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Recurrence after sentinel lymph node biopsy in cutaneous melanoma: a single-center experience in Slovak patients

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The standard approach in the management of cutaneous malignant melanoma is considered to be a complete excision of the primary lesion with an appropriate margin of the normal tissue according to Breslow thickness. Usually sentinel lymph node biopsy (SLNB) can help to determine the nodal status, and thus improve the accuracy of staging of the disease. However, the role of SLNB in melanoma treatment remains controversial. NCCN guidelines strongly support routine performance of therapeutic lymphadenectomy in all melanoma patients with clinically positive nodes without radiographic evidence of distant metastases. Patients with positive SLNB should have had completion lymph node dissection (CLND) for regional disease control. Between 2012 and 2016, 168 consecutive patients underwent surgery for primary cutaneous malignant melanoma at St. Elisabeth Cancer Institute in Bratislava. The indication for SLNB and the procedure was made according to international guidelines. In this retrospective study, a cohort of 78 patients was analyzed (35 women and 43 men). Inclusion criteria comprised patients with cutaneous melanoma with no evidence of distant metastases or clinical lymphadenopathy. SLNB comprised a dual labelling method (Tc-99m Nanocolloid/blue dye) in a one-day protocol. Median follow-up was 657 days. The primary composite outcome was the time to the first disease-related event (death, reintervention, worsening of symptoms). Primary outcome measures were overall (disease-specific) and disease-free survival. The overall identification rate of SLN in melanoma patients by dual labelling method was 98.5%. All patients with positive SLNB on frozen section underwent complete regional lymphadenectomy. Using multivariable analysis Breslow thickness of the lesion (p=0.00004, HR 4.03 on logarithmic scale) was identified as the strongest independent predictor of the disease-free survival (DFS) and male gender was significant predictor of DFS. An increase in tumor thickness was associated with significantly higher risk of an event. Neither SLN positivity nor initial S-100 level proved to be significant predictors of the event at the 0.05 level of probability. Multidisciplinary approach represents the gold standard of care for melanoma patients and surgery remains the best option for most localized cases. Although the usefulness of SLNB procedure has been questioned, it provides an excellent staging method, moreover, it can identify high-risk patients. The routine use of completion lymphadenectomy after a positive SLNB is still controversial. It is not clear whether CLND following a positive SLN biopsy improves survival but it could provide regional disease control.

Key words: Sentinel lymph node biopsy, malignant melanoma, recurrence of melanoma, completion lymphadenectomy

Basic principle in the management of primary cutaneous malignant melanoma has remained the wide surgical excision for decades [1–4]. Complete excision of the primary skin lesion along with removal of adjacent subcutaneous fatty tissue with an appropriate margin of normal tissue according to Breslow thickness is considered the standard approach [5]. Sentinel lymph node biopsy (SLNB) can determine the nodal status hence improves the accuracy of staging of the disease [5]. SLNB represents the most accurate staging tool for melanoma patients [6]. The procedure is indicated especially for intermediate thickness melanoma (pT2/3). SLNB can also be of value in patients with thin melanoma (>0.75 mm in thickness) with adverse prognostic factors, and in thick melanomas (pT4), although T4 patients are already at high risk of disease progression [7–9].

The objective of the study was to identify the independent predictors of disease-free survival (DFS) in cutaneous malignant melanoma patients with clinically negative lymph node with performed SLNB.

Patients and methods

Ethics approval to conduct this study was obtained from the Research Ethics Committee in the St. Elisabeth`s Cancer Institute in Bratislava. Data were retrieved from the institutional registry for all consecutive patients who underwent surgery for primary cutaneous malignant melanoma at the Department of Surgical Oncology between January 2012 and December 2016. From a total of 168 patients 84 were excluded based on our selection criteria: to analyze patients who underwent SLNB. The indication for SLNB and the procedure was made according to international ASCO/ NCCN/SSO guidelines [4, 7, 9]. Additional six patients were excluded due to a short follow-up.

Criteria for inclusion into the study were patients first diagnosed with cutaneous melanoma with no evidence of distant metastases or clinical lymphadenopathy and with SLNB performed.

Variables extracted for each patient were age at the diagnosis, gender, anatomic site of primary melanoma (axial or extremities melanoma), Breslow thickness, Clark level of invasion, clinicopathological type, the number of SLN, number of positive SLN, initial level of tumor marker S-100, changes in PET/CT findings, and CLND execution. The age was analyzed as a continuous variable (in years) in the bivariable analysis and categorized at the sample median age (59.5 years) in multivariable modeling. The anatomic location of the melanoma was divided into two categories, axial (defined by the presence of the melanoma on the trunk, head, or neck) and extremity sites. Breslow thickness was categorized into thin lesions no more than 1.00 mm thick, intermediate thickness melanoma from 1.01 to 4.00 mm, and the thick melanoma greater than 4.00 mm. Clark's staging system delineates five levels of tumor invasion based on the depth of penetration of a melanoma into the skin according to anatomic layer. SLNB comprised a dual labelling method (Tc-99m Nanocolloid / blue dye – Patent blau) in a one-day protocol. Nodal dissection was guided by a hand-held gamma detection probe along with visual identification of the blue staining, and dissection was performed using harmonic scalpel. Tumor marker S-100 was analyzed by an enzyme-linked immunosorbent assay (ELISA kit), reference values: 15.6–90.0 ng/l.

Finally a cohort of 78 patients was retrospectively analyzed (35 women and 43 men) with a median follow-up of 657 days. The primary outcome under assessment was the disease-free survival that relates to the time "survived" from the start of treatment (surgery) to a composite event defined as the occurrence or realization in a patient of any one of the specified components: local and/ or nodal recurrence, distant metastases appearance or death. The composite endpoint was assessed as the time to first occurrence of any one of the components. A patient who had not experienced an event by the time of the study closure was censored.

The cohort of patients was statistically analyzed by bivariable and multivariable methods. The collected data were summarized using descriptive statistics. Continuous variables are presented as means with the respective standard deviations (SD). The assumption of normality for continuous variables was assessed using histograms and the Shapiro-Wilk test. Categorical variables are presented as counts and relative frequencies.

Bivariable analysis between-group differences in all relevant baseline characteristics were investigated. Continuous data were analyzed with the Student´s t test for independent samples. If the data were asymmetrically distributed, a non-parametric Mann-Whitney U test was used instead. Categorical variables grouped in two-way contingency tables were analyzed using chi-square tests. In case of numerical calculability, exact tests were applied. For binary predictors, an odds ratio (OR) as a measure of association between a particular predictor and the outcome was expressed. From the definition, the OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.

The survival probability was estimated nonparametrically from observed survival times, both censored and uncensored, using the Kaplan-Meier method. Kaplan-Meier survival curves were stratified by each of the statistically and/ or clinically significant covariates detected in the bivariable analysis.

Multivariable analysis: the association of selected predictors (explanatory variables) with SLN positivity was assessed using logistic regression. The baseline characteristics, which were assumed to influence disease- specific and disease-free survival, were further used as covariates for developing a multivariable survival model using Cox regression. Interassociations among selected predictors were identified in order to avoid multicollinearity. Effect size for significant or clinically important predictors was estimated using hazard ratio (HR) in the Cox regression.

Statistical analyses were performed using StatsDirect 3.0.198 software (Stats Direct Ltd., Cheshire, UK) and Statistica 13 software (Dell-StatSoft, Inc. Tulsa, OK, USA). All presented p-values are two sided. Values of $p<0.05$ were considered to indicate a statistically significant difference.

Results

The overall identification rate of SLN in melanoma patients by dual labelling method was 98.5%. All but one patient (N(sn)mi+) with positive SLNB detected on frozen section underwent complete regional lymphadenectomy.

Table 1 shows reductions in risk (odds ratios of less than one) in the bivariable analysis for female gender

Table 1. Patients' characteristics and outcomes.

		Composite endpoint	Event-free	Total	OR*	p-value
Number of cases	(percent of row total)	20 (25.6%)	58 (74.4%)	78 (100%)	n.a.	n.a.
Age (years)	mean±SD	63.2±13.45	57.2±12.43	58.3±12.89		
	median (Q_1–Q_3)	67.5 (56.0–71.5)	59.0 (50.0–66.0)	59.5 (52.0–69.0)	n.a.	0.071
	min - max	32–82	25–78	25–82		
Age cat.	≥60 years	13 (16.7%)	26 (33.3%)	39 (50%)	2.29	0.131
	<60 years	7 (9.0%)	32 (41%)	39 (50%)		
Sex	male	28 (48.3%)	15 (75.0%)	43 (55.1%)	3.21	0.042
	female	30 (51.7%)	5 (25.0%)	35 (44.9%)		
Thickness	mean±SD	4.4±2.57	2.2±3.25	2.8±3.22		
	median (Q_1-Q_3)	3.5 (2.45–6.25)	1.7 (0.90–2.50)	2 (1.02–3.00)	n.a.	< 0.001
Thickness cat.	min – max	0.1–25	1.2.2009	0.1–25		
	<1 mm	0 (0%)	19 (32.7%)	19 (24.3%)		
	>1 mm and ≤4 mm	11 (55.0%)	36 (62.1%)	47 (60.3%)	n.a.	< 0.001
	>4 mm	9 (45.0%)	3 (5.1%)	12 (15.4%)		
Location of primary lesion	extremity	28 (48.3%)	15 (75.0%)	43 (55.1%)	0.31	0.042
	axial site	30 (51.7%)	5 (25.0%)	35 (44.9%)		
SLN	positive	4 (6.9%)	5 (25.0%)	9 (11.5%)	4.5	0.043
	negative	54 (93.1%)	15 (75.0%)	69 (88.5%)		
S100 initial	median (Q_1–Q_3)	41 (18.7–64.0)	35.6 (26.6–51.8)	36 (26.2–56.6)	n.a.	0.884
S100 last	median (Q_1–Q_3)	64.0 (13.7–1895)	25.7 (10.0–38.9)	26.9 (10.0–50.4)	n.a.	0.003
Excision+CLND	yes	10 (50%)	3 (5.2%)	13 (16.7%)	18.3	<0.001
	no	10 (50%)	55 (94.8%)	65 (83.3%)		

Continuous data are presented as means±standard deviations, or medians with quartiles. Categorical data are presented as absolute counts with percent of column total, unless otherwise stated. OR* - the ratio of the odds of having an event in the upper row category the to odds of having an event in the lower row category of the predictor variable. Abbreviations: OR, Odds Ratio; SD., standard deviation; Q_1, lower quartile; Q_3, upper quartile; n.a., not applicable; cat., categorized; SLN, sentinel lymph nodes; CLND, completion lymph node di ssection.

Table 2. Patients' outcomes stratified by Breslow thickness.

Thickness category	Composite endpoint			Event-free			Grand total
	SLN negat	SLN posit	Total	SLN negat	SLN posit	Total	
≤1 mm	0 (0%)	0 (0%)	0 (0%)	19 (24.4%)	0 (0%)	19 (24.4%)	19 (24.4%)
>1 mm and ≤4 mm	9 (11.6%)	2 (2.5%)	11 (14.1%)	33 (42.4%)	3 (3.8%)	36 (46.2%)	47 (60.3%)
>4 mm	6 (7.7%)	3 (3.8%)	9 (11.5%)	2 (2.5%)	1 (1.3%)	3 (3.8%)	12 (15.3%)
Total	15 (19.3%)	5 (6.3%)	20 (25.6%)	54 (69.3%)	4 (5.1%)	58 (74.4%)	78 (100%)

Categorical data are presented as absolute counts with percent of sample total; SLN, sentinel lymph nodes.

(OR=1/3.21=0.31), lesion on extremities and without metastases in SLN (OR=1/4.5=0.22). Initial value of S100 did not differ between the patients who remained in remission and those who experienced any one of the components of the composite endpoint during the follow-up. However, the S100 levels at the time of study termination were significantly higher for the latter (p=0.003).

An event occurred totally in 20 patients (Table 2). In the first group no event occurred, in the second group there were 11 patients detected with the event and in the third one there were 9 patients with the event detected. Histopathologically we did not confirm positivity of SLN in the first group, in the second group there were five patients with positive SLN (in two cases a micrometastasis was found in the section) and in the third group 4 patients with metastasis in SLN were detected.

Multivariable modeling. As expected, Breslow thickness of the primary lesion was identified as the strongest independent predictor of disease-free survival (DFS). An increase in tumor thickness was associated with significantly higher risk of an event (p=0.00004, HR 4.03 on logarithmic scale). Neither SLN positivity nor initial S-100 level proved to be significant predictors of the event at the 0.05 level of probability. Adjusted Kaplan-Meier curves of disease-free survival of melanoma patients stratified by Breslow thickness are presented in Figure 1.

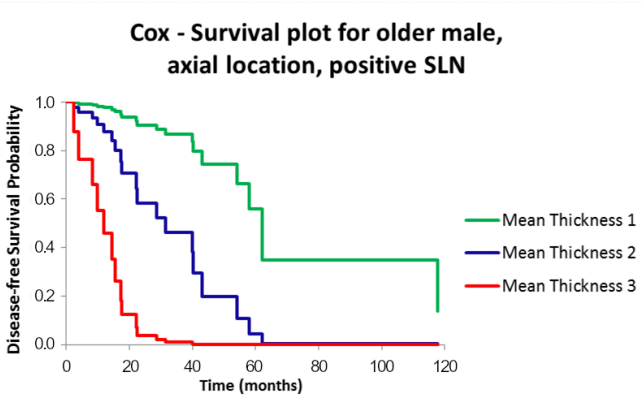

Figure 1. Kaplan-Meier curves of disease-free survival stratified by Breslow thickness (categories 1–3 are represented by their logarithmic mean values in mm). The curves are adjusted for age, gender and location.

Discussion

The role of sentinel lymph node biopsy in the treatment of melanoma patients with clinically negative lymph node remains controversial despite a lot of efforts expended worldwide for analysis of its therapeutical benefit. The American Society of Clinical Oncology (ASCO), Society of Surgical Oncology (SSO) and NCCN published guidelines recommend SLNB in patients with intermediate thickness of the lesion (Breslow of 1–4 mm) of any anatomic site. In the case of thick melanomas SLNB may be recommended for staging purposes. There is an insufficient evidence to support routine SLNB for patients with thin melanomas (Breslow of less than 1 mm). These studies strongly support routine performance of therapeutic lymphadenectomy in all melanoma patients with clinically positive nodes without radiographic evidence of distant metastases [5, 6]. Patients with positive SLN should be offered CLND for regional disease control [7, 9] despite the fact that CLND in sentinel node (SN) positive melanoma patients can lead to substantial morbidity and costs, while only approximately 20% have a metastasis in non-sentinel nodes (NSNs). The Dutch study in its 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). Moreover, in multivariable analysis, S-100B showed to have the strongest association with non-sentinel lymph node (NSN) positivity [10].

Surgical management of the regional lymphatic area still remains controversial. In general, probability of metastatic involvement of sentinel lymph node increases with the thickness of the primary lesion. Patients with primary melanomas measuring less than 1 mm have only a 4 percent chance of having a positive lymph node [11]. Current data show that performing SLNB confers no increases in overall survival, regardless of SLNB results. Additionally, 10 to 15 percent of patients who have negative SLNB will develop metastatic spread. On the other hand, approximately one-third of patients with positive nodal status will not develop metastatic disease. In some studies, micrometastatic SLNB-positive patients have the same long-term survival as SLNB-negative patients. SLNB has a maximum accuracy if it is carried out simultaneously with the primary tumor excision. Completion lymph node dissection (CLND) after positive SN yields additional non-sentinel lymph nodes (NSNs) in 20% of cases. Number of predictive risk factors for NSN positivity are concerned, such as primary tumor characteristics and SN tumor burden. The most commonly used tumor burden parameters are the maximum diameter of the SN metastasis, microanatomic location of the metastasis in the SN and tumor penetrative depth that could be useful to stratify risk and select patients for appropriate treatment modality. There might be a role for US-FNAC in melanoma staging [12].

The MSLT-I study confirmed the staging value of sentinel lymph node biopsy and showed a therapeutic advantage of early treatment of nodal metastases among patients with intermediate-thickness melanoma. The findings of that trial provided support for the use of sentinel-node biopsy, which is now recommended in the guidelines. In MSLT-2 Clinical Trial immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases [13].

Sentinel lymph node biopsy is the standard staging procedure for melanoma patients, and sentinel node status is the most important prognostic factor for disease outcome in AJCC stage I/II disease. In general, approximately 80 – 85% of all sentinel lymph node positive patients could be subjected to unnecessary surgery, moreover it is not clear whether the 15–20% of patients who do have additional nodal involvement detected at completion lymph node dissection, actually realize a survival benefit from this procedure. Analysis of a multicentre, randomized, phase III, trial conducted in Germany by the Dermatologic Cooperative Oncology Group (DeCOG-SLT trial) has shown that patients with melanoma and a positive sentinel lymph node biopsy gained no survival benefit by having complete lymph node dissection compared with patients in an observation group. As a result, complete lymph node dissection should not be recommended in patients with melanoma with lymph node micrometastases of at least a diameter of 1 mm or smaller [14].

The EORTC Melanoma Group conducted the largest retrospective analysis (1080 patients) which seems to indicate that patients with minimal sentinel node tumor burden have similar prognostic factors and outcome to sentinel node negative patients [15]. The risk of NSN involvement using a nomogram for patient risk stratification was recently published by an Italian Melanoma Intergroup (IMI) Study [16].

The routine use of completion lymphadenectomy after a positive SLNB in melanoma patients still remains a controversial issue due to the limited availability of data on this topic. It is not clear whether CLND following a positive SLN biopsy improves survival but CLND can provide regional disease control. However, assessment of the effect of CLND in our cohort was not completely plausible because of low number of positive SLN patients. The DeCOG-SLT study failed to demonstrate a survival benefit for CLND after a positive SLNB. MSLT-2 and EORTC 1208 (MINITUB) trials focusing on the role of CLND in SLNB positive patients were reported [17]. There might be a role for new modalities like US-FNAC in melanoma staging [18, 19].

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