Original article

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

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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 tumour. 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 β 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 (i.q.r. 18·5–81·5) months. Recurrences and deaths from melanoma numbered 793 (18·7 per cent) and 456 (10·8 per cent) 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, tumour 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.

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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 per cent[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[3,5–9,17,18] have identified risk factors for recurrence in SN-negative melanoma. 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 centres, and included as parameters: Breslow thickness, ulceration and primary tumour 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 validated externally. 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

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 sentinel node biopsy

A SN was defined as a lymph node on the direct lymphatic drainage pathway from the primary tumour[20]. SNB was offered to patients without clinical evidence of metastatic disease whose melanoma was at least 1 mm thick, or thinner if adverse histopathological features were present, such as ulceration, Clark level IV or V, or a tumour mitotic rate of 1 per mm^2 or higher. Technical details of lymphoscintigraphy and SNB at MIA have been described previously[21,22]. In short, preoperative dynamic and static lymphoscintigraphy were done using ^{99m}Tc-labelled antimony sulphide colloid. Since 2008 single-photon emission CT with integrated CT has been added routinely. The biopsy was performed using Patent Blue dye and, since May 1995, a γ-ray detection probe has also been employed. Pathologists examined multiple sections and used S100, human melanoma black 45 and, since 2010, MelanA immunohistochemistry[23].

Data collection

Data on patient demographics (sex, age), primary tumour characteristics (location, Breslow thickness, Clark level, tumour type, ulceration, tumour 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 (i.q.r.) 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 done using the Mann–Whitney *U* test and categorical variables were compared using 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 tumour 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 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[3,5,6,11,26,27]: sex, age, ulceration, Breslow thickness, primary tumour site, melanoma subtype, Clark level, tumour mitotic rate, regression, number of SN fields and total number of SNs. 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 with $P \leq 0{\cdot}200$ 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

Table 1 Clinicopathological characteristics of the model development and validation cohorts

	EORTC (*n* = 3180)	MIA (*n* = 4235)	*P*†
Age at diagnosis (years)*	55 (44–67)	58 (47·5–68·5)	
Sex			< 0·001
M	1668 (52·5)	2463 (58·2)	
F	1510 (47·5)	1772 (41·8)	
Missing	2 (0·1)	0 (0)	
Primary tumour 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)	
Missing	9 (0·3)	0 (0)	
Breslow thickness*	1·7 (1·1–3·0)	1·8 (1·0–2·6)	
Tumour mitotic rate (per mm^2)*	n.a.	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
No	2264 (71·2)	2890 (68·2)	
Yes	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			
None	n.a.	1228 (29·0)	
Early/intermediate	n.a.	2011 (47·5)	
Late	n.a.	348 (8·2)	
Missing	n.a.	648 (15·3)	
Vascular invasion			
No	n.a.	3371 (79·6)	
Yes	n.a.	81 (1·9)	
Missing	n.a.	783 (18·5)	
Lymphovascular invasion			
No	n.a.	2876 (67·9)	
Yes	n.a.	77 (1·8)	
Missing	n.a.	1282 (30·3)	
Total no. of SNs*	1 (1–2)	2 (1–3)	
Drainage site of identified SNs			
Axilla	n.a.	2215 (52·3)	
Groin	n.a.	1174 (27·7)	

Table 1 Continued

	EORTC (*n* = 3180)	MIA (*n* = 4235)	*P*†
Neck	n.a.	794 (18·7)	
Other	n.a.	52 (1·2)	
No. of drainage sites			
1	n.a.	3436 (81·1)	
2	n.a.	717 (16·9)	
3	n.a.	73 (1·7)	
4	n.a.	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 (i.q.r). EORTC, European Organisation for Research and Treatment of Cancer; MIA, Melanoma Institute Australia; n.a., not available; SN, sentinel node. †Pearson's χ^2 test.

proportional hazards assumption was checked for all variables using Schoenfeld residual plots and corresponding test statistics. *P* values were two-sided and $P < 0{\cdot}050$ was considered statistically significant. Statistical analyses were performed with SAS® version 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 per cent) were SN-negative and 1012 (18·6 per cent) 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 (58·2 *versus* 52·5 per cent; $P < 0{\cdot}001$), and had more head and neck melanomas (16·9 *versus* 8·1 per cent; $P < 0{\cdot}001$). Superficial spreading melanoma was more common in the EORTC cohort, whereas patients at MIA presented more frequently with desmoplastic melanomas ($P < 0{\cdot}001$). The MIA cohort more often had SNs in multiple node fields (18·9 *versus* 13·0 per cent; $P < 0{\cdot}001$), and had more SNs identified and removed (median 2 *versus* 1).

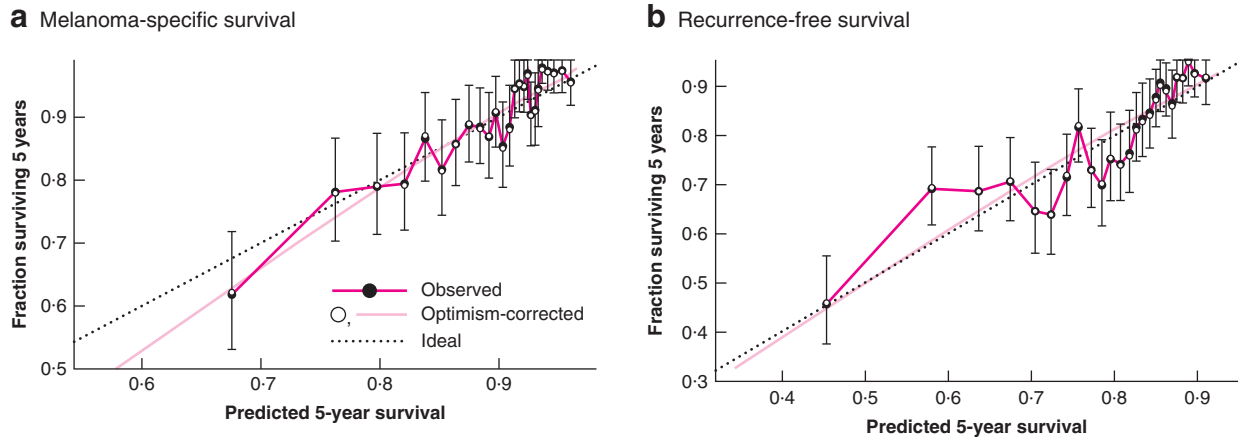
Recurrence and survival

The median duration of follow-up was 50 (i.q.r. 18·5–81·5) months. Melanoma recurred in 793 patients (18·7 per cent), with a median time to recurrence of 26 (i.q.r. 8·5–43·5) months. A first recurrence occurred 5 years or more after the diagnosis of melanoma in 144 of these patients (18·2 per cent) and 28 patients (3·5 per cent) had their first recurrence after 10 years or more. Regional node recurrence was seen in 192 patients (24·2 per cent) and 335 (42·2 per cent) 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 tumour-free, was 15·9 per cent. There were 456 deaths from melanoma (10·8 per cent). The MSS rates at 5 and 10 years were 88·6 (95 per cent c.i. 87·4 to 89·8) and 80·3 (78·3 to 82·3) per cent respectively. The respective RFS rates at 5 and 10 years were 79·6 (78·2 to 81·0) and 70·8 (68·8 to 72·8) per cent.

External validation and improvement of the EORTC model

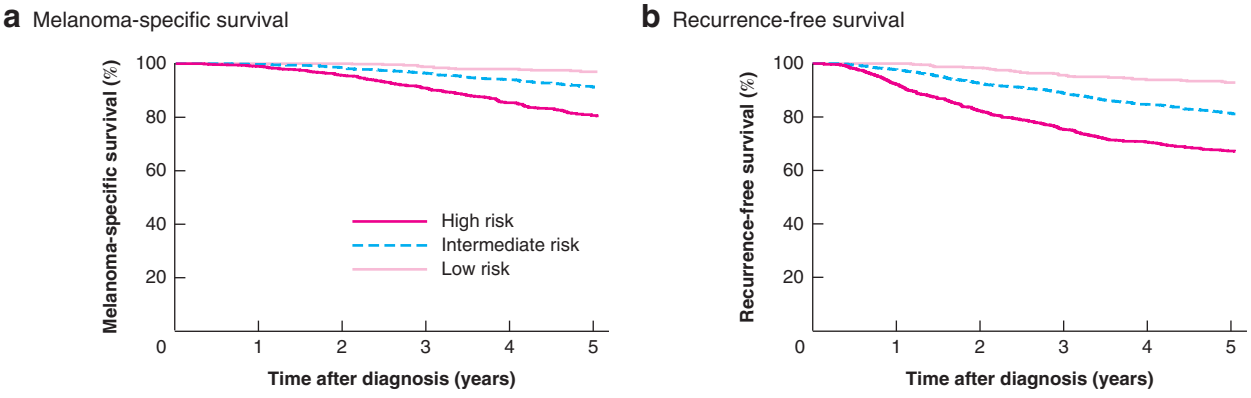
The predictive ability of the EORTC model was assessed by calculating the c-index. The c-indices of the externally validated EORTC model were 0·69 (95 per cent c.i. 0·67 to 0·71) and 0·69 (0·66 to 0·72) for RFS and MSS respectively. The prognostic models appeared well calibrated as the observed 5-year survival rates were close to the predicted 5-year rates (*Fig. 1*). *Fig. 2* shows the Kaplan–Meier curves for the three risk classes.

Fig. 1 Calibration plots of the Cox proportional hazards model for the prediction of 5-year recurrence-free survival and melanoma-specific survival



a Melanoma-specific survival and b recurrence-free survival. a Bootstrap used 200 replications based on observed rate minus predicted rate. Mean absolute error = 0.009, 90th percentile = 0.013. b Bootstrap used 200 replications based on observed rate minus predicted rate. Mean absolute error = 0.009, 90th percentile = 0.014. Error bars denote 95% c.i. of the observed rate.

Fig. 2 Kaplan–Meier plots for the low-, intermediate- and high-risk groups



No. at risk

High risk	1315	1204	1005	820	658	491
Intermediate risk	1798	1650	1424	1183	968	786
Low risk	775	685	573	486	424	362

No. at risk

High risk	1315	1121	867	686	536	401
Intermediate risk	1798	1613	1338	1086	864	687
Low risk	775	685	566	473	408	346

a Melanoma-specific survival and **b** recurrence-free survival.

Eight potential prognostic factors for RFS and MSS were added to the EORTC models: sex, age, melanoma subtype, Clark level, mitotic rate, regression, total number of SNs removed and number of SN fields. After backward selection, regression, Clark level, total number of SNs removed and multiple SN fields did not add enough to the prediction of outcomes to justify their inclusion in the final model. *Table S1* (supporting information) shows the final model that included sex, age, melanoma subtype, tumour mitotic rate, Breslow thickness, ulceration and primary tumour site. The c-index was 0·71 (0·69 to 0·73) for the RFS model and also 0·71 (0·68 to 0·74) for the MSS model.

Discussion

This single-institution study 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 the MIA population, compared with 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 per cent 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. Tumours 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 tumour 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 tumour site, Breslow thickness, ulceration, melanoma subtype and tumour mitotic rate. The tumour 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[5,8,11], some with up to 95 per cent missing values, failed to show an association between tumour mitotic rate and survival in SN-negative melanoma. In multivariable analysis, the present study confirmed the independent prognostic effect of this parameter. Another tumour 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[5,6], independent prognostic value was not proven for SN-negative melanoma in the present analysis. Adding sex, age, melanoma subtype and tumour mitotic rate to the EORTC model improved the predictive ability of the models by only 2 per cent (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 recurrence in SN-negative melanoma 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 and should not have been included. According to the eighth edition of the AJCC melanoma staging system[2], these patients are classified as having at least stage IIIB melanoma and are eligible for adjuvant systemic therapy.

The recurrence rate of 18·7 per cent in the present cohort is comparable to previously reported rates ranging from 6 to 29 per cent[3–11]. Importantly, all previous studies[4,6,7,11,12] with a median follow-up of at least 5 years reported a recurrence rate of over 14 per cent. The present study has shown that first recurrences are frequently (18·2 per cent) 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. As 42·2 per cent of all patients with a recurrence had their first relapse at a distant site, these patients with aggressive tumour 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 (30·3 per cent)[34,35]. The retrospective design and short follow-up of some patients are other limitations.

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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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.