1. Stage IA and IB patients did not differ regarding sex, age, site, or presence of TILs. Of the T1a lesions, 45.2% were $\leq$ 0.50 mm compared with 26.3% of T1b lesions, and 24.9% of T1a lesions were more than 0.75 mm compared with 43.7% of T1b lesions. Among the 1,115 T1b patients, 982 (88.1%) had MR $\geq$ 1 and 530 (47.5%) had ulceration. LVI was present in 19.1% of T1a patients and was present in 43.6% of T1b patients. T1a patients were less likely than T1b patients to have regression: less than 50% regression, 17.4% versus 21.9%; $\geq$ 50% regression, 10.3% versus 18.0%.

SNB

Overall, 794 patients (35.4%) received SNB (Table 2). The percentage of patients undergoing SNB (propensity) tended to decrease with advancing age (from 36% to 28.8%). As expected, patients with worse prognostic factors underwent SNB more often. Thus, propensity to undergo SNB increased with increasing Breslow thickness (11.3% for $\leq$ 0.50 mm; 60.2% for $>$ 0.75 mm) and increasing MR (from 28.1% to 44.8%).

Multivariable analysis showed that characteristics significantly associated with propensity to undergo SNB were age, Breslow thickness, ulceration, and LVI (all $P < .001$). Sixty-eight patients (8.6%)

Table 1. Characteristics of the 2,243 Patients With Thin Melanoma, According to Stage at Diagnosis

Characteristic	Stage T1a		Stage T1b			Whole Series	
	No.	%	No.	%	*P**	No.	%
Total No. of patients	1,128	50.3	1,115	49.7	NA	2,243	100.0
Year of diagnosis					< .001		
1996-1998	220	19.5	257	23.0		477	21.3
1999-2000	228	20.2	177	15.9		405	18.1
2001-2002	217	19.2	301	27.0		518	23.1
2003-2004	463	41.0	380	34.1		843	37.6
Sex					.930		
Female	612	54.3	608	54.5		1,220	54.4
Male	516	45.7	507	45.5		1,023	45.6
Age, years					.767		
Median	43.5		43			43	
IQR	36-53		36.5-52			36-52	
≤ 40	445	39.5	424	38.0		869	38.7
> 40 to ≤ 50	323	28.6	315	28.3		638	28.4
> 50 to ≤ 60	228	20.2	236	21.2		464	20.7
> 60 to ≤ 70	79	7.0	89	8.0		168	7.5
> 70	53	4.7	51	4.6		104	4.6
Site					.966		
Head and neck	227	20.1	223	20.0		450	20.1
Trunk	470	41.7	460	41.3		930	41.5
Upper or lower limbs	431	38.2	432	38.7		863	38.5
Breslow thickness, mm					< .001		
Median	0.52		0.71			0.63	
IQR	0.33-0.72		0.50-0.79			0.41-0.78	
≤ 0.50	510	45.2	293	26.3		803	35.8
> 0.50 to ≤ 0.75	337	29.9	335	30.0		672	30.0
> 0.75 to ≤ 1	281	24.9	487	43.7		768	34.2
Mitoses, No. per mm^2					< .001		
< 1	1,128	100.0	133	11.9		1,261	56.2
≥ 1	0	0.0	982	88.1		982	43.8
Ulceration					< .001		
Absent	1,128	100.0	585	52.5		1,713	76.4
Present	0	0.0	530	47.5		530	23.6
Lymphovascular invasion					< .001		
Absent	912	80.9	629	56.4		1,541	68.7
Present	216	19.1	486	43.6		702	31.3
Clark level					< .001		
II or III	727	64.5	428	38.4		1,155	51.5
IV	401	35.5	687	61.6		1,088	48.5
Tumor-infiltrating lymphocytes					.633		
Absent	587	52.0	568	50.9		1,155	51.5
Present	541	48.0	547	49.1		1,088	48.5
Regression					< .001		
Absent	816	72.3	670	60.1		1,486	66.3
Present (< 50%)	196	17.4	244	21.9		440	19.6
Present (≥ 50%)	116	10.3	201	18.0		317	14.1

NOTE. Stage is according to the 2009 American Joint Committee on Cancer classification.
Abbreviations: IQR, interquartile range; NA, not applicable.
*χ^2 or Wilcoxon-Mann-Whitney test, as appropriate.

Table 2. Demographic and Tumor Characteristics of the 794 Patients Who Underwent SNB, and Association of Characteristics With SN Positivity

Characteristic	Undergoing SNB		Percent of Whole Series*	Association With SN Positivity		
	No.	%		No.	%	P†
Sex						.999
Female	414	52.1	33.9	35	8.5	
Male	380	47.9	37.1	33	8.7	
Age, years						.059
≤ 40	355	44.7	40.9	37	10.4	
> 40 to ≤ 50	188	23.7	29.5	16	8.5	
> 50 to ≤ 60	158	19.9	34.1	10	6.3	
> 60 to ≤ 70	63	7.9	37.5	4	6.3	
> 70	30	3.8	28.8	1	3.3	
Site						.993
Head and neck	155	19.5	34.4	13	8.4	
Trunk	322	40.6	34.6	28	8.7	
Upper or lower limbs	317	39.9	36.7	27	8.5	
Breslow thickness, mm						< .001
≤ 0.50	91	11.5	11.3	3	3.3	
> 0.50 to ≤ 0.75	241	30.4	35.9	11	4.6	
> 0.75	462	58.2	60.2	54	11.7	
Mitoses, No. per mm^2						< .001
< 1	354	44.6	28.1	5	1.4	
≥ 1	440	55.4	44.8	63	14.3	
Ulceration						< .001
Absent	373	47.0	21.8	12	3.2	
Present	421	53.0	79.4	56	13.3	
Lymphovascular invasion						< .001
Absent	436	54.9	28.3	24	5.5	
Present	358	45.1	51.1	44	12.3	
Clark level						.962
II or III	370	46.6	32.0	31	8.4	
IV	424	53.4	39.0	37	8.7	
Tumor-infiltrating lymphocytes						.945
Absent	353	44.5	30.6	31	8.8	
Present	441	55.5	40.5	37	8.4	
Regression						.212
Absent	444	55.9	29.9	33	7.4	
Present (extent < 50%)	141	17.8	32.0	11	7.8	
Present (extent ≥ 50%)	209	26.3	65.9	24	11.5	

Abbreviations: SN, sentinel node; SNB, sentinel node biopsy.
*Percentage of the total patients in each category.
†Wilcoxon-Mann-Whitney test (age and Breslow thickness evaluated as continuous variables) and χ^2 test (other variables).

were SN positive and underwent regional nodal dissection. Increasing Breslow thickness, high MR, ulceration, and LVI were significantly associated with SN positivity (Table 2). The low number of patients with a positive SN made reliable multivariable analysis of factors associated with SN positivity impossible.

Relapse and Survival

Median follow-up was 124 months (interquartile range, 106 to 157 months). There were nine local relapses, 169 regional appearances, and 70 distant metastases as first event. Fifty-five patients developed another malignancy as first event, and six died (first event) of causes unrelated to melanoma. Median times to local, regional, and distant first events were 79, 78, and 107 months, respectively.

Twelve-year estimates of crude cumulative incidences of regional relapse and distant metastasis, in relation to age, Breslow thickness, MR, ulceration, LVI, and regression, are provided in Table 3. Crude cumulative incidence of local relapse was not estimated for low numbers of events. All factors listed in Table 3 significantly (all $P < .001$) influenced crude cumulative incidences of regional relapse and distant metastases. In general, incidence was lower and subgroup differences

Table 3. OS and Cumulative Incidence of Recurrence at 12 Years

Characteristic	Crude Cumulative Incidence				OS	
	Regional Relapse		Distant Metastasis			
	%	95% CI	%	95% CI	%	95% CI
Age, years						
≤ 40	1.2	0.6 to 2.3	2.1	1.2 to 3.5	96.8	95.3 to 98.2
> 40 to ≤ 50	6.5	4.7 to 8.9	4.6	2.6 to 8.2	88.0	84.3 to 92.0
> 50 to ≤ 60	7.7	5.5 to 10.7	6.2	4.1 to 9.4	82.9	78.7 to 87.4
> 60 to ≤ 70	38.6	30.4 to 49.0	10.8	5.9 to 19.7	40.3	31.0 to 52.5
> 70	37.6	28.9 to 48.9	5.7	2.4 to 13.6	43.3	32.0 to 58.6
Breslow thickness, mm						
≤ 0.50	1.1	0.5 to 2.3	1.9	1.0 to 3.7	96.8	95.2 to 98.5
> 0.50 to ≤ 0.75	3.3	2.1 to 5.0	3.2	1.9 to 5.5	92.2	89.6 to 94.8
> 0.75 to ≤ 1	19.8	17.1 to 23.0	7.0	5.2 to 9.4	70.8	67.0 to 74.9
Mitotic rate, No. per mm^2						
< 1	1.8	1.1 to 2.8	2.4	1.5 to 3.7	95.3	93.8 to 96.8
≥ 1	16.5	14.2 to 19.2	6.2	4.7 to 8.3	74.7	71.4 to 78.2
Ulceration						
Absent	1.5	1.0 to 2.3	2.7	1.9 to 3.8	95.3	94.1 to 96.6
Present	29.4	25.6 to 33.8	8.7	6.2 to 12.1	57.7	52.5 to 63.3
Lymphovascular invasion						
Absent	1.4	0.9 to 2.1	2.8	1.9 to 4.0	95.3	94.0 to 96.6
Present	23.1	20.0 to 26.8	7.1	5.1 to 9.8	65.6	61.1 to 70.3
Regression						
Absent	1.8	1.3 to 2.7	3.4	2.4 to 4.9	94.1	92.6 to 95.7
Present (< 50%)	1.5	0.7 to 3.2	2.9	1.6 to 5.2	94.1	91.5 to 96.8
Present (≥ 50%)	44.7	39.4 to 50.7	8.1	5.4 to 12.0	48.5	42.7 to 55.0

Abbreviation: OS, overall survival.

less marked for distant metastasis than regional relapse. The poorer prognosis categories were age older than 60 years, Breslow thickness more than 0.75 mm, MR ≥ 1, presence of ulceration, LVI, and regression ≥ 50%.

Regarding mortality, 231 patients died of melanoma and nine of other causes; 12-year OS was 85.3% (95% CI, 83.4% to 87.2%). Regional relapse and distant metastasis had a major impact on mortality: five of the nine who developed local relapse, 156 of the 169 who developed regional relapse, and all 70 patients who developed distant metastasis died of melanoma.

Table 3 also depicts (right-most two columns) 12-year OS estimates according to age, Breslow thickness, MR, ulceration, LVI, and regression. As for relapse, all factors investigated were significantly associated with OS, and prognostic trends were similar.

In the Cox model analysis of OS, SNB use was included as a stratification factor so that OS estimates could differ according to whether or not SNB was performed. The following were evaluated: age, Breslow thickness, MR, ulceration, LVI, regression, and SN status (conditional to receiving SNB). The results of the final Cox model are provided in Table 4. As a result of the selection procedure, Breslow thickness was excluded, and the categories "regression absent" and "regression present with extent less than 50%" were fused. All remaining factors were highly significant predictors of OS. The exclusion of Breslow thickness from the model was the result of the strong association between Breslow thickness and the other factors retained in the model: greater thickness was associated with older age, MR ≥ 1, presence of ulceration, LVI, and regression ≥ 50%.

The nomogram based on the final Cox model is shown in Figure 1. By using the nomogram, 12-year OS probability can be estimated from individual patient and tumor characteristics, conditional to SNB or not. Negative prognostic factors contributed points so that increasing total points were associated with increasingly worse prognosis. A more detailed description of nomogram use is given in the Figure 1 legend. Notably, a given point score implies worse survival for a patient not receiving SNB compared with a node-negative patient receiving SNB. The discrepancy, usually in the 5% to 10% range, may be explained by considering that unrecognized node-positive patients

Table 4. Multivariable Cox Regression Model of OS After Backward Selection of Variables

Variable	HR	95% CI	*P**
Age 52 *v* 36 years†	3.88	2.69 to 5.59	< .001
No. of mitoses per mm^2 ≥ 1 *v* < 1	1.58	1.06 to 2.37	.026
Ulceration present *v* absent	3.81	2.51 to 5.80	< .001
Lymphovascular invasion present *v* absent	1.81	1.24 to 2.65	.002
Regression ≥ 50% *v* absent or < 50%	3.32	2.31 to 4.77	< .001
SN status positive *v* negative‡	2.97	1.86 to 4.76	< .001

NOTE. Hazard ratio (HR) estimate is the risk of death for a given category or value compared with the reference category or value. HR > 1 indicates greater risk than reference; HR < 1 indicates lower risk than reference. The larger the HR, the greater the association between the variable and risk of death. CIs that do not include the value of one indicate a significant difference for the category compared with reference.

Abbreviations: OS, overall survival; SN, sentinel node; SNB, sentinel node biopsy.

*Two-sided *P* value from Wald test.

†Third and first quartiles of age distribution, respectively.

‡Positive indicates undergoing SNB.

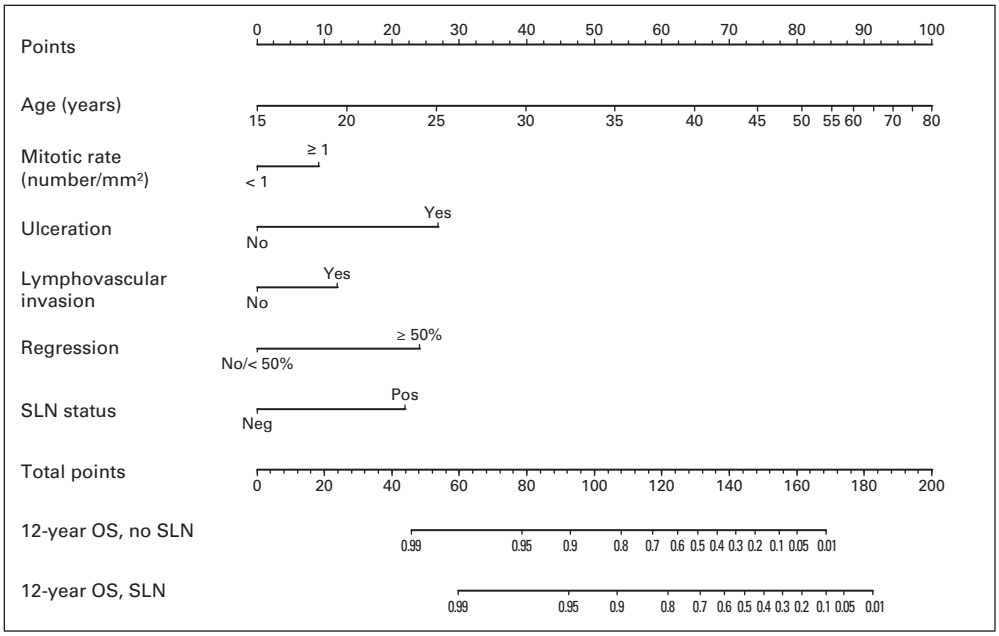

Fig 1. Nomogram for 12-year overall survival (OS) in thin cutaneous melanoma. To calculate the survival probability for a specific patient, locate patient age and draw a line straight upward to the Points axis to determine the score associated with that age. Repeat the process for mitotic rate, ulceration, lymphovascular invasion, regression, and sentinel node (SN) status (when sentinel node biopsy [SNB] was performed), sum the scores for each factor, and locate this sum on the Total Points axis. Then, depending on whether or not SNB was performed, draw a line straight down to the corresponding 12-year OS axis to find the predicted OS probability. SLN, sentinel lymph node.

are also present in the subset not receiving SNB, which in turn influences survival.

The nomogram was internally validated by the calibration plot in Figure 2, and by computing the bootstrap-corrected Harrell C statistic. The calibration plot suggests that the nomogram was well calibrated; predicted and observed survival were in good agreement (circles lying almost directly on the reference line), with only minor discrepancies between observed (circles) and corrected-for-optimism (Xs) survival. A fairly high C statistic (0.88) was obtained, indicating good model discriminative ability.

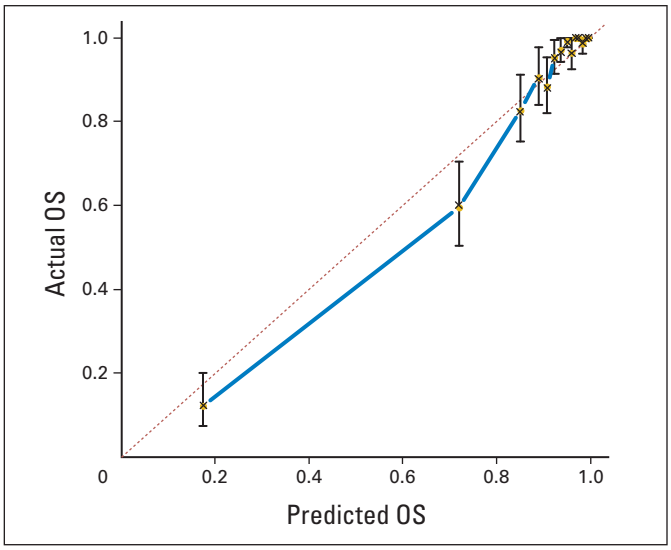

Fig 2. Calibration plots for internal validation of the overall survival (OS) nomogram. Nomogram-predicted probabilities were stratified in subgroups and, for each subgroup, the average predicted probability (*x* axis) was plotted against the Kaplan-Meier probability observed in the present case series (*y* axis). The 95% CIs of the Kaplan-Meier estimates are indicated by vertical lines. The Xs represent observed survival corrected for optimism in the same subgroup. The dashed line is the reference line, indicating where an ideal nomogram would lie.

DISCUSSION

Indications for treating clinically node-negative melanoma ≤ 1 mm are continually being refined.[3,9,10] One aim of this study was to investigate whether prognostic factors might predict regional lymph node involvement. We found that MR ≥ 1, LVI in the primary tumor, or both were significantly associated with SN positivity. Among patients with metastatic SNs, MR ≥ 1 or LVI were significantly more likely than MR less than 1 or no LVI ($P < .001$ in both cases). Previous studies have investigated MR as a determinant of SN status in smaller series. Kesmodel et al[6] evaluated 181 patients with melanoma ≤ 1 mm undergoing SNB; they found that all patients with positive SNs also had MR more than 0. Sondak et al[18] developed a probabilistic model based on 419 patients with melanoma who had SNB. They found that patients younger than age 35 years with tumors less than 1 mm had a substantial risk of a positive SN, particularly if MR was high. Murali et al[19] also found that LVI was associated with SN positivity in melanomas ≤ 1.0 mm and concluded that SNB should be considered in patients with lymphatic permeation of melanoma at the primary site.

We also found that Breslow thickness of more than 0.75 mm and tumor ulceration were significantly related to SN positivity; however, these variables are established independent predictors of SN status.[3] Regarding regression, we found that the proportion of patients with a positive SN increased in the order of no regression, less than 50% regression, and ≥ 50% regression, but the association was not significant. Our findings therefore support the performance of SNB in patients with one or more of the following: more than 0.75 mm thickness, ulceration, MR one or more per square millimeter, and LVI.

Regarding outcomes, our findings provide support for the current melanoma staging system[3] by showing that high MR and ulceration were significantly predictive of poorer survival.

In our multivariable analysis, SN status emerged as an independent factor predicting survival. However, SN status was not included

as a prognostic factor in the most recent AJCC staging system,[3] and the value of SN status has been debated. Han et al[20] retrospectively evaluated 271 patients with melanomas ≤ 1 mm and showed that OS did not differ between patients with positive and negative SNs ($P = .53$); however, this study was characterized by short follow-up (median 2.1 years). Venna et al[21] examined SN status as a predictor of OS in 484 patients with thin melanoma, 34 of whom had a positive SN; by multivariable analysis, SN status was the most powerful predictor of survival ($P = .009$). That SN status predicts survival is in line with the idea that regional lymph node involvement is an indicator of the biologic aggressiveness of the disease and thus greater probability of extraregional spread and suggests that SN status can contribute to improving the risk stratification in patients with thin melanoma.

This study also found that LVI and extensive regression were independent predictors of OS, again in contrast to the current melanoma staging system.[3] Xu et al[22] evaluated LVI as an independent prognostic factor in 251 patients with primary melanoma. Multivariable logistic regression for 10-year metastasis was used to define independent prognostic factors, from which a prognostic tree was developed to identify different risk groups. Among thin melanomas, the prognostic tree identified T1b melanomas with LVI as having poor prognoses. Egger et al[23] investigated LVI in a cohort with primary melanoma of all thicknesses. They found that, although LVI was not an independent OS predictor, it was a powerful predictor of worse OS among patients with evidence of regression.

In our multivariable analysis, extensive regression—≥ 50% of the entire lesion—was strongly associated with poor OS. Some studies have reported similar findings[24,25]; however, other studies have reported that regression has no effect on prognosis.[26,27] It is possible that thin melanomas with regression are actually thicker, but that the measured thickness of residual melanoma in the regressed tumor is an underestimate of original thickness. In such cases, the metastatic potential of the tumor might be better predicted by the original thickness rather than the thickness of residual melanoma in the regressed tumor, thereby explaining the association of regression with metastasis. The effect of regression in masking thickness is likely to be proportionally greater in thin melanomas, a hypothesis supported by Massi et al,[24] who found that tumor thickness and regression thickness were strong independent predictors of progression in thin melanomas.

On the basis of the hypothesis that the greater the extent of regression, the greater the underestimate of true thickness, we divided thin melanomas into two groups: one without regression or not exceeding 50%, the other with regression ≥ 50%. We found that in the latter group, regression was a reliable prognostic variable.

Because our series was large with long follow-up and strong prognostic associations were observed, we decided to develop a nomogram to predict 12-year OS. We propose the nomogram as a useful predictor of survival in individual patients and as a useful tool for risk stratification in clinical studies. It is noteworthy that the nomogram includes age as an important determinant of prognosis, because older age at diagnosis was significantly related to a poorer outcome. Other recent studies have also reported that older age was significantly associated with lower survival.[28,29]

Another interesting finding of our study was that most recurrences developed more than 5 years after diagnosis, and often 8 to 10 years later. In general, disease recurrence 10 years after initial treatment is rare; however, late recurrences are known, and they seem more common in patients with thin primary lesions.[30]

To conclude, we have found that LVI and extensive regression are independent predictors of survival in patients with thin melanomas, and we propose that these variables should be included in a revised melanoma staging system. We have also shown that SN status is an independent predictor of survival and that high MR and presence of LVI predict SN positivity, so their presence should suggest performing an SNB. In the absence of data from randomized controlled trials, our retrospective data provide rational bases for making treatment decisions in patients with thin melanoma by identifying those at relatively high risk of dying from their disease who may benefit from more aggressive treatments and long-term follow-up. Nevertheless, further studies on independent series are advisable to assess the reproducibility of our results, externally validate the nomogram, and confirm its utility for decision making.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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