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The predictive power of serum S-100B for non-sentinel node positivity in melanoma patients

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Abstract

Background: Completion lymph node dissection (CLND) in sentinel node (SN) positive melanoma patients leads to substantial morbidity and costs, while only approximately 20% have a metastasis in non-sentinel nodes (NSNs). The aim of this study was to investigate if the biomarkers S-100B and Lactate Dehydrogenase (LDH) are associated with NSN positivity, to identify patients in whom CLND could safely be omitted.

Methods: All SN positive patients who underwent CLND at the University Medical Centre Groningen between January 2004 and January 2015 were analysed. Patient and tumor characteristics, and serum S-100B and LDH values measured the day before CLND were statistically tested for their association with NSN positivity.

Results: NSN positivity was found in 20.6% of the 107 patients undergoing CLND. Univariate analysis revealed male gender ($p = 0.02$), melanoma of the lower extremity ($p = 0.05$), Breslow thickness ($p = 0.004$), ulceration ($p = 0.04$), proportion of involved SNs ($p = 0.045$) and S-100B value ($p = 0.01$) to be associated with NSN positivity. LDH level was not significantly associated with positive NSNs ($p = 0.39$). In multivariable analysis, S-100B showed to have the strongest association with NSN positivity, within its reference interval of 0.20 μg/l ($p = 0.02$, odds ratio 5.71, 95% confidence interval 1.37–23.87).

Conclusion: In this study, the preoperatively measured S-100B value is the strongest predictor for NSN positivity in patients planned for CLND. Fluctuations of the S-100B level within the reference interval might give important clues about residual tumor load. Although further validation will be needed, this new closer look of S-100B could be of value in patient selection for CLND in the future.
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Keywords: Melanoma; Sentinel lymph node biopsy; S100B protein; Biological tumor markers; Lymph node excision; Lymphatic metastasis

Introduction

Sentinel lymph node biopsy (SLNB) is recommended in all patients with an American Joint Committee on Cancer (AJCC) stage IB-IIC cutaneous melanoma.[1] After a positive SLNB, positive non-sentinel nodes (NSNs) are found in only approximately 15–20% of the patients undergoing a subsequent completion lymph node dissection (CLND). This means a great number of sentinel node (SN) positive patients might not benefit from this procedure.[2,3] Therefore, the indication for CLND should be considered carefully, as the procedure causes significant morbidity and economic burden.[4] Currently, there is no evidence that CLND improves melanoma-specific survival.[2,3,5–7] Nevertheless, CLND remains the standard of care in SN positive patients, until the final results of

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the second Multicenter Selective Lymphadenectomy Trial (MSLT-II) will be available, in which CLND versus ultrasonographic nodal observation is being compared.[8]

Various parameters have been investigated to select patients with a low risk for NSN positivity. An association with NSN positivity is described for male gender,[9] Breslow thickness,[10–12] regression,[9] ulceration,[7] number of positive lymph nodes in SLNB,[7,9] maximum size of metastasis in SN,[3,10–15] invasion depth of metastasis in SNs,[7,16] non-subcapsular location of metastasis in SN,[9,17] extranodal extension of metastasis in SN,[7,13] and the presence of perinodal lymphatic invasion.[9] Independently, those parameters lack predictive strength to stratify risk for NSN involvement, so risk scores based on conjunction of the significant factors in multivariable models were developed and validated.[6,9,11] However, these scores still show false negatives and the assessment of histologic parameters of melanoma deposits in SNs is prone to inter-observer variation.[18] Although serum biomarkers could have better reproducibility, their predictive value for the selection of these patients has not been investigated before.

For melanoma, the biomarkers S-100B and Lactate Dehydrogenase (LDH) have been described extensively. LDH was implemented in the AJCC system in 2001 to classify stage IV patients.[19] The melanoma-associated molecule S-100B was found to be a prognostic tumor marker in AJCC stage III and IV disease.[20] Compared to LDH, elevated levels of serum S-100B are stronger associated with recurrence risk and decreased survival in melanoma patients presenting with palpable nodal metastases.[21] More recently, C-Reactive Protein (CRP) was also reported to be a prognostic marker in all stages of cutaneous melanoma.[22]

Hypothetically, biomarkers could increase the accuracy of risk stratification for NSN involvement in SN positive melanoma patients. The aim of present study was to investigate whether levels of preoperatively measured serum S-100B and LDH are associated with NSN positivity in these patients, and to evaluate the potential value of biomarkers in the selection of patients for CLND.

Methods

All SN positive cutaneous melanoma patients who underwent a CLND between January 2004 and January 2015 were prospectively registered. SLNB was performed in patients presenting with a primary melanoma AJCC stage IB to IIC, except for one AJCC stage IA patient, who had opted for SLNB. The study cohort consisted of patients who underwent wide local excision and SLNB at the University Medical Centre Groningen (UMCG, a melanoma centre), as well as patients referred to the UMCG with a positive SN. In case of referral, histopathologic review of the primary tumor and the sentinel lymph nodes was performed.

Histopathologic processing of the SNs consisted of blocking in paraffin and cutting of 4 μm sections, with a distance of 250 μm between them, at four different levels for routine haematoxylin and eosin staining, with additional immunohistochemistry for S-100B and Melan-A. If metastatic melanoma was found during this procedure, the SLNB was considered positive and CLND was scheduled and performed by an experienced melanoma surgeon. For NSNs harvested during CLND, histopathologic analysis was done by cross-section of each lymph node with subsequent haematoxylin and eosin staining.

Characteristics of the patients, the primary tumours, SLNB, and CLND were collected in a database. The recorded parameters included: age, gender, site of primary melanoma, histologic type, Breslow thickness, Clark level, ulceration, mitotic rate (number of cells in mitosis per mm^2), lymphovascular invasion (the presence of melanoma cells in lymphatic or blood vessels), regression (defined as partial or complete replacement of invasive melanoma by angiofibroplasia with/without associated inflammation and melanophages), total number of harvested SNs, number of involved SNs, proportion of involved SNs, size of the largest metastasis in SN, extranodal growth pattern of the metastasis, site of CLND, number of harvested NSNs, and number of involved NSNs. Serum S-100B and LDH values were measured the day prior to CLND.

Biomarker assay and reference cut-off

S-100B levels were calculated on the basis of a calibration curve and checked against internal standards with a known concentration of S-100B. The S-100B cut-off value was determined by analysis of S-100B values in 120 healthy individuals (median 0.07 μg/l; range 0.01–0.59 μg/l) according to the Clinical and Laboratory Standards Institute EP28-A3c guideline (formerly C28-A2), resulting in a reference cut-off point of 0.20 μg/l at our institution.[23] LDH was analysed routinely by means of Roche Modular (Hitachi) with an enzymatic activity measurement. Normal values of LDH were considered to be below the reference cut-off of 250 U/l.

Statistical analysis

Characteristics of the patient (age and gender), primary melanoma (site, histologic type, Breslow thickness, Clark level, ulceration, mitotic rate, lymphovascular invasion and regression), harvested SNs (total number of nodes, number of involved nodes, proportion involved SN, size of the largest nodal metastasis, extranodal growth pattern), and preoperatively measured S-100B and LDH levels were analysed for their association with NSN positivity using the Chi-squared test for univariate analyses and logistic regression analysis for the multivariable model (IBM SPSS Statistics version 22).

S-100B and LDH were both analysed in three different ways: 1) continuous, 2) categorical with the cut-off value

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