Development and validation of a novel model to predict recurrence-free survival and melanoma-specific survival after sentinel lymph node biopsy in patients with melanoma: an international, retrospective, multicentre analysis

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Summary

Background The introduction of adjuvant systemic treatment for patients with high-risk melanomas necessitates accurate staging of disease. However, inconsistencies in outcomes exist between disease stages as defined by the American Joint Committee on Cancer (8th edition). We aimed to develop a tool to predict patient-specific outcomes in people with melanoma rather than grouping patients according to disease stage.

Methods Patients older than 13 years with confirmed primary melanoma who underwent sentinel lymph node biopsy (SLNB) between Oct 29, 1997, and Nov 11, 2013, at four European melanoma centres (based in Berlin, Germany; Amsterdam and Rotterdam, the Netherlands; and Warsaw, Poland) were included in the development cohort. Potential predictors of recurrence-free and melanoma-specific survival assessed were sex, age, presence of ulceration, primary tumour location, histological subtype, Breslow thickness, sentinel node status, number of sentinel nodes removed, maximum diameter of the largest sentinel node metastasis, and Dewar classification. A prognostic model and nomogram were developed to predict 5-year recurrence-free survival on a continuous scale in patients with stage pT1b or higher melanomas. This model was also calibrated to predict melanoma-specific survival. Model performance was assessed by discrimination (area under the time-dependent receiver operating characteristics curve [AUC]) and calibration. External validation was done in a cohort of patients with primary melanomas who underwent SLNB between Jan 30, 1997, and Dec 12, 2013, at the Melanoma Institute Australia (Sydney, NSW, Australia).

Findings The development cohort consisted of 4071 patients, of whom 2075 (51%) were female and 1996 (49%) were male. 889 (22%) had sentinel node-positive disease and 3182 (78%) had sentinel node-negative disease. The validation cohort comprised 4822 patients, of whom 1965 (41%) were female and 2857 (59%) were male. 891 (18%) had sentinel node-positive disease and 3931 (82%) had sentinel node-negative disease. Median follow-up was 4·8 years (IQR 2·3–7·8) in the development cohort and 5·0 years (2·2–8·9) in the validation cohort. In the development cohort, 5-year recurrence-free survival was 73·5% (95% CI 72·0–75·1) and 5-year melanoma-specific survival was 86·5% (85·3–87·8). In the validation cohort, the corresponding estimates were 66·1% (64·6–67·7) and 83·3% (82·0–84·6), respectively. The final model contained six prognostic factors: sentinel node status, Breslow thickness, presence of ulceration, age at SLNB, primary tumour location, and maximum diameter of the largest sentinel node metastasis. In the development cohort, for the model's prediction of recurrence-free survival, the AUC was 0·80 (95% CI 0·78–0·81); for prediction of melanoma-specific survival, the AUC was 0·81 (0·79–0·84). External validation showed good calibration for both outcomes, with AUCs of 0·73 (0·71–0·75) and 0·76 (0·74–0·78), respectively.

Interpretation Our prediction model and nomogram accurately predicted patient-specific risk probabilities for 5-year recurrence-free and melanoma-specific survival. These tools could have important implications for clinical decision making when considering adjuvant treatments in patients with high-risk melanomas.

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Introduction

Melanoma is among the ten most common cancer types and accounts for most skin cancer-related deaths.[1,2] Adequate disease staging is essential for risk stratification and treatment planning. Globally, the American Joint Committee on Cancer (AJCC) staging system is the most frequently used tool for melanoma staging. In the 8th edition of the AJCC Cancer Staging Manual,

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Research in context

Evidence before this study

Although various prediction tools have been developed for personal risk assessment in patients with melanoma, few models are available for patients with stage II or stage III disease. We searched PubMed with the terms "prediction tool", "prediction model", "cutaneous melanoma", "recurrence", and "survival" for research articles published in English between Jan 1, 2009, and Dec 31, 2021. We excluded studies of patients with stage I or stage IV melanoma and those in which patients did not undergo sentinel lymph node biopsy. Most models for predicting outcomes in patients with stage II or stage III melanoma, including the 2023 population-based study by Lyth and colleagues, predicted only survival (melanoma-specific or overall) and were not externally validated. The externally validated model developed by Callender and colleagues, which predicted overall and recurrence-free survival in patients staged by sentinel lymph node biopsy, was similar to the model that we aimed to develop. However, we were not able to formally validate their model in our dataset because of incomplete reporting of the regression coefficients and baseline hazards of the final model. Furthermore, Callender and colleagues' model uses a dichotomous variabel for sentinel lymph node status.

Added value of this study

We developed a robust and well performing model based on a large cohort of patients with stage II and stage III melanomas after sentinel lymph node biopsy in three European countries for predicting 5-year recurrence-free and melanoma-specific survival. We also externally validated the model in a large Australian cohort. By transcending stage II and III melanoma, this model could support clinical decision making as to which patients could forgo adjuvant treatment, because it is able to accurately identify patients who are at an increased risk for recurrence and mortality. Unlike other models, our model incorporates mainly continuous variables, and it has improved predictive performance.

Implications of all the available evidence

Although previous attempts have been made to develop tools to improve prognostication for patients with melanoma, our model is one of only a few that works for both stage II and III disease and that predicts recurrence-free survival. Our model could potentially be used to provide personalised information for both medical practitioners and patients to inform decisions about whether to use adjuvant therapy in patients with stage II or III melanomas.

published in 2018, changes were made to determinants of substaging for melanoma—eg, removal of mitotic rate as a T-category criterion and revision of N subcategories—to increase the accuracy of prognostic estimates.[3,4]

Despite these improvements in substaging, the association between cancer stage and outcomes remains inconsistent, particularly in patients with stage II and III melanomas. For example, 5-year recurrence-free survival is 26·5% (95% CI 12·8–55·1) and melanoma-specific survival is approximately 82·0% in patients with stage IIC melanomas, whereas in patients with stage IIIA disease 5-year recurrence-free survival is 56·0% (37·0–84·7) and melanoma-specific survival is approximately 93·0%.[3,4] More robust, accurate, and personalised prognostic estimates for melanoma are thus needed.[5] Although several models have been developed to improve the accuracy of melanoma prognosis,[6–9] they have generally been based on variables that are not always readily available (eg, mitotic index), rely on categorised continuous variables, and have not undergone sufficient external validation to assess outcomes in patients with intermediate-to-thick (stage ≥pT1b) clinically localised melanomas. In this population, sentinel lymph node biopsy (SLNB) is a crucial tool for prognostication that identifies clinically occult lymph node metastases, aiding in determination of the N stage of the tumour and subsequently guiding adjuvant therapy eligibility.

After complete resection of high-risk melanoma, adjuvant systemic treatment with anti-PD-1 monotherapy (nivolumab or pembrolizumab) or targeted therapy (dabrafenib and trametinib) has increased recurrence-free survival for patients with stage III melanoma.[10–12] In patients with high-risk stage II melanomas (ie, stage IIB or IIC), early results[13] also suggest improved recurrence-free survival with adjuvant anti-PD-1 monotherapy, and as a result the US Food and Drug Administration has approved both pembrolizumab and nivolumab for use in these patients. Moreover, the KEYNOTE-716 trial[14] has also shown increased distant metastasis-free survival with pembrolizumab in patients with stage IIB or IIC melanoma. However, despite these advances in treatment, 5-year recurrence-free survival varies greatly within stage II (26·5–75·0%) and stage III (13·7–56·0%) melanomas.[4] Thus, many patients gain little absolute benefit from adjuvant treatments but are exposed to potentially severe and sometimes lifelong adverse events. For patients with an intermediate risk of recurrence (ie, those with pT1b or higher-stage disease and no clinically apparent metastases), accurate risk prediction is of great clinical importance both to guide adjuvant treatment decisions and to ensure that patients are well informed about the implications of their disease.

In this study, we aimed to develop and externally validate a model, based on readily available clinical characteristics, to predict recurrence-free and melanoma-specific survival in patients with stage pT1b or higher melanomas after SLNB.

Methods

Study design and participants

We did a retrospective, multicentre analysis to develop and validate a model to predict 5-year recurrence-free and

melanoma-specific survival in patients with melanoma. The development cohort comprised patients aged 13 years or older with confirmed primary melanomas who underwent SLNB between Oct 29, 1997, and Nov 11, 2013, at four melanoma centres associated with the European Organization for Research and Treatment of Cancer (EORTC; Charité Comprehensive Cancer Centre, Berlin, Germany; Netherlands Cancer Institute, Amsterdam, the Netherlands; Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; and Erasmus Medical Centre, Rotterdam, the Netherlands) as previously described.[15] The validation cohort consisted of patients of any age with confirmed primary melanoma who underwent SLNB between Jan 1, 1997, and Dec 31, 2013, at the Melanoma Institute Australia (Sydney, NSW, Australia). Patients with diverse histological subtypes and varied mutation statuses were eligible for inclusion in both cohorts. Patients with microsatellites, in-situ melanomas, in-transit, nodal, or any other overt metastases at diagnosis or a history of another malignancy were excluded from both cohorts. We chose to study patients in 1997–2013 to minimise the potential effect of efficacious systemic therapies for melanoma on outcomes.

The study was approved by the Erasmus Medical Centre Ethics Committee (MEC2017-375), the Melanoma Institute Australia Research Committee (MIA2022/453), and the Sydney Local Health District Ethics Committee (protocol No X15-0311 & 2019/ETH06854), all of which waived the requirement for informed consent because of the retrospective nature of the study. The study was reported according to Transparent Reporting of multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.

Procedures

In both cohorts, diagnosis of the primary melanoma was based on histopathological examination of an excision, punch, or shave biopsy sample. All biopsies were performed according to the local guidelines, which differed from each other only in minor details. For excision biopsy samples in the development cohort, the total thickness of the growth was excised with narrow circumferential margins.[16,17] In the validation cohort, excision, punch, or shave biopsies were done according to Cancer Council Australia guidelines.[18]

In both cohorts, all included patients were candidates for SLNB according to the international guideline criteria at the time of the procedure. Before 2009, patients with a primary diagnosis of melanoma were staged according to the 6th edition of the AJCC Cancer Staging Manual and were eligible for SLNB if Breslow thickness of the suspected melanoma was greater than 1·0 mm or if other risk factors (eg, ulceration or Clark level IV or V invasion) were present. After 2009, patients were staged according to the 7th edition of the AJCC Cancer Staging Manual, in which regression and more than one mitosis per mm² were added as criteria for SLNB. For our analysis, we retrospectively staged all patients according to the 8th edition of the AJCC Cancer Staging Manual. Typically, wide local excision was performed at the same time as the SLNB with a margin of 1·0–2·0 cm according to local protocols.

Histopathological analysis of sentinel node biopsy samples was done according to the EORTC Melanoma Group pathology protocol for the development cohort.[19] Histopathological analysis in the validation cohort was done according to a different protocol;[20] the differences between the two protocols have been described previously.[21] Follow-up strategies were mostly similar in both cohorts, with clinical examination every 3–6 months for 5–10 years.

For our analysis, we collected the following data from the development and validation cohort databases: patient characteristics (ie, age and sex), date of melanoma diagnosis, primary tumour characteristics (ie, Breslow thickness, presence of ulceration, location of the primary melanoma, histology, and mitosis), date of SLNB, sentinel node characteristics (ie, tumour burden [defined as the maximum diameter of the largest sentinel node metastasis], microanatomic location of the metastasis [Dewar criteria], and number of positive sentinel nodes). We also extracted follow-up data, including disease recurrence and melanoma-specific mortality. Patient sex and age were defined as per the electronic patient records. Data for race or ethnicity were not available. The development data were extracted in 2014 and updated up to Nov 30, 2015. The validation data were extracted up to Dec 31, 2022.

Outcomes

We built a model to predict the 5-year probability of experiencing the composite outcome recurrence or all-cause death, which we refer to as the composite recurrence outcome, in patients with stage pT1b or higher melanomas after SLNB. We then calibrated this model to predict 5-year melanoma-specific mortality in this patient group. To align with international nomenclature, 5-year recurrence-free survival and 5-year melanoma-specific survival were reported as main outcomes. Recurrence-free survival and melanoma-specific survival were calculated as 1–(composite recurrence outcome) and 1–(melanoma-specific mortality), respectively. Recurrence was defined as any form of recurrent disease, including in-transit metastasis or satellites, regional recurrence in the previously biopsied sentinel node basin (with or without concurrent locoregional disease), or distant nodal or systemic recurrence (with or without concurrent regional nodal or local or in-transit disease). Recurrence-free survival was defined as the time from SLNB to first recurrence of melanoma or death from any cause, whichever occurred first. Melanoma-specific mortality was defined as death due to melanoma and was calculated as the time from SLNB to death due to melanoma.

Statistical analysis

Because all participants who met the inclusion criteria during the period of interest for our analysis were included in our study, we did not do a sample size calculation. We identified ten variables as potential prognostic factors for inclusion in our model predicting the composite recurrence outcome on the basis of clinical experience, a literature review, and the availability of sufficient data: sex, age, presence of ulceration, melanoma location, histological subtype, Breslow thickness, number of sentinel nodes removed, number of positive sentinel nodes, tumour burden (defined as the maximum diameter of the largest sentinel node metastasis), and Dewar classification (microanatomic location of metastasis in the sentinel node). We used the Cox proportional hazards model to study associations between these possible prognostic factors and clinical outcomes (ie, recurrence or death and melanoma-specific mortality).

We obtained estimates of recurrence-free and melanoma-specific survival unadjusted for case-mix using Kaplan–Meier curves. Patients lost to follow-up were censored for recurrence-free survival, and those lost to follow-up or who died from other or unclear causes were censored for melanoma-specific mortality. There was no informative censoring in the Kaplan–Meier analysis. To obtain optimal 5-year predictions, follow-up was restricted to 5 years from the date of SLNB. We used multivariate imputation by chained equations (R-package mice) for multiple imputation of missing predictor values.

The proportional hazards assumption was tested and met based on Schoenfeld residuals (appendix p 1). The possible non-linearity of the continuous variables (age at SLNB date, Breslow thickness, and tumour burden) was modelled using restricted cubic splines and incorporated into our model using appropriate transformations. We included the interactions of all prognostic factors with sentinel node status in the full model to allow for differential prognostic effects across node-negative and node-positive patients. To obtain a parsimonious model, we selected independent prognostic factors for the composite recurrence outcome using multivariable backward selection on the full development cohort. Only those factors for which the p value was less than 0·01 were included in the model. Variable importance of each predictor was measured by comparing the partial log likelihood between the Cox proportional hazards model that contained or did not contain all terms involving the predictor. We used the corresponding Wald test (χ^2 statistic) to examine whether the indicated variable significantly improved the model fit.

The model predicting melanoma-specific mortality was based on the final version of the model developed to predict recurrence. The baseline hazard and the slope of the composite recurrence prediction model were calibrated to melanoma-specific mortality because recurrence and melanoma-specific mortality are strongly related.[22] Our approach offers the advantage of calculating one risk score for patients that predicts the probabilities of both the composite recurrence outcome and melanoma-specific mortality (and consequently recurrence-free and melanoma-specific survival) without having to develop two separate models. Potential loss of predictive performance was assessed by comparing the calibrated melanoma-specific mortality prediction model with a refitted melanoma-specific mortality model—ie, a model with the same covariates as the recurrence model but with newly estimated coefficients for the development cohort. The absolute risk prediction of recurrence and melanoma-specific mortality was plotted against the risk score. To reduce the overestimation of events occurring in patients with extremely high scores, we truncated the score at an integer corresponding to the 99th percentile of the score distribution.

We assessed model performance by examining its discrimination and calibration. Discrimination was assessed using receiver operating characteristics (ROC) curves and quantified using the concordance index: Harrell's C-index, Uno's C-index, and the area under the time-dependent ROC curve (AUC).[23–25] We used Harrell's bootstrap validation technique—including the same variable selection strategy as our modelling strategy—to adjust Harrell's C-index for overfitting and optimism in the full development cohort.[23] Calibration was assessed visually by plotting the predicted probability against the observed frequency in quintiles of the predicted composite recurrence outcome and predicted melanoma-specific mortality. If the model was perfectly calibrated, then the predicted value of the model would perfectly

See Online for appendix

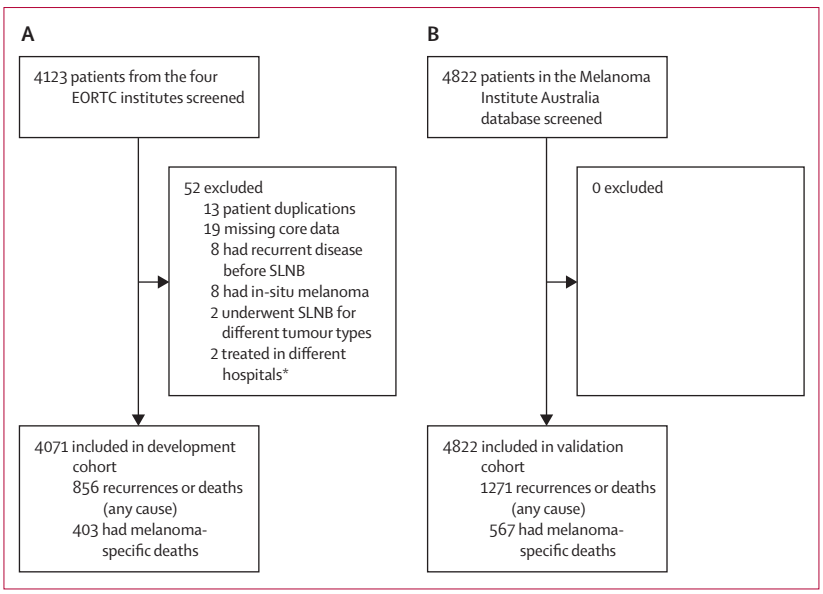

Figure 1: **Patient inclusion in the development (A) and validation (B) cohorts**
EORTC= European Organization for Research and Treatment of Cancer. SLNB=sentinel lymph node biopsy.
*Patients underwent treatment for melanoma at a hospital other than Charité Comprehensive Cancer Centre (Berlin, Germany), Netherlands Cancer Institute (Amsterdam, the Netherlands), Maria Skłodowska-Curie National Research Institute of Oncology (Warsaw, Poland), or Erasmus Medical Centre (Rotterdam, the Netherlands).

match the actual risk of patients in that quintile—ie, on a line plotted at 45° with an intercept of 0 and a slope of 1. To assess the generalisability of the model across different centres, we did leave-one-centre-out cross-validation for each centre by fitting the model with data from three centres of the development cohort and validating the model against data from the centre that was left out.[26] We developed a nomogram to graphically represent the models. Furthermore, we calculated model performance in predicting the composite recurrence outcome and melanoma-specific mortality according to both the 7th and 8th editions of the AJCC Cancer Staging Manual. We externally validated the final model by assessing discrimination and calibration in the Australian validation cohort. We used R (version 4.1.0) for all statistical analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

For the development cohort, 4123 patients were assessed for eligibility, of whom 4071 were included (2075 [51%] female, 1996 [49%] were male). The validation cohort included all 4822 potentially eligible patients (1965 [41%] female, 2857 [59%] male; figure 1, table 1). In the development cohort, 889 (22%) patients had sentinel node-positive disease and 3182 (78%) had sentinel node-negative disease; the corresponding figures in the validation cohort were 891 (18%) and 3931 (812%). Median age was 55·0 years (IQR 43·0–66·0) in the development cohort and 58·0 (46·0–68·0) in the validation cohort.

Median follow-up was 4·8 years (IQR 2·3–7·8) in the development cohort and 5·0 years (2·2–8·9) in the validation cohort (table 1). Overall recurrence-free survival at 5 years was 73·5% (95% CI 72·0–75·1) in the development cohort and 66·1% (64·6–67·7) in the validation cohort. 5-year melanoma-specific survival was 86·5% (95% CI 85·3–87·8) in the validation cohort and 83·3% (82·0–84·6) in the validation cohort. Recurrence-free survival and melanoma-specific survival in both cohorts by sentinel node status is shown in table 2. Further details of outcomes and follow-up in the different centres of the development cohort are presented in the appendix (p 3).

In the developed model, Breslow thickness and sentinel node status emerged as the strongest prognostic factors for the composite recurrence outcome (table 3). The non-linearity of the normally distributed predictors Breslow thickness and sentinel node tumour burden were well represented by logarithmic transformation. The normally distributed predictor age at date of SLNB was modelled linearly (appendix p 4). The final multivariable Cox model for the composite recurrence outcome after backwards selection included six independent prognostic factors: age, melanoma location (upper limb, lower limb, trunk, or head or neck), presence of ulceration, increased Breslow thickness, positive sentinel node status, and sentinel node tumour burden (table 3). These prognostic factors were more strongly associated with melanoma-specific mortality than with the composite recurrence outcome (calibration slope 1·14 [95% CI 1·03–1·25]). For the model's prediction of the composite recurrence

	Development cohort (N=4071)	Validation cohort (N=4822)
Sentinel node status		
Negative	3182 (78%)	3931 (82%)
Positive	889 (22%)	891 (18%)
Sex		
Female	2075 (51%)	1965 (41%)
Male	1996 (49%)	2857 (59%)
Age, years	55·0 (43·0–66·0; 13·0–94·0)	58·0 (46·0–68·0; 5·0–94·0)
Ulceration*	1171 (29%)	1298 (27%)
Location		
Upper limb	615 (15%)	893 (19%)
Lower limb	1189 (29%)	1238 (26%)
Trunk	1815 (45%)	1855 (38%)
Head or neck	314 (8%)	836 (17%)
Missing	138 (3%)	0
Histology		
Superficial spreading melanoma	2164 (53%)	1982 (41%)
Nodular melanoma	1226 (30%)	1562 (32%)
Acral lentiginous melanoma	126 (3%)	89 (2%)
Other	202 (5%)	561 (12%)
Missing	353 (9%)	628 (13%)
Breslow thickness, mm†	2·0 (1·2–3·5; 0·1–90·0)	2·0 (1·3–3·2; 0·6–47·0)
Multiple sentinel node fields	374 (9%)	NA
Number of negative sentinel nodes‡	1·0 (1·0–2·0; 1·0–15·0)	2·0 (1·0–3·0; 1·0–17·0)
Number of positive sentinel nodes§	1·0 (1·0–1·0; 0·0–5·0)	1·0 (1·0–1·0; 1·0–8·0)
Sentinel node tumour size, mm¶	1·1 (0·4–3·0; <0·1–38·0)	1·1 (0·5–3·0; <0·1–23·0)
Location of metastasis in sentinel node		
Subcapsular‖	137 (15%)	339 (38%)
Combined	213 (24%)	0
Parenchymal	86 (10%)	0
Multifocal	45 (5%)	0
Extensive	105 (12%)	0
Not subcapsular	0	379 (43%)
Missing	303 (34%)	173 (19%)
Mitotic rate ≥1 mm²**	135/176 (77%)	4241/4616 (92%)
Time to recurrence or death, years	5·0 (95% CI 2·4–7·9)	5·1 (95% CI 2·4–9·6)
Median follow-up, years	4·8 (IQR 2·3–7·8)	5·0 (IQR 2·2–8·9)

Data are n (%), median (IQR; range), or n/N (%), unless otherwise indicated. Time to recurrence and follow-up were calculated with the reverse Kaplan-Meier method. NA=not available. *Data were missing for 141 (3%) patients in the development cohort and 279 (6%) in the validation cohort. †Data were missing for 59 (1%) patients in the development cohort. ‡Only for patients with sentinel node-negative disease; data were missing for 141 (4%) patients in the development cohort. §Only for patients with sentinel node-positive disease; data were missing for one (<1%) patient in the development cohort. ¶Only for patients with sentinel node-positive disease; data were missing for 301 (34%) patients in the development cohort and 153 (17%) in the validation cohort. For single cell-positive sentinel nodes, minimum tumour burden was measured as 0·01 mm, which is represented here as <0·1 mm. ‖Includes single cell-positive disease in development cohort. **Data were missing for 3895 (96%) patients in the development cohort and 206 (4%) in the validation cohort.

Table 1: **Baseline patient and tumour characteristics for the development and validation cohorts**

	Recurrence or death (%)	Melanoma-specific deaths (%)	5-year recurrence-free survival (95% CI)	5-year melanoma-specific survival (95% CI)
Development cohort				
Overall (N=4071)	856 (21%)	403 (10%)	73·5% (72·0–75·1)	86·5% (85·3–87·8)
Sentinel node negative (N=3182)	490 (15%)	207 (7%)	80·3% (78·7–81·9)	91·1% (89·9–92·3)
Sentinel node positive (N=889)	366 (41%)	196 (22%)	49·0% (45·3–53·1)	69·1% (65·4–73·0)
Validation cohort				
Overall (N=4822)	1271 (26%)	567 (12%)	66·1% (64·6–67·7)	83·3% (82·0–84·6)
Sentinel node negative (N=3931)	799 (20%)	301 (8%)	72·2% (70·5–73·9)	88·3% (87·1–89·6)
Sentinel node positive (N=891)	472 (53%)	266 (30%)	43·0% (39·7–46·6)	65·5% (62·1–69·0)

Table 2: **Melanoma recurrences or deaths within 5 years of diagnosis and 5-year Kaplan-Meier estimates of recurrence-free and melanoma-specific survival in the development and validation cohorts**

	Hazard ratio (95% CI)	Importance*
Sentinel node status	..	153
Negative	1 (ref)	..
Positive	2·96 (2·48–3·54)	..
Age at SLNB (IQR 66 years *vs* 43 years)†	1·37 (1·23–1·53)	31
Ulceration present	..	41
No	1 (ref)	..
Yes	1·61 (1·39–1·87)	..
Location	..	21‡
Upper limb	1 (ref)	..
Lower limb	1·14 (0·89–1·46)	..
Trunk	1·29 (1·02–1·63)	..
Head or neck	1·89 (1·41–2·54)	..
Breslow thickness (IQR 3·5 mm *vs* 1·2 mm)†	..	..
Sentinel node negative	2·43 (2·14–2·76)	199
Sentinel node positive	1·52 (1·29–1·80)	21
Sentinel node tumour burden§ (IQR 38·0 *vs* <0·0)†	5·74 (2·67–12·30)	20

Hazard ratios were calculated with a Cox proportional hazards model predicting the probability of recurrence or death, whichever occurs first. The model is selected using backward selection with p values <0·01. *Defined by the χ^2 Wald statistic (p<0·0001 for all variables). †The hazard ratios for these continuous predictors are based on these IQRs. ‡This represents the variable importance of the interaction term between Breslow thickness and sentinel node status. §In patients with sentinel node-positive disease; defined as maximum diameter of the largest sentinel node metastasis.

Table 3: **Variables comprising the final predictive model for 5-year recurrence or death from any cause**

For the **online calculator** see https://erasmusmcpublichealth.shinyapps.io/MelanomaWebapp/

outcome, the AUC was 0·80 (95% CI 0·78–0·81); for prediction of melanoma-specific survival, the AUC was 0·81 (0·79–0·84; table 4). The time-dependent ROC curves showed good discrimination in the development and validation cohorts (appendix p 5). The calibrated melanoma-specific mortality model had similar HRs and performance to the refitted model in the development data (appendix pp 2, 6).

In the leave-one-centre-out cross-validation of the 5-year composite recurrence model, the AUC ranged from 0·74 (95% CI 0·70–0·78) to 0·81 (0·77–0·85), with adequate calibration across the four centres included in the development cohort (appendix pp 7–8). The AUC of the calibrated melanoma-specific mortality model ranged between 0·79 (95% CI 0·75–0·83) and 0·84 (0·79–0·88), with reasonable calibration (appendix p 9). In external validation of the model in the Australian cohort, the AUC was 0·73 (95% CI 0·71–0·75) for the 5-year composite recurrence model and 0·76 (0·74–0·78) for the 5-year melanoma-specific mortality model (appendix pp 10–11).

We developed a six-item risk score, assigning points to each prognostic factor on the basis of the magnitude of the regression coefficients of the final Cox model. We truncated the risk score to 18 to prevent overestimation. A nomogram to calculate a score that predicts both melanoma recurrence or death and melanoma-specific mortality, including explanation on how to use it, is presented in figure 2. To facilitate clinical use, we also developed an online calculator.

Discussion

In this retrospective cohort study, we developed a model that combines histopathological information from SLNB with easily accessible characteristics of the primary melanoma and clinical risk factors that can successfully predict 5-year recurrence of melanoma or death and 5-year melanoma-specific mortality, and, by extension, patient-specific recurrence-free and melanoma-specific survival, in a development cohort of individuals who underwent SLNB. This model was externally validated in an equally large independent patient cohort.

The introduction of adjuvant immune checkpoint inhibitors and targeted therapies has prolonged recurrence-free survival for patients with stage IIB, IIC, and III melanomas. In adjuvant trials, pembrolizumab reduced the risk of recurrence to a similar extent in patients with stage IIB or IIC melanomas (HR 0·62 [95% CI 0·51–0·71])[10] and in those with stage III melanomas (0·61 [0·45–0·81]).[13] To select patients for adjuvant treatment in clinical practice, SLNB is usually recommended for patients with stage pT1b or higher melanomas. Given the diverse prognoses in this

	Discriminative ability measures
Recurrence-free survival	
Harrell's C-index	0·77 (0·75–0·78)
Optimism-corrected Harrell's C-index*	0·76 (0·74–0·78)
Uno's C-index	0·76 (0·74–0·77)
AUC	0·80 (0·78–0·81)
Melanoma-specific survival	
Harrell's C-index	0·79 (0·77–0·81)
Optimism-corrected Harrell's C-index*	0·79 (0·77–0·81)
Uno's C-index	0·79 (0·76–0·81)
AUC	0·81 (0·79–0·84)

AUC=area under the time-dependent receiver operating characteristic curve.
*Corrected for optimism of 0·0061.

Table 4: **Discriminative ability of developed models to predict 5-year recurrence-free and melanoma-specific survival**

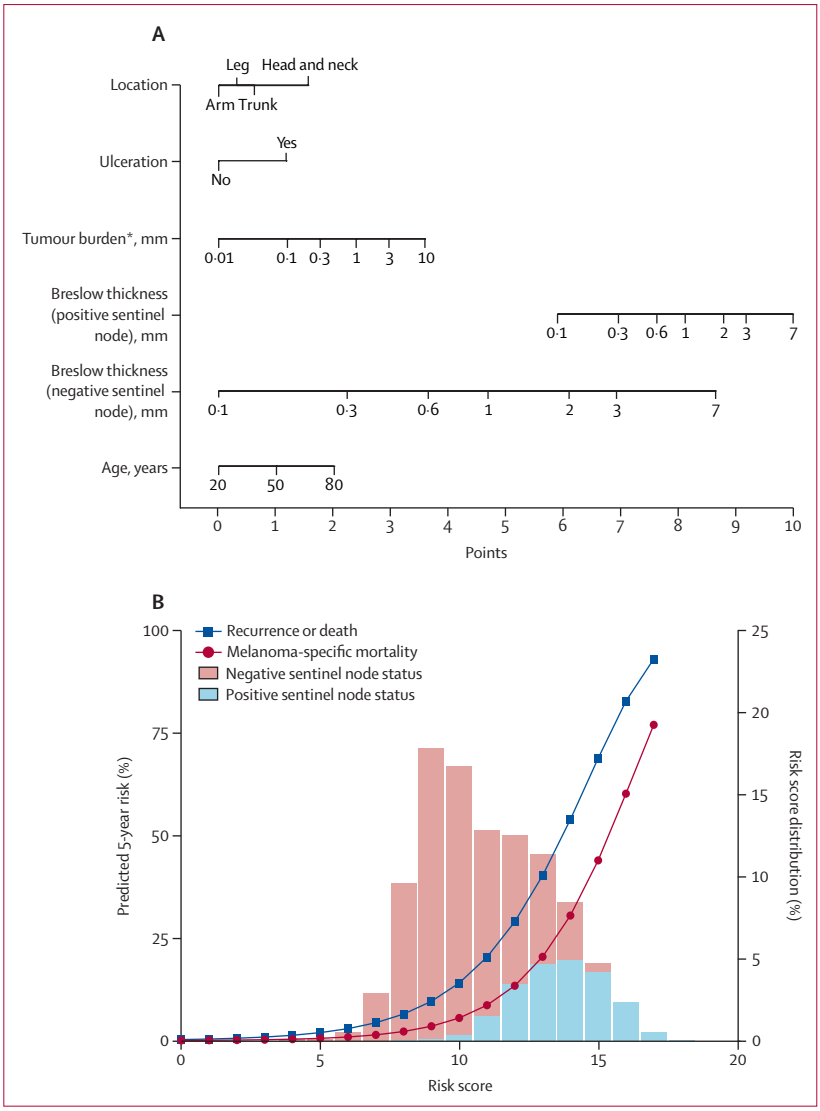

Figure 2: **Prediction of 5-year melanoma-specific mortality and recurrence**
(A) Nomogram to calculate risk scores based on patient and tumour characteristics. To use the nomogram, locate the patient's position on the line for each individual covariate, and then draw a straight line to the points axis to establish the score associated with that covariate. Add the scores for each covariate together to calculate the patient's total risk score. (B) Risk distribution chart. Risk scores calculated with the nomogram in panel A are plotted on the x-axis of this figure, enabling the inference of predicted 5-year risk of melanoma-specific mortality and recurrence or death by correlating each score with the appropriate plotted lines. The histogram depicts the risk score distribution, by sentinel node status, of the development cohort as an example of the distribution of risk scores across the patient population (each bar represents the proportion of patients in the cohort that was assigned that specific score). *ie, maximum diameter of largest sentinel node metastasis.

population, individualised risk assessments are urgently needed to identify those at greatest risk of recurrence or death (and therefore potentially more likely to benefit from adjuvant treatment).

Because our model can provide absolute estimates before treatment with adjuvant therapy, and the relative risk reduction in recurrence or death due to immunotherapy is known (ie, the hazard ratio), the potential absolute risk reduction after adjuvant therapy can now be calculated. For example, for a patient with stage III melanoma whose 5-year recurrence-free survival without adjuvant systemic therapy is predicted to be 70% by our model, the absolute risk reduction due to adjuvant therapy would be 11·7%—calculated by multiplying the 5-year risk of recurrence or death of 30% by the relative risk reduction from adjuvant therapy of 39% (ie, 1–0·61 [the HR for pembrolizumab *vs* placebo])—thereby improving 5-year recurrence-free survival to 81·7%. Thus, patients at increased risk of recurrence are likely to gain greater absolute benefit from therapy, whereas patients for whom the absolute benefit is likely to be small might refrain from adjuvant therapy, thereby reducing overtreatment and avoiding treatment-related toxic effects.

Over the past two decades, many different prognostic tools for patients with melanoma have been developed.[8] However, these models only predicted survival (either melanoma-specific or overall survival) or focused on different stages of melanoma. As risk assessment for individual patients became increasingly important with the introduction of adjuvant systemic therapies, Verver and colleagues published separate models and nomograms for patients with sentinel node-negative disease and for those with sentinel node-positive disease.[6,7] These models presented risk estimates for recurrence, melanoma-specific mortality, or overall mortality, and were subsequently combined into a unified model to improve accuracy and clinical usefulness.[27] A tool similar to the model that we developed in this study is the online Melanoma Calculator developed by Callender and colleagues,[28] which includes sentinel node status and calculates locoregional recurrence-free survival, disease-free survival, and overall survival.[28] However, because of incomplete reporting of the regression coefficients and baseline hazard of the final model, we could not formally validate Callender and colleagues' model in our data to compare model performance.

For the **Melanoma Calculator** see http://melanomacalculator.com/

In Callender and colleagues' Melanoma Calculator, sentinel node status is treated as a dichotomous variable only (ie, patients are classed as sentinel node positive or negative), rather than as a continuous variable, leading to potential issues including loss of information, reduced statistical power to detect associations between variables and outcomes, and potential underestimation of variations in outcome between patients.[29] In our model, we supplemented the dichotomous variable sentinel node status with the continuous variable tumour burden. Tumour burden was found to be an important prognostic factor for recurrence-free and melanoma-specific survival by van Akkooi and colleagues in 2008.[30] Because data on tumour size are widely available, we included them in our model, and found a strong association between size of sentinel node metastasis and recurrence-free survival.[6,30] To our knowledge, our models are the only tools that provide both recurrence-free and melanoma-specific survival on a continuous scale for patients with melanoma who have undergone SLNB and that are mostly based on continuous variables (with the exception of ulceration and anatomical site).

Unlike most other prediction tools for patients with melanoma, our model was developed and validated using high-quality datasets from high-volume melanoma centres in Europe and Australia.[8] All the data needed to use the model and nomogram are commonly collected and easily ascertainable in hospitals worldwide.

Our study has some limitations. Known prognostic factors for recurrence, including mitotic rate and lymphovascular infiltration, were not incorporated into the model. Although recommended for reporting by the AJCC, mitotic rate was excluded from the 8th edition of the AJCC staging system for melanoma. Consequently, mitotic rate is no longer reported in most European countries and was not recorded for most patients in the development cohort (>95%). Although only readily available variables were included in the model, model performance could be improved by expansion to incorporate data gained from genetic profiling or biomarker analysis in the future. A very small percentage of patients (0·02%) included in this study received treatment after recurrence (radiotherapy, chemotherapy interferon alfa-2b, isolated limb perfusion, or targeted therapy; data not shown). None of these patients received anti-PD-1 checkpoint inhibitors during follow-up. Because treatment was initiated after recurrence in all cases, it would not have affected recurrence-free survival. However, there is a possibility that these treatments could have a minor influence on melanoma-specific survival.

Another limitation is that our study was not population based. Use of population-based cohorts typically increases generalisability by encompassing a diverse group of people. In our study, by including patients from four different countries, we increased the heterogeneity and generalisability of our study population to develop and validate the model. All the data we used to develop and validate the model were gathered at expert melanoma centres, and thus the potential for selection bias should be considered. However, we anticipate that any such bias is likely to be minimal because substantial proportions of patients are typically directly referred to these centres by primary care physicians. Because the Australian data were not used for model development, variable selection for this population could be suboptimal. However, because the sample size of the European data was deemed sufficient to develop an accurate prediction model, we aimed to assess transportability of the model by external validation in Australian patient data. A final limitation of this model is that race and ethnicity were not considered. Most patients in the development cohort were of White or European descent, which potentially limits the generalisability of the models in view of distinct racial disparities in melanoma survival exist.

In conclusion, the model that we developed not only offers patient-specific risk predictions for recurrence-free and melanoma-specific survival but will also enable physicians to calculate the risk of recurrence at which it is judged necessary to start adjuvant therapy. Such an approach could lead to a notable reduction in the number of patients being considered for adjuvant treatments and hence reduce the likelihood of overtreatment. Relevant clinical cutoffs for the use of the model should be established to quantify this potential cost reduction.

Contributors

DJG conceived and supervised the study. RCS, CCHMM, DvK, ACJvA, and DJG developed the methods. RCS, CCHMM, SNL, RPMS, AHRV, RAS, GVL, JFT, PR, UK, ACJvA, and CV acquired data, which CCHMM, SNL, and DvK analysed and validated. RCS, CCHMM, AAMvdV, SNL, RPMS, AHRV, RAS, GVL, JFT, PR, UK, ACJvA, CV, DvK, and DJG interpreted the results. RCS, ACJvA, CV, and DJG were responsible for project administration. RCS and CCHMM wrote the original draft and accessed and verified all study data. All authors had access to the data, were involved in reviewing and editing the Article, and vouch for the accuracy of the data reported. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

RCS reports honoraria (paid to their institution) from Amgen. AAMvdV reports consultancy fees (paid to their institution) from Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Pierre Fabre, Ipsen, Eisai, Merck, Pfizer, Novartis, and Roche. RPMS has received honoraria for advisory board participation from Merck Sharp & Dohme, Novartis, and Qbiotics, and speaker fees from Bristol Myers Squibb and Novartis. AHRV has received honoraria from Novartis. RAS has received fees for professional services from MetaOptima Technology, F Hoffmann-La Roche, Evaxion, Provectus, Qbiotics, Novartis, Merck Sharp & Dohme, NeraCare, Amgen, Bristol Myers Squibb, Myriad Genetics, and GlaxoSmithKline. GVL reports consultancy or advisory fees from Agenus, Amgen, Array Biopharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion, Hexal, Highlight Therapeutics, Innovent Biologics, Novartis, OncoSec, PHMR, Pierre Fabre, Provectus, Qbiotics, and Regeneron. JFT has received honoraria for advisory board participation from Bristol Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, and Provectus, and travel and conference support from GlaxoSmithKline, Provectus, and Novartis. PR reports research funding (paid to their institution) from Merck Sharp & Dohme and Pfizer, and has received honoraria for lectures and advisory board participation from Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Pierre Fabre, Sanofi, Merck, Philogen, and Blueprint

Medicines. UK has received consulting fees from Merck Sharp & Dohme, travel support from Merck Serono and Pfizer, and grants for educational activities from Merck Serono, Bristol Myers Squibb, and Pierre-Fabre. ACJvA reports honoraria for consultancy and serving on advisory boards (all paid to their institution) from Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Merck, Pfizer, Neracare, Novartis, Pierre Fabre, Provectus, Sanofi, Sirius Medical, and 4SC, and research grants (paid to their institution) from Amgen, Merck, and Pfizer. DvK has participated on the data and safety monitoring boards of the FAST CABG and Multivessel Talent trials. DJG has served on data and safety monitoring boards for Amgen and Novartis (funds paid to their institution). All other authors declare no competing interests.

Data sharing

Requests for access to the deidentified patient data that form the basis of our findings should be directed to the corresponding author. However, access to the data is at the authors' discretion. The code used for the development of the model is available on GitHub.

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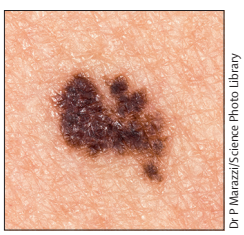
For more on **GitHub** see https://github.com/CHMMaas/PaperMelanoma

A new era of risk prediction for patients with high-risk melanoma



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In *The Lancet Oncology*, Robert C Stassen and colleagues[1] report the development of a new model to predict recurrence-free survival and melanoma-specific survival in people with stage II or III melanoma. Since the introduction in 2018 of adjuvant systemic therapies for use after surgical resection of high-risk melanoma, there has been growing awareness of the need for individualised assessment of the risk of recurrence to guide treatment decisions. According to the 8th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual, on which current treatment recommendations are based, the distinction between stage II and III disease is based on lymph node status and the presence of satellite or in-transit metastases, rather than the risk, per se, of melanoma recurrence or death. Patients with stage IIIA melanoma per the AJCC staging system actually have better prognoses than those with stage IIC disease, but adjuvant treatment was not recommended for the latter patient group until late 2021.[2] The recurrence-free survival benefit associated with treatment is very similar across all stages, and adjuvant PD-1 inhibitors are now approved for use in patients with stage IIB–IIID disease.[3] However, adjuvant immunotherapy is costly and is associated with the potential for enduring life-long adverse events. In view of the limitations of the AJCC staging system, we congratulate Stassen and colleagues for providing a new tool for personalised risk stratification.

Stassen and colleagues developed their novel statistical model (which they have made available as an online tool) using a cohort of 4071 patients with melanoma treated at four European centres. They subsequently validated the model in an Australian cohort (n=4822). The final model contains six clinical prognostic factors: age, melanoma location, presence of ulceration, Breslow thickness, positive sentinel node status, and sentinel node tumour burden. In the development cohort, the area under the time-dependent receiver operating characteristics curve (AUC) was 0·80 (95% CI 0·78–0·81) for recurrence-free survival and 0·81 (0·79–0·84) for melanoma-specific survival. The external validation showed a similarly good calibration for both outcomes, with corresponding AUCs of 0·73 (95% CI 0·71–0·75) and 0·76 (0·74–0·78). A limitation of this model is that it is not population-based, but rather based on patients treated at highly specialised melanoma centres. However, we anticipate that future external validations could confirm the robustness of the model. Unlike the other calculators of the risk of melanoma recurrence that are available,[4,5] Stassen and colleagues' model includes patients with both sentinel lymph node-positive and sentinel lymph node-negative disease, and calculates both recurrence-free survival and melanoma-specific survival, which means that the absolute benefit of adjuvant treatments can be estimated.

The next question to address is the risk level at which adjuvant treatment for melanoma should be recommended. The recurrence-free survival benefit with adjuvant immunotherapy is consistently associated with hazard ratios for recurrence of 0·60–0·70 (compared with placebo), independent of staging per the AJCC criteria, but absolute benefit depends on the risk of recurrence, which can now be calculated with Stassen and colleagues' tool. A limitation of adjuvant immunotherapy is that overall survival data for comparisons of the available adjuvant PD-1 inhibitors versus placebo have yet to be reported. In CheckMate-238,[6] the increased recurrence-free survival associated with nivolumab compared with ipilimumab did not translate to increased overall survival. The assumption that improvements in recurrence-free survival will automatically lead to improvements in overall survival is thus being questioned. There is also debate around the validity of using recurrence-free survival as an endpoint for trials of adjuvant treatments if overall survival is not reported.[3] Furthermore, we argue that it is close to unethical not to disclose even preliminary results for overall survival for treatments that have been recommended for more than 5 years. In a trial[7] in urothelial carcinoma, the adjuvant PD-1 inhibitor pembrolizumab was associated with longer disease-free survival (29 months [95% CI 22–not reached] *vs* 14 months [10–20]), but shorter overall survival (51 months [44–not reached] *vs* 56 months [53–not reached]) compared with placebo, raising concerns. These conflicting results show the importance of reporting overall survival data. An advantage of a model that can predict the risk of recurrence and

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melanoma-specific mortality, such as that of Stassen and colleagues, is that when overall survival data are presented, discussions with patients about the potential risks and benefits of adjuvant therapy are improved.

In summary, the online risk prediction model developed by Stassen and colleagues will not only offer patients robust, individualised estimations of the risks of melanoma recurrence and death but also provide great value in guiding adjuvant treatment recommendations. Health-care professionals and patients can now start to discuss the absolute potential benefits of adjuvant treatment weighted against the risk of potential toxic effects. Further work to model not just prognosis, but prediction of response to adjuvant treatments is needed, but Stassen and colleagues' work is a fundamental first step towards a new era in which adjuvant treatment recommendations are more personalised and precise.

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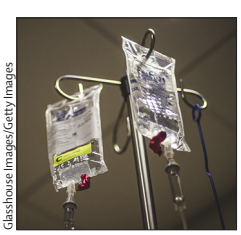
Combining chemotherapy and immunotherapy for advanced anal cancer: are we ready?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Advanced squamous cell carcinoma of the anus is a rare disease with few established treatment options. To date, a combination of platinum-based chemotherapy with taxane or fluorouracil is the standard of care as first-line treatment.[1–3] In the refractory setting, immune checkpoint inhibitors have shown antitumour activity in a subset of patients. Thus, the use of immunotherapy in earlier lines of therapy in addition to a chemotherapy backbone might represent an appealing treatment strategy.[4]

In *The Lancet Oncology*, Prof Stefano Kim and colleagues present the results of the SCARCE C17-02 PRODIGE 60 randomised, non-comparative phase 2 trial, evaluating the addition of the PD-L1 inhibitor atezolizumab to the modified docetaxel, cisplatin, and fluorouracil (mDCF) regimen (group A) compared with mDCF alone (group B) as front-line treatment in 97 patients with advanced squamous cell carcinoma of the anus.[5] The investigators should be congratulated for conducting and completing a randomised trial in this clinically challenging population. Unfortunately, the primary endpoint of 12-month progression-free survival was not met, with the lower value of the CI below the threshold to reject the null hypothesis. Within the constraints of a non-comparative study, with a higher proportion of patients in the combinatory group A having more advanced disease and poor performance status compared with group B, no difference in terms of antitumour activity and clinical outcomes was reported. Furthermore, the chemo-immunotherapy strategy led to a higher incidence of grade 3–4 adverse events (39 [61%] of 64 *vs* 14 [42%] of 33) and serious adverse events (16 [25%] of 64 *vs* four [12%] of 33) compared with the chemotherapy-only group. Between the different subgroups, no difference was