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Prognostic factors in distinct melanoma types

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Citation

Ipenburg, N. A. (2022, March 2). *Prognostic factors in distinct melanoma types*. Retrieved from <https://hdl.handle.net/1887/3277983>

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

CHAPTER 7

External validation of a prognostic model to predict survival of sentinel node-negative melanoma patients

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ABSTRACT

Background. Identifying patients with sentinel node-negative melanoma at high risk of recurrence or death is important. The European Organisation for Research and Treatment of Cancer (EORTC) recently developed a prognostic model including Breslow thickness, ulceration and site of the primary tumor. The aims of the present study were to validate this prognostic model externally and to assess whether it could be improved by adding other prognostic factors.

Methods. Patients with sentinel node-negative cutaneous melanoma were included in this retrospective single-institution study. The beta values of the EORTC prognostic model were used to predict recurrence-free survival and melanoma-specific survival. The predictive performance was assessed by discrimination (c-index) and calibration. Seeking to improve the performance of the model, additional variables were added to a Cox proportional hazards model.

Results. Some 4235 patients with sentinel node-negative cutaneous melanoma were included. The median follow-up time was 50 (IQR 18.5–81.5) months. Recurrences and deaths from melanoma numbered 793 (18.7%) and 456 (10.8%) respectively. Validation of the EORTC model showed good calibration for both outcomes, and a c-index of 0.69. The c-index was only marginally improved to 0.71 when other significant prognostic factors (sex, age, tumor type, mitotic rate) were added.

Conclusion. This study validated the EORTC prognostic model for recurrence-free and melanoma-specific survival of patients with negative sentinel nodes. The addition of other prognostic factors only improved the model marginally. The validated EORTC model could be used for personalizing follow-up and selecting high-risk patients for trials of adjuvant systemic therapy.

INTRODUCTION

Sentinel node biopsy (SNB) has become a standard staging procedure in patients with clinically-localized primary cutaneous melanoma. The status of the sentinel node (SN) is the strongest independent prognostic factor in clinical stage I and II melanoma.¹ SN-negative melanoma has a better survival rate than SN-positive melanoma.^{1,2} However, a negative SN does not guarantee disease-free survival, with reported recurrence rates in this group varying between 6% and 29%.³⁻¹² Initial trial results showed that adjuvant postoperative systemic therapies are effective for stage III melanoma, and trials with adjuvant programmed cell death protein 1 inhibitors in high-risk SN-negative stage II melanoma have recently been initiated (NCT03553836 and NCT03405155).¹³⁻¹⁶ As these drugs can have serious side-effects, identifying patients who are at high risk of recurrence is important. Multiple smaller studies have identified risk factors for recurrence in SN-negative melanoma.^{3,5-9,17,18} However, combining risk factors is essential when estimating the recurrence risk of an individual patient.

A recently published prognostic model and nomogram for recurrence and melanoma-specific mortality addressed this issue.¹¹ This prognostic model was built using 3180 patients from four European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group centers, and included as parameters: Breslow thickness, ulceration and primary tumor site. Clinical prognostic models must be validated externally to ensure that the prediction is accurate and applicable to other populations.¹⁹ This EORTC model has not yet been externally validated. Therefore, it is not known how applicable it is to other populations. The primary aim of the present study was to validate the EORTC model in a large external cohort of patients with SN-negative melanoma. The secondary aim was to assess whether adding other known prognostic factors would improve the accuracy of the model.

METHODS

Patients

This study used prospectively collected data from the database of Melanoma Institute Australia (MIA). Data were extracted from the MIA Research Database, with written informed patient consent and institutional review board approval (Sydney South West Area Health Service institutional ethics review committee Protocol Number X15-0081).

Lymphoscintigraphy and SNB

A SN was defined as a lymph node on the direct lymphatic drainage pathway from the primary tumor.²⁰ SNB was offered to patients without clinical evidence of metastatic disease whose melanoma was ≥ 1 mm thick, or thinner if adverse histopathological features were present, such as ulceration, Clark level IV or V, or tumor mitotic rate of 1 per mm² or higher. Technical details of lymphoscintigraphy and SNB at MIA have been described previously.^{21,22} In short, preoperative dynamic and static lymphoscintigraphy were performed using ^{99m}Tc labeled antimony sulphide colloid. Since 2008, single photon emission computed tomography with integrated computerized tomography (SPECT/CT) has been routinely added. The biopsy was performed using Patent Blue Dye and, since May 1995, a gamma ray detection probe has also been employed. Pathologists examined multiple sections and used S100, HMB-45 and, since 2010, MelanA immunohistochemistry.²³

Data collection

Data on patient demographics (sex, age), primary tumor characteristics (location, Breslow thickness, Clark level, tumor type, ulceration, tumor mitotic rate, regression, lymphovascular invasion, vascular invasion), SN characteristics (number of SNs, drainage sites), recurrence (date, site and type of recurrence), type of treatment after recurrence and follow-up (date of last follow-up, status at last follow-up) were recorded.

Statistical analysis

Patient characteristics were summarized using median (interquartile range (IQR)) for continuous variables and proportions for categorical variables. Baseline characteristics of the MIA cohort were compared with those of the EORTC cohort that was used to build the prognostic model. Comparison of continuous variables was performed using the Mann-Whitney *U* test and values of categorical variables were compared using the Pearson's χ^2 test. Melanoma-specific survival (MSS) was calculated as the interval from initial diagnosis to melanoma-related death. Patients who died from a non-melanoma cause and those still alive at last follow-up were censored. Recurrence-free survival (RFS) was calculated from the date of diagnosis to the date of recurrence or death from any cause. Censoring occurred at the end of follow-up.

The final EORTC model for RFS and MSS included Breslow thickness (logarithmically transformed), ulceration and primary tumor site.¹¹ To assess model discrimination, Harrell's

concordance index (c-index) was calculated.²⁴ For each patient in the cohort, a risk score was calculated using the EORTC nomogram. Based on these risk scores, patients were classified as having a low risk (score 0 – 6), an intermediate risk (score 7 – 9) or a high risk (score 10 or more) of recurrence or melanoma-specific death.¹¹ Kaplan-Meier curves were produced for each risk group. Internal validation was performed on the MIA cohort using the bootstrap method. Model calibration was assessed by plotting the predicted survival and recurrence against the observed frequency.

New co-variables were added to investigate whether the predictive performance of the EORTC model could be improved. The American Joint Committee on Cancer (AJCC) acceptance criteria for individualized prognostic models were taken into account when building the model.²⁵ The following potential prognostic factors were selected based on clinical experience and literature review: gender, age, ulceration, Breslow thickness, primary tumor site, melanoma subtype, Clark level, tumor mitotic rate, regression, number of SN fields, and total number of SNs.^{3,5,6,11,26,27} To address the possibility of a non-linear association with outcomes, the continuous variables age and Breslow thickness were modelled by logarithmic transformation.¹¹ A full model was built with all variables that had a $P \leq 0.20$ in univariable analysis. Variables were removed from the full model by backward stepwise elimination using the Akaike information criterion to achieve the smallest value.²⁸ Model performance was assessed with calibration plots and c-indices. The proportional hazards assumption was checked for all variables using Schoenfeld residual plots and corresponding test statistics. P-values were two-sided and considered statistically significant if <0.05 . Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between January 1992 and December 2015, 5443 patients with a clinically localized primary cutaneous melanoma underwent SNB at MIA. Of these, 4431 (81.4%) were SN-negative and 1012 (18.6%) were SN-positive. Patients were excluded if they had melanoma in situ (7), (micro)satellites (135), in-transit metastases (10) or if preoperative ultrasound examination had revealed nodal metastasis (6). Thirty-eight patients who participated in the Multicenter Selective Lymphadenectomy Trial II and had a negative SN on histological assessment, but a positive reverse transcriptase-PCR finding in their SNs, were also excluded. Ultimately, 4235 patients were included in this study.

Cohort characteristics

Baseline characteristics of the 4235 SN-negative patients from MIA and 3180 in the EORTC cohort are shown in Table 1. Compared with the EORTC cohort, patients in the MIA cohort were significantly more often male (58% vs 52%, $P < 0.001$), and had more head and neck melanomas (17% vs 8%, $P < 0.001$). Superficial spreading melanoma was more common in EORTC patients, whereas patients at MIA presented more frequently with desmoplastic melanomas ($P < 0.001$). The MIA cohort more often had SNs in multiple node fields (19% vs. 13%, $P < 0.001$) and had more SNs identified and removed (median 2 vs. 1).

Table 1. Clinicopathologic characteristics of the model development (EORTC) and validation cohort (MIA).

Characteristic	EORTC	MIA	P-value#
Total number of patients	3180	4235	
Gender			< 0.001
Male	1668 (52.5)	2463 (58.2)	
Female	1510 (47.5)	1772 (41.8)	
Missing	2 (0.1)	0 (0)	
Age at diagnosis (years)*	55 (44 – 67)	58 (47.5 – 68.5)	
Primary tumor site			< 0.001
Head and neck	259 (8.1)	716 (16.9)	
Upper limb	556 (17.5)	844 (19.9)	
Lower limb	996 (31.3)	1060 (25.0)	
Trunk	1360 (42.8)	1615 (38.1)	
Breslow thickness*	1.7 (1.1 – 3.0)	1.8 (1.0 – 2.6)	
Tumor mitotic rate/mm²*	NA	3.0 (0.5 – 5.5)	
0	39 (1.2)	417 (9.8)	< 0.001
≥1	112 (3.5)	3631 (85.7)	
Missing	3029 (95.3)	187 (4.4)	
Ulceration			0.944
Absent	2264 (71.2)	2890 (68.2)	
Present	788 (24.8)	1002 (23.7)	
Missing	128 (4.0)	343 (8.1)	
Melanoma subtype			< 0.001
Superficial spreading melanoma	1739 (54.7)	1731 (40.9)	
Nodular melanoma	885 (27.8)	1295 (30.6)	
Acral lentiginous melanoma	93 (2.9)	62 (1.5)	
Lentigo maligna melanoma	139 (4.4)	85 (2.0)	
Other	46 (1.4)	442 (10.4)	
Missing	278 (8.7)	620 (14.6)	

Clark level			< 0.001
I-II	271 (8.5)	58 (1.4)	
III	1230 (38.7)	1147 (27.1)	
IV	1354 (42.6)	2615 (61.7)	
V	140 (4.4)	326 (7.7)	
Missing	185 (5.8)	89 (2.1)	
Regression			
Absent	NA	1228 (29.0)	
Early/Intermediate	NA	2011 (47.5)	
Late	NA	348 (8.2)	
Missing	NA	648 (15.3)	
Vascular invasion			
Absent	NA	3371 (79.6)	
Present	NA	81 (1.9)	
Missing	NA	783 (18.5)	
Lymphovascular invasion			
Absent	NA	2876 (67.9)	
Present	NA	77 (1.8)	
Missing	NA	1282 (30.3)	
Total no. of SNs*	1 (1 – 2)	2 (1 – 3)	
Drainage site of identified SNs			
Axilla	NA	2215 (52.3)	
Groin	NA	1174 (27.7)	
Neck	NA	794 (18.7)	
Other	NA	52 (1.2)	
No. of drainage sites			
1	NA	3436 (81.1)	
2	NA	717 (16.9)	
3	NA	73 (1.7)	
4	NA	9 (0.2)	
No. of SN fields			< 0.001
1	2768 (87.0)	3436 (81.1)	
>1	412 (13.0)	799 (18.9)	

Values in parentheses are percentages unless indicated otherwise; *values are median (IQR); #Pearson's χ^2 test; NA not available.

Survival

The median duration of follow-up was 50 (IQR 18.5 – 81.5) months. Melanoma recurred in 793 patients (19%), with a median time to recurrence of 26 (IQR 8.5 – 43.5) months. A first recurrence occurred 5 years or more after the melanoma diagnosis in 144 of these patients

(18%) and 28 patients (4%) had their first recurrence after 10 years or more. Regional node recurrence was seen in 192 of the patients (24%) and 335 (42%) had a distant site as the first site of recurrence. The incidence of false-negative SNB, defined as a regional nodal recurrence in a patient whose SNs had been found to be tumor-free, was 16%. MSS rates at 5 and 10 years were 89% (95% confidence interval (CI): 87% – 90%) and 80% (95% CI: 78% – 82%). RFS rates at 5 and 10 years were 80% (95% CI: 78% – 81%) and 71% (95% CI: 69% – 73%).

External validation and improvement of the EORTC model

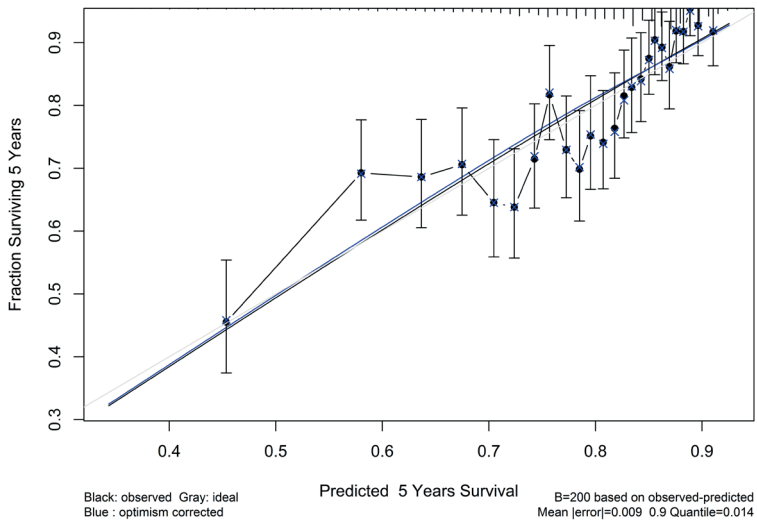
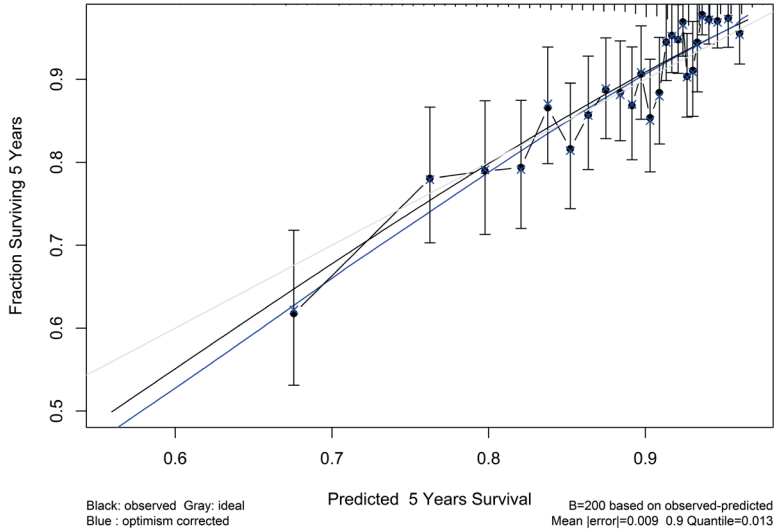
The predictive ability of the EORTC model was assessed by calculating the c-index. The c-indices of the externally validated EORTC model were 0.69 (95% CI: 0.67 – 0.71) and 0.69 (95% CI: 0.66 – 0.72) for RFS and MSS respectively. The prognostic models appeared well calibrated as observed 5-year survival rates were close to the predicted 5-year rates (Figure 1). Figure 2 displays the Kaplan-Meier curves for the three risk classes. Eight potential prognostic factors for RFS and MSS were added to the EORTC models: gender, age, melanoma subtype, Clark level, mitotic rate, regression, total number of SNs removed and number of SN fields, were added to the EORTC models.

After backward selection, regression, Clark level, total number of SNs removed and multiple SN fields did not add enough to the prediction of the outcomes to justify their inclusion in the final model. Table 2 shows the final model that included gender, age, melanoma subtype, tumor mitotic rate, Breslow thickness, ulceration, and primary tumor site. The c-index was 0.71 (95% CI: 0.69 – 0.73) for the RFS model and also 0.71 (95% CI: 0.68 – 0.74) for the MSS model.

Figure 1. Calibration plots of the Cox proportional hazards model for the prediction of five-year recurrence-free survival and melanoma-specific survival.

1A Melanoma-specific survival

1B Recurrence-free



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Figure 2. Kaplan-Meier plots for the low-, intermediate- and high-risk group.
 2A Melanoma-specific survival
 2B Recurrence-free survival

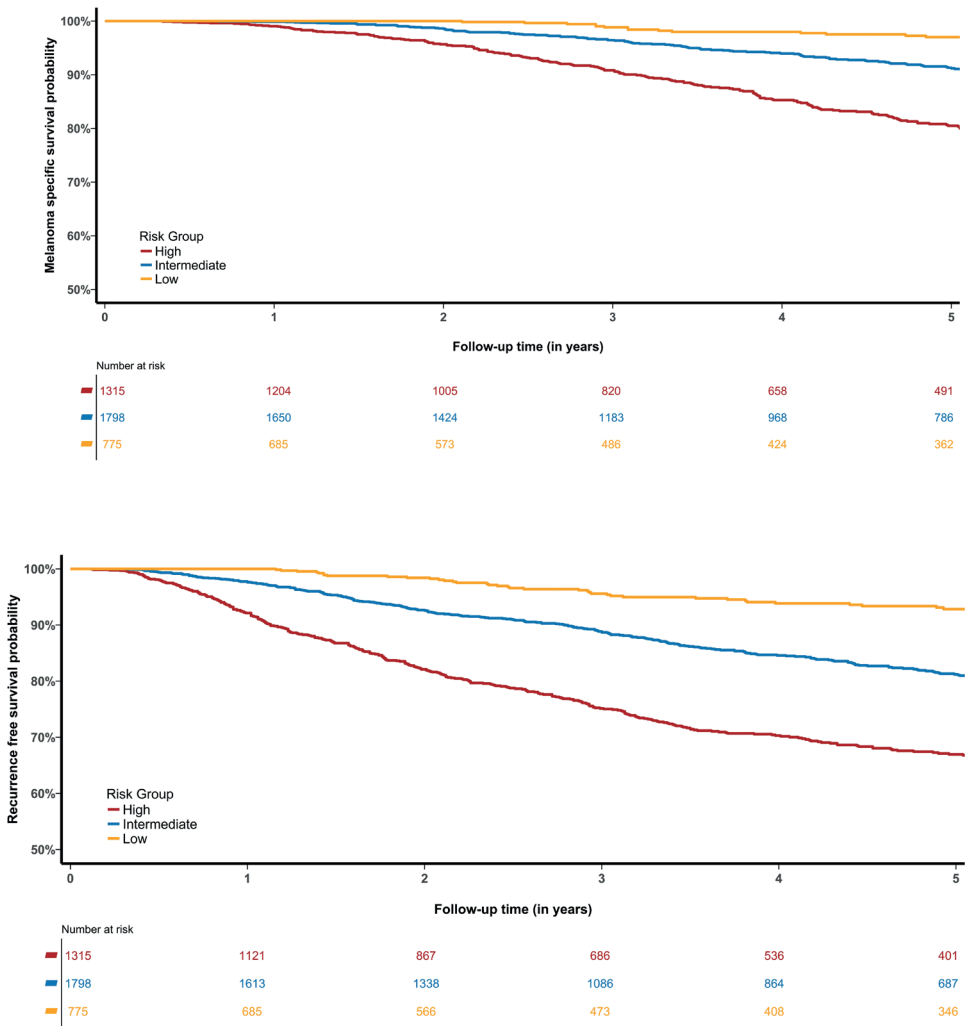


Table 2. Updated model for prediction of recurrence-free survival and melanoma-specific survival.
2A Melanoma-specific survival

Variable	Univariable		Multivariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR	P-value
Gender						
Female	1	< 0.001	1	< 0.001	1	< 0.001
Male	1.71 (1.40 - 2.08)		1.50 (1.19 - 1.90)		1.50 (1.18 - 1.89)	
Age at diagnosis (years)	2.75 (1.94 - 3.89)	< 0.001	1.76 (1.18 - 2.61)	0.005	1.79 (1.21 - 2.66)	0.004
Breslow thickness (mm)	2.04 (1.79 - 2.33)	< 0.001	1.46 (1.18 - 1.81)	< 0.001	1.56 (1.29 - 1.89)	< 0.001
Tumor mitotic rate	1.04 (1.03 - 1.05)	< 0.001	1.02 (1.00 - 1.03)	0.017	1.02 (1.00 - 1.03)	0.039
Ulceration						
Absent	1	< 0.001	1	< 0.001	1	< 0.001
Present	2.30 (1.90 - 2.79)		1.60 (1.27 - 2.01)		1.57 (1.25 - 1.96)	
Primary tumor site						
Head and Neck	1	< 0.001	1	0.026	1	0.037
Lower Limb	0.74 (0.56 - 0.98)		0.88 (0.64 - 1.22)		0.91 (0.66 - 1.26)	
Trunk	0.88 (0.68 - 1.13)		0.92 (0.69 - 1.23)		0.92 (0.69 - 1.21)	
Upper Limb	0.49 (0.35 - 0.68)		0.57 (0.39 - 0.84)		0.59 (0.41 - 0.86)	
Clark level						
II/III	1	< 0.001	1	0.260		
IV	1.41 (1.12 - 1.77)		1.21 (0.93 - 1.57)			
V	2.54 (1.84 - 3.52)		1.40 (0.88 - 2.21)			
Melanoma subtype						
Superficial spreading	1	< 0.001	1	0.008	1	0.013
Nodular	1.75 (1.41 - 2.17)		1.14 (0.89 - 1.47)		1.15 (0.90 - 1.48)	
Acral lentiginous	3.60 (2.21 - 5.88)		2.89 (1.62 - 5.15)		2.80 (1.58 - 4.96)	
Desmoplastic	1.20 (0.85 - 1.70)		0.86 (0.58 - 1.29)		0.92 (0.63 - 1.35)	
Lentigo maligna	0.96 (0.42 - 2.16)		0.86 (0.37 - 1.98)		0.90 (0.39 - 2.06)	
Other	1.91 (0.47 - 7.72)		1.57 (0.38 - 6.49)		1.56 (0.38 - 6.39)	

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Regression				
Absent	1	0.762		
Early/Intermediate	0.96 (0.78 - 1.19)			
Late	0.87 (0.59 - 1.28)			
Total no. of SNs	1.02 (0.94 - 1.10)	0.676		
No. of SN fields				
1	1	0.054	1	0.648
>1	1.25 (1.00 - 1.56)		0.94 (0.71 - 1.24)	

2B Recurrence-free survival

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Female	1	< 0.001	1	0.014
Male	1.42 (1.24 - 1.64)		1.25 (1.05 - 1.49)	
Age at diagnosis (years)	2.92 (2.26 - 3.77)	< 0.001	1.67 (1.23 - 2.26)	0.001
Breslow thickness (mm)	2.06 (1.87 - 2.27)	< 0.001	1.52 (1.28 - 1.80)	< 0.001
Tumor mitotic rate	1.05 (1.04 - 1.05)	< 0.001	1.03 (1.02 - 1.04)	< 0.001
Ulceration				
Absent	1	< 0.001	1	< 0.001
Present	2.07 (1.79 - 2.39)		1.46 (1.22 - 1.74)	
Primary tumor site				
Head and Neck	1	< 0.0001	1	0.001
Lower Limb	0.77 (0.63 - 0.93)		0.98 (0.77 - 1.25)	
Trunk	0.64 (0.53 - 0.77)		0.73 (0.58 - 0.91)	
Upper Limb	0.50 (0.40 - 0.63)		0.67 (0.51 - 0.88)	

Variable	Univariable			Multivariable		
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR	P-value
Clark level						
II/III	1	<0.001	1	0.138		
IV	1.50 (1.26 - 1.78)		1.21 (0.99 - 1.47)			
V	2.86 (2.25 - 3.64)		1.33 (0.94 - 1.88)			
Melanoma subtype						
Superficial spreading	1	<0.001	1	0.006	1	0.003
Nodular	1.73 (1.48 - 2.04)		1.14 (0.94 - 1.38)		1.13 (0.94 - 1.36)	
Acral lentiginous	3.28 (2.21 - 4.88)		2.03 (1.27 - 3.26)		2.05 (1.29 - 3.24)	
Desmoplastic	1.21 (0.94 - 1.56)		0.82 (0.60 - 1.11)		0.86 (0.64 - 1.15)	
Lentigo maligna	1.63 (1.02 - 2.60)		1.25 (0.73 - 2.14)		1.33 (0.81 - 2.17)	
Other	3.13 (1.40 - 7.04)		2.15 (0.86 - 5.35)		2.46 (1.07 - 5.65)	
Regression						
Absent	1	0.046	1	0.763		
Early/Intermediate	0.87 (0.75 - 1.02)		0.94 (0.79 - 1.11)			
Late	0.72 (0.54 - 0.96)		0.98 (0.71 - 1.35)			
Total no. of SNs	1.00 (0.95 - 1.06)	0.894				
No. of SN fields						
1	1	0.236				
>1	1.11 (0.94 - 1.31)					

DISCUSSION

This single institution study successfully validated the EORTC model for prediction of RFS and MSS in patients with SN-negative melanoma. External validation is an essential step in assessing the generalizability of a prognostic model.^{19,25} As expected, the model performance was not as good as in the derivation data.¹⁹ The c-indices for the recurrence and melanoma-specific mortality models were both 0.69 in our population, compared to 0.74 and 0.76 in the EORTC cohort.¹¹ A c-index of 0.69 means that the model correctly predicted recurrence or melanoma-specific death in 69% of the patients.²⁹

The present cohort of patients with SN-negative melanoma differed from the EORTC cohort with respect to several important clinicopathological characteristics. More of the present patients were men, more had head and neck primary melanomas, and the melanomas drained more frequently to multiple node fields and to more SNs. Tumors in the EORTC cohort had a lower Clark level in general and superficial spreading melanomas were more numerous. Despite these differences in patient characteristics, the EORTC model proved to be a strong predictive tool in the present population.

Simplicity is a strength of the EORTC model, as it is based on three common tumor characteristics. Although ease of use in clinical practice is important, this should not come at the cost of leaving out strong but more complex prognostic factors. The present study therefore investigated whether the model performance could be improved by adding co-variables, and confirmed the independent prognostic value of sex, age, primary tumor site, Breslow thickness, ulceration, melanoma subtype and tumor mitotic rate. The tumor mitotic rate is one of the most important risk factors for recurrence and melanoma-specific mortality^{26,30} It was an essential part of the AJCC/UICC melanoma staging classification for almost 10 years.^{2,30} Smaller studies, some with up to 95% missing values, failed to show an association of tumor mitotic rate with survival in SN-negative melanoma.^{5,8,11} In multivariable analysis, the present study confirmed the independent prognostic effect of this parameter. Another tumor characteristic of interest is regression. Regression has been found to be an independent prognostic factor for patients with melanoma in general.²⁷ In line with previous studies, the independent prognostic value was not proven for SN-negative melanoma in our analysis.^{5,6} Adding gender, age, melanoma subtype and tumor mitotic rate to the EORTC model improved the predictive ability of the models by only 2% (with overlapping confidence intervals). The authors consider that this improvement is insufficient to justify changing the simple EORTC model.

Only one other prognostic model for predicting melanoma recurrence in SN-negative patients has been published.³ In that study, combining Breslow thickness, ulceration and microsatellites yielded a c-index of 0.75. Microsatellites are caused by lymphovascular dissemination and their presence is well known to be associated with worse survival.^{31,32} Patients with non-nodal regional metastases (microsatellites, satellites, or in-transit metastases) are already regarded as high-risk patients and should not have been included. According to the AJCC 8th edition melanoma staging system, these patients are classified as having at least stage IIIB melanoma and they are eligible for adjuvant systemic therapy.²

The recurrence rate of 19% in the present cohort is comparable to previously reported rates ranging from 6 to 29%.³⁻¹¹ Importantly, all previous studies with a median follow-up of at least 5 years reported a recurrence rate of over 14%.^{4,6,7,11,12} The present study has shown that first recurrences are frequently (18%) found after more than 5 years of follow-up. Identifying these patients is important, as follow-up is considered unnecessary after 5 years in some countries.³³ This prediction model could help in designing individualized follow-up regimens. As 42% of all patients with a recurrence had their first relapse at a distant site, these patients with aggressive tumor biology might be those who could benefit most from adjuvant systemic therapy. The externally validated EORTC model could help to identify patients with the highest risk of recurrence or melanoma-related death.

The present study has several limitations. Lymphatic invasion is a known prognostic factor in melanoma, but could unfortunately not be assessed reliably in this study because there were too many missing values (30%).^{34,35} The retrospective design and short follow-up of some patients are other limitations.

CONCLUSION

This external validation confirmed the value of the EORTC prognostic model for RFS and MSS of SN-negative melanoma. Addition of other known prognostic factors only marginally improved the model. The validated EORTC model can be used for patient counselling, personalizing follow-up and selection of high-risk patients for clinical trials of adjuvant systemic therapies.

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