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LETTER TO THE EDITOR

Long-term prognostic value of sentinel lymph node tumor burden in survival of melanoma patients

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Introduction

Sentinel lymph node (SLN) status is the most accurate predictor of survival in melanoma patients with clinically negative regional lymph nodes [1,2]. Until recently, most patients with metastatic SLN were advised to undergo early completion lymph node dissection (CLND) to remove non-sentinel lymph nodes (NSNs), which may harbor metastases [1,3]. The two large prospective studies MSLT-II and DeCOG-SLT failed to show a significant survival benefit of CLND [4,5]. This led to a paradigm shift; instead of trying to recognize patients with positive SLN who could be observed instead of undergoing the CLND procedure and its adverse events, we are now focusing on selecting high-risk patients for more intense follow-up and adjuvant treatments, and patients who might actually benefit from early CLND [6–8].

Histopathologic parameters in both primary melanoma tumors and SLNs have prognostic value in disease-free survival (DFS) and melanoma-specific survival (MSS) and can be used to predict NSN positivity [9–13]. These parameters include tumor burden of metastatic SLNs [9,14–16]. The maximum diameter of the largest metastatic focus in the SLN is arguably the most employed SLN tumor burden parameter [11,16].

In this study, we employed the maximum diameter of the largest metastatic deposit, number of positive SLNs, and microanatomic location of the SLN metastasis and examined their influence on long-term survival and predictive value for NSN positivity.

Patients and methods

The Helsinki University Hospital institutional review board approved the study protocol.

We performed an electronic search using the QPATI database of the Department of Pathology of Helsinki University Hospital for all patients who underwent melanoma re-excision and SNB from 1 January 2001 to 31 December 2008 and identified 191 patients with a metastatic SLN. Eighteen patients were excluded; eight patients presented with a recurrent and/or metastasized disease at the time of SNB and 10 patients did not have follow-up data available. Patients had a previously diagnosed melanoma with Breslow thickness $\geq$1 mm and/or other high-risk histological features, for example, ulceration. Patients with Breslow thickness $\geq$4 mm were routinely examined with ultrasound. Patients with no clinically detected metastasis underwent wide local excision and SNB.

On the day prior to surgery, patients received Technetium-99m–labeled colloidal albumin (Albu-Res, Nanocoll) 80 MBq in 0.2 ml injected intradermally into the primary tumor site and then proceeded to lymphoscintigraphy with static images 30 min and 2 h from injection. Blue dye (Patent Blue V, 1 ml) was injected intradermally into the site of the primary tumor just prior to surgery. The surgeon used a gamma-detecting probe (Navigator, Tyco Health Care and Neo2000, Neoprobe Corp.) intraoperatively and harvested all blue-stained and/or radioactive nodes until no focal residual activity could be detected.

Each node was embedded in paraffin and serially cut into 1 mm slices and stained with hematoxylin–eosin. Immunohistochemical staining with melanoma-specific antigens S-100, Melan-A and HMB-45 was performed. The metastases were measured (length and width of lesion), and the location of the metastases (subcapsular or parenchymal) within the node was reported.

The CLND specimen was weighed and half of each node was subjected to histopathological analysis (hematoxylin–eosin). Immunohistochemistry was not used routinely. Metastases were recorded according to size in one dimension and according to the number of positive nodes of all nodes in the basin.

DFS and MSS were calculated from the time of SNB until first recurrence or death from melanoma, respectively, and censored if no such events had occurred by the last follow-up. Different cutoff values for the diameter of the largest metastatic focus were set in order to demonstrate the impact

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on survival and to determine a high-risk group of patients for poor survival and NSN positivity. The diameter of the largest metastatic focus was also analyzed as a continuous variable. Univariate analyses of survival were performed using the Kaplan–Meier method and the log rank test. Covariables showing statistical significance in univariate analysis were evaluated in a multivariate Cox proportional hazards model. Due to multicollinearity of different tumor burden parameters, separate analyses were performed. The hazard ratios, confidence intervals, and *p*-values regarding age, gender, primary melanoma thickness, and ulceration were obtained when using the median cutoff value of 1 mm for the maximum diameter of SLN metastasis. Chi-squared test and univariate logistic regression model were used to test the association of various parameters with NSN positivity. Factors with a significant univariate association were analyzed in multivariate logistic regression model. We used SPSS version 25 to perform statistical analyses. *p*-values of less than 0.05 were considered statistically significant.

Results

The specific inclusion criteria resulted in 173 patients. Table 1 provides an overview of their clinical and pathologic characteristics. Altogether 150 (87%) patients underwent a subsequent CLND, and 23 had no CLND for the following reasons: they were randomized into the follow-up group of the MSLT-II trial ($n = 10$), refusal ($n = 7$), poor general condition ($n = 5$), metastasis in interval node ($n = 1$).

The median follow-up was 8.3 years (i.e. 100 months, range 4–189 months). The overall five-year DFS and MSS were 55.3% (SE 0.04) and 67.4% (SE 0.04), respectively. Altogether 80 (46%) had a recurrent disease during follow-up. Seventy-nine patients (46%) were alive at the last follow-up, 66 (38%) had died of melanoma, and 28 (16%) had died of another cause.

Table 1. Baseline characteristics of 173 patients.

Age	
Mean	60.15
Median (Range)	61 (14–90)
Gender	
Male	103 (59.5%)
Female	70 (40.5%)
Location of primary tumor	
Extremity	77 (44.5%)
Trunk	77 (44.5%)
Head and neck	19 (11.0%)
Breslow (mm)	
Mean	3.32
Median (Range)	2.5 (0.8–21)
Ulceration	
Yes	45 (26.2%)
No	127 (73.8%)
Number of SLNs	
Mean	4.80
Median (Range)	4 (1-15)
Number of positive SLN	
Mean	1.52
Median (Range)	1 (1–6)
1	110 (63.6%)
2	44 (25.4%)
≥3	19 (11.0%)
Positive SLN/Total SLN ratio	
Mean	0.43
Median (Range)	0.33 (0.071–1)
CLND	
Positive	17 (11.3%)
Negative	133 (88.7%)
Number of positive nodes in CLND	
0	133
1	14
≥ 2	3
Diameter of the largest metastatic foci in SLN (mm)	
Mean	2.10
Median (Range)	1.00 (0.05–15)
Microanatomic location of SLN metastasis	
Subcapsular	66 (38.2%)
Parenchymal	107 (61.8%)
Follow-up time, mean	7.3 years/88 months
Type of first recurrence	
No recurrence	93 (53.8%)
Local	34 (19.6%)
Regional	23 (13.3%)
Systemic	23 (13.3%)
D/A	94/79 (54.3%/45.7%)

SLN: sentinel lymph node; CLND: completion lymph node dissection.

Survival

In univariate analysis, the most important adverse prognosticators for survival were older age, increasing Breslow thickness, the presence of ulceration, increasing maximum diameter of SLN metastasis, parenchymal location of the SLN metastasis, increasing number of positive SLNs, and presence of positive NSNs (Supplementary Table 1). In multivariate analysis, maximum diameter of SLN metastasis, number of positive SLNs (>2), location of metastasis within SLN, and the presence of positive NSNs remained independent prognosticators for survival (Supplementary Table 2).

The location of the primary tumor was not a significant prognosticator for survival. Neither the number of removed nodes nor the ratio of positive SLNs to harvested SLNs was found to have significant prognostic value.

The diameter of the SLN metastasis was an independent prognostic factor both as a continuous variable ($p < 0.001$) and with every cutoff value (i.e. 0.2 mm, 0.3 mm, 1 mm, 2 mm, 3 mm, and 4 mm) tested (Supplementary Tables 1 and 2). Patients with smaller metastases had better outcomes in all subgroups according to diameter. Patients with a metastasis diameter <0.2 mm had 77.0% (SE 0.08) 5-year DFS ($p = 0.035$) and 86.2% (SE 0.06) 5-year MSS ($p = 0.042$). Conversely, patients with metastasis of >4 mm had 33.6% (SE 0.10) 5-year DFS ($p = 0.003$) and 38.5% (SE 0.10) 5-year MSS ($p < 0.001$). Cutoffs at 3 mm and 4 mm significantly delineated the subgroup of patients with shortest DFS and MSS. Figure 1(a) demonstrates Kaplan–Meier-estimated MSS according to maximum diameter of SLN metastasis as a categorical variable with cutoffs at 0.3 mm and 3 mm.

Parenchymal location of metastasis within SLN was an adverse prognosticator for survival (Figure 1(b)). Patients with SLN metastases located only in the subcapsular area had more favorable outcome, with 64.7% (SE 0.06) five-year DFS ($p = 0.068$) and 84.1% (SE 0.05) five-year MSS ($p = 0.007$). For patients with parenchymal metastases, the five-year DFS and MSS were 49.4% (SE 0.05) and 56.9% (SE 0.05), respectively.

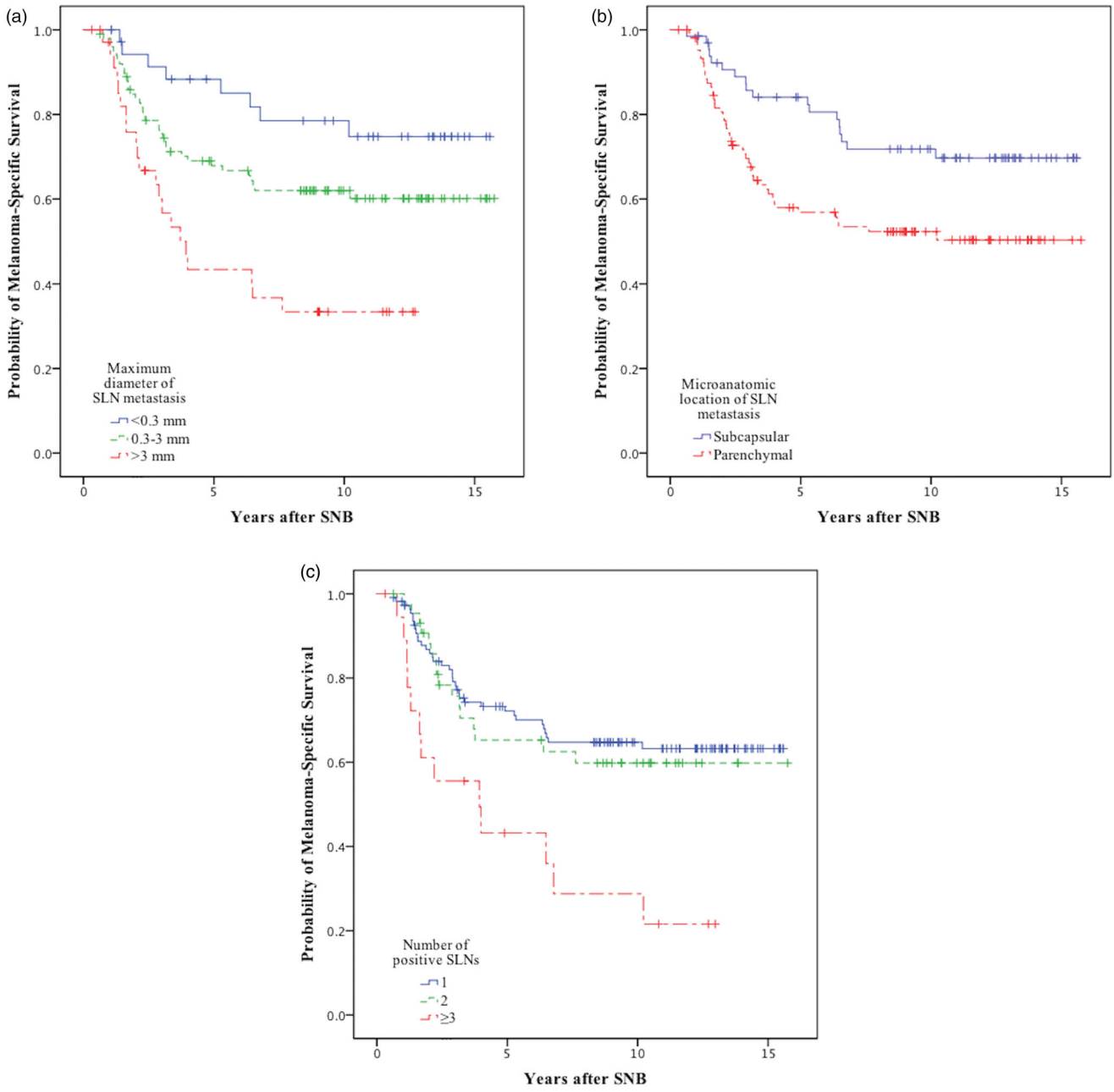

Figure 1. Kaplan–Meier-estimated melanoma-specific survival according to (a) maximum diameter of SLN metastasis with cutoffs at 0.3 mm and 3 mm, (b) microanatomic location of SLN metastasis, and (c) number of positive SLNs. SLN = sentinel lymph node, SNB = sentinel lymph node biopsy.

The number of positive nodes also predicted outcomes; patients with three or more positive nodes had worse outcomes (Figure 1(c)). The five-y DFS and MSS for patients with three or more positive SLNs were 20.9% (SE 0.10) and 43.2% (SE 0.12) and for patients with less than three positive SLNs DFS and MSS were 59.3% (SE 0.04) and 70.3% (SE 0.04), respectively ($p < 0.001$).

NSN metastasis

Of 150 patients undergoing CLND, 17 (11%) had metastases in NSNs. The number of positive NSNs was one in 14 cases (82%), and two in one case (6%), and three in two cases (12%).

The strongest predictive parameters of positive NSNs in univariate analysis were the diameter of the largest tumor foci in SLN, number of positive SLNs, and location of metastasis in SLN (Supplementary Table 3). Of patients with diameter of SLN metastasis >4 mm, 36% and of patients with SLN metastasis ≤ 4 mm 7% had one or more positive NSNs ($p < 0.001$). Of patients with three or more positive SLNs, 29% and of patients with less than three positive SLNs 9% presented with further positive nodes in CLND ($p = 0.013$). Of patients with parenchymal SLN metastasis, 15% had NSN metastases compared with 5% of patients with subcapsular SLN metastasis ($p = 0.040$).

In multivariate analysis, the maximum diameter of SLN metastasis – both as a continuous variable and with cutoffs >2 mm – and the number of positive SLNs (>2) were the

most important prognosticators for NSN metastases (Supplementary Table 4).

Presence of metastatic NSNs predicted an unfavorable outcome. Patients with positive NSNs had 18.8% (SE 0.10) five-year DFS and 26.9% (SE 0.12) five-year MSS and patients without positive NSNs 58.0% (SE 0.04) and 70.5% (SE 0.04), respectively ($p < 0.001$).

Discussion

We examined the long-term survival of melanoma patients, focusing on SLN tumor burden to assess its applicability in predicting additional metastases in CLND and survival. The diameter of the largest metastatic deposit in SLN, the number of positive nodes, and the presence of positive NSNs each provided valuable prognostic information.

Abandoning CLND as a routine procedure for melanoma patients with positive SLNs has brought new challenges regarding both treatment and follow-up. The prognostic value of NSN metastases was very evident in our study as well as in others [4,13]. CLND has been useful for staging and recruiting patients into clinical trials [17,18]. The morbidity of the CLND procedure is simply too high for a staging tool with little if any therapeutic value. The role of SLN tumor burden has been highlighted and it has already been incorporated in inclusion criteria in clinical trials [19,20].

MSLT-II and DeCOG-SLT studies were unable to pinpoint a subgroup of patients who would benefit from CLND according to the characteristics of the primary tumor or SLN, including tumor burden [4,5]. The relatively low number of patients with large SLN tumor deposits in these trials may partly explain this. Yet, it is uncertain whether early CLND will bring effective survival benefit to any group of patients. The rationale for considering the procedure is reducing nodal recurrences in a high-risk group of patients. However, these patients are also at a high risk of harboring distant metastases [2,4,5]. In our study, the diameter of SLN metastasis was correlated with both survival and positive NSNs. Currently, the decision to perform CLND is individual, and potential risks and benefits are carefully discussed with each patient.

The eighth edition of the American Joint Cancer Committee (AJCC) staging manual does not include microscopic tumor burden of the SLN [2]. Its importance and the growing evidence were discussed, however, and the future AJCC staging manuals will undoubtedly feature SLN tumor burden to further clarify the N category [2]. The key question around implementing SLN tumor burden into the classification is determining optimal cutoffs [11,13,21,22]. Cutoffs from 1 mm to 5 mm for the diameter SLN metastasis have been suggested in other studies to differentiate between subgroups of patients in survival [11,23–26]. Our data suggest cutoffs at 3 mm and 4 mm be considered for the high-risk subgroup. Although not reaching the statistical significance of the maximum diameter of SLN metastasis, the microanatomic location adds to the prognostic information gained from SNB.

The number of SLNs harvested per patient was rather high in our study [9,10]. SLNs were removed until no focal radioactivity remained rather than following the widely used 10% rule, that is, harvesting SLNs with radioactivity of 10% or more of the most radioactive node [27]. This allowed us to compare the subgroups of patients according to the number of positive SLNs; patients with more positive nodes, both $1>$ vs. 1 and >2 vs. ≤ 2, had worse prognosis and increased risk for positive NSNs.

In conclusion, the diameter of SLN metastasis and the number of positive SLNs were strong independent prognosticators for survival. Specifically, the diameter of SLN metastasis >4 mm and number of positive SLNs >2 delineate a high-risk group of patients in terms of survival and non-sentinel lymph node involvement. These criteria can be used to select patients for adjuvant treatments and to more intense follow-up protocols.

Disclosure statement

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