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A prediction tool incorporating the biomarker S-100B for patient selection for completion lymph node dissection in stage III melanoma

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Abstract

Introduction: Completion lymph node dissection (CLND) in sentinel node (SN)-positive melanoma patients is accompanied with morbidity, while about 80% yield no additional metastases in non-sentinel nodes (NSNs). A prediction tool for NSN involvement could be of assistance in patient selection for CLND. This study investigated which parameters predict NSN-positivity, and whether the biomarker S-100B improves the accuracy of a prediction model.

Methods: Recorded clinicopathologic factors were tested for their association with NSN-positivity in 110 SN-positive patients who underwent CLND. A prediction model was developed with multivariable logistic regression, incorporating all predictive factors. Five models were compared for their predictive power by calculating the Area Under the Curve (AUC). A weighted risk score, 'S-100B Non-Sentinel Node Risk Score' (SN-SNORS), was derived for the model with the highest AUC. Besides, a nomogram was developed as visual representation.

Results: NSN-positivity was present in 24 (21.8%) patients. Sex, ulceration, number of harvested SNs, number of positive SNs, and S-100B value were independently associated with NSN-positivity. The AUC for the model including all these factors was 0.78 (95%CI 0.69–0.88). SN-SNORS was the sum of scores for the five parameters. Scores of ≤9.5, 10–11.5, and ≥12 were associated with low (0%), intermediate (21.0%) and high (43.2%) risk of NSN involvement.

Conclusions: A prediction tool based on five parameters, including the biomarker S-100B, showed accurate risk stratification for NSN-involvement in SN-positive melanoma patients. If validated in future studies, this tool could help to identify patients with low risk for NSN-involvement.

Keywords: Melanoma; Non-sentinel node status; Completion lymph node dissection; S-100B; Biomarkers; Prediction tool

Introduction

Sentinel lymph node biopsy (SLNB) is the standard procedure for accurate staging in melanoma patients, with a minimal treatment related morbidity.[1,2] SLNB identifies patients with nodal metastases, who may benefit from immediate completion lymph node dissection (CLND).[3] Despite the current recommendation on performing CLND in all sentinel node (SN)-positive patients, its therapeutic value is highly debated.[4–9] Currently, about 80% of patients yield

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no additional metastases in non-sentinel nodes (NSNs), and the procedure is accompanied with morbidity and costs.[10,11] The availability of an accurate prediction tool for the identification of patients with a low risk for NSN-involvement, could improve future patient' selection for CLND.

Several prediction tools for survival and prognosis in melanoma have been described and some are used in clinical practice.[12] For SLNB patient selection, the Memorial Sloan Kettering Cancer Center (MSKCC) developed and validated a nomogram for SN-status prediction.[13] Although not yet included in clinical guidelines, prediction models based on independently associated parameters were developed and validated, to enable risk stratification for NSN-positivity.[14,15]

Recently, serum S-100B was also found to be independently associated with NSN-involvement in SN-positive melanoma patients.[16] Besides, elevated levels of S-100B appeared to be associated with recurrence risk and worse survival in patients presenting with palpable nodal metastases, suggesting a relation with melanoma tumor burden.[17] Although S-100B has been reported to be a prognostic biomarker in cutaneous melanoma patients since the nineties, no consensus has been achieved on its implementation in clinical follow-up.[18] To date, only German and Swiss national guidelines recommend evaluation of serum S-100B in melanoma follow-up.[19]

The predictive value of S-100B could possibly be used to increase the accuracy of a risk stratifying model for NSN-involvement in SN-positive melanoma patients. The aim of this study was to develop such a prediction model, and to test whether incorporation of S-100B would improve its accuracy. A reproducible prediction tool could be used to optimize the selection of patients at low risk for NSN-involvement, in whom CLND could safely be omitted.

Methods

Patients and procedure

At the University Medical Center Groningen (UMCG), SLNB is performed routinely in AJCC stage IB–IIC cutaneous melanoma patients, followed by a subsequent CLND in case of SN-positivity. All SN-positive patients, diagnosed at the UMCG or referred from other hospitals, who underwent a CLND between 2005 and 2015 were prospectively registered. The study was conducted in accordance with the Declaration of Helsinki, and conforms to the guidelines of the central medical ethics committee.

For the SNs, the histologic protocol consisted of blocking in paraffin and cutting of 4 μm sections, with 250 μm distance, at four different levels in the SN for routine hematoxylin and eosin staining, with additional immunohistochemistry for S-100B and Melan-A. In CLND specimens, all NSNs were sectioned at one level with subsequent hematoxylin and eosin staining.

Clinical features and primary tumor characteristics were recorded. Histologic features assessed for the SNs were the number of harvested SNs, number of involved SNs, proportion of involved SN, size of the largest metastasis in SN, and extranodal growth pattern. If more than one SN contained metastases, the highest score for each parameter was recorded. Serum S-100B and LDH values were measured preoperatively, one day before CLND was performed.

S-100B concentrations were determined by performing the S-100B assay (Diasorin) on an ELISA Robot platform (DS2, Dynex Technologies). The reference range was determined according to the Clinical and Laboratory Standards Institute EP28-A3c guideline, resulting in a cut-off value of 0.20 μg/l.[20] LDH was analyzed routinely by Roche Modular (Hitachi) with an enzymatic activity measurement. The reference cut-off used for LDH was 250 U/l.

Statistical analysis

Univariable logistic regression analysis was used to investigate the association of clinicopathologic variables with NSN-positivity. All variables were entered in a logistic regression model; backwards stepwise selection was used to build a multivariable model. Log-transformation was used for the skewed distribution of S-100B. Factors associated with NSN-positivity on a 10% significance level were selected in the final model. Extra-nodal growth was excluded in the model, due to the limited number of patients ($n = 3$).

Five different multivariable logistic regression models were assessed, and the Area Under the Curve (AUC) was calculated and compared for these five models. The model with the highest AUC was used as final model, and an ROC-curve was constructed. Based on these results, a weighted scoring system, the '*S*-100B *N*on-*S*entinel *N*ode *R*isk *S*core' (SN-SNORS), was devised. SN-SNORS was assessed for its ability to predict NSN-positivity using the AUC. All statistical analyses were performed, using IBM SPSS statistics version 22 (SPSS Inc, Chicago, IL), with p-values < 0.05 considered statistically significant.

Subsequently, a nomogram was developed in R version 3.2.1 (Auckland, New Zealand), using the 'rms' package, based on the sum of scores for the five predictive parameters. First, the data distribution was set to logistic regression. Next, the model was built with the five parameters; estimates from the model and the effects of each predictor on the response variable were calculated and plotted together with the predicted probability from the multivariable model (Supplementary file).

Results

A total of 110 AJCC stage IB–IIC melanoma patients with a positive SLNB were analyzed. The median age at diagnosis of the primary melanoma was 55 (range 5–88)

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