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Sentinel node for malignant melanoma: An observational study of a consecutive single centre experience

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ABSTRACT

Introduction: Sentinel node biopsy (SNB) for melanoma gives prognostic information, however the success is dependent on several factors. The aim of this study was to describe outcome data after the introduction of the technique at our centre, including analysis of false negative rate (FNR), predictive factors for positive sentinel node (SN) and non-sentinel node (NSN), as well as prognostic factors for melanoma-specific survival (MSS).

Materials and methods: This is a retrospective observational study of a prospectively kept database at Sahlgrenska University Hospital. Between March 2000 and December 2013, 769 consecutive patients with cutaneous malignant melanoma undergoing SNB were included. The median follow-up time was 55 months (2–179 months). Tumour load in the SN was categorized according to the largest tumour deposit, low when $\leq$1 mm and high when >1 mm.

Results: The FNR was 20% and the SN positivity rate was 14% with a decrease in both FNR and SN positivity rate during the study period. In multivariate analysis the only predictive factor for a positive SN was Breslow thickness. The 5-year melanoma specific survival (MSS) was 81% and in multivariate analysis the prognostic factors were SN-status (low metastatic load HR = 2.6, p = 0.001; high metastatic load HR = 2.7, p = 0.004) followed by Breslow thickness and ulceration.

Conclusions: In this study Breslow thickness was the only independent predictive factor for a positive SN, no predictive factors were identified for NSN. Independent prognostic factors for MSS were SN status, Breslow thickness and ulceration. Interestingly, there was no survival difference depending on SN tumour burden when using 1 mm as cut-off.

Introduction

Malignant melanoma is a cancer arising from melanocytes with a rapidly increasing incidence, especially in the Nordic countries [1]. The most important prognostic factors are Breslow thickness, ulceration and sentinel node (SN) status [2,3]. The sentinel node biopsy (SNB) technique was introduced by Morton et al. and is a minimally invasive and low-morbidity surgical procedure. The technique is based on the use of blue dye and radiolabelled colloids injected in the primary tumour area, to track the main lymphatic drainage and to find the first draining lymph node [4,5].

In the literature there are several predictive factors for SN positivity reported, and these include Breslow thickness, ulceration, mitotic rate, age, localization of primary tumour, lympho-vascular invasion (LVI), Clarks level of invasion, amount of tumour infiltrating lymphocytes (TIL) and gender [6]. The Multicentre Selective Lymphadenectomy Trial 1 (MSLT-1) verified the SN status as the most important prognostic factor together with Breslow thickness and ulceration [7]. As predictive factors for metastatic non-sentinel nodes (NSN), after a completion lymph-node dissection (CLND), Breslow thickness, gender, regression of the primary tumour and extra capsular extension in the SN have been reported [8].

In Sweden, the SNB technique was evaluated by the Swedish Melanoma Study Group (SMSG) and was recommended in the Swedish national guidelines in the year 2000. Initially SNB was recommended for primary lesions thicker than 1.5 mm, and in 2004 this recommendation was changed to include patients with melanomas thicker than 1.0 mm [9].

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The purpose of this study is to describe a complete consecutive series, including all patients with cutaneous melanoma treated at a single centre, with the specific aims to investigate false negative rate (FNR), predictive factors for positive SN and NSN, as well as to define prognostic factors for melanoma-specific survival (MSS).

Patients and methods

Patients

At Sahlgrenska University Hospital 769 consecutive patients underwent surgery due to cutaneous malignant melanoma with wide local excision (WLE) and SNB between March 2000 and December 2013. All patients were included in a prospectively kept database containing clinical information including age, gender, date of surgery, Breslow thickness, Clark level (I–V), presence of ulceration and the location of the primary tumour (arm, trunk or leg). Clinical outcomes regarding SN included the lymph node basins (axilla, inguinal or other) and the status where positive nodes were recorded as having a low metastatic load (≤1 mm) or high metastatic load (>1 mm). The first recurrence was recorded as either local, in-transit, nodal or general. Post-operative complications were recorded as local events related to the SNB surgery. Data concerning survival and melanoma-specific survival were obtained from the Swedish Cause of Death register. The median follow-up time was 55 months (2–179 months) and the patients were followed according to clinical routine for 3–5 years. The Study was approved by the Regional Ethical Review Board at the University of Gothenburg (reference number 908–14).

Technique

After a diagnostic excision confirming the diagnosis of malignant melanoma the patients underwent WLE and SNB. A preoperative lymphoscintigraphy was performed for all patients using 99mTc labelled human albumin colloid injected intra-dermally. Patent Blue Violet (Patent Blue V 2.5%; Guerbet, Aulnay-sous-Bois, France) was injected intra-dermally before sterile washing. Intraoperative identification of the SN was done with a handheld gamma probe. The removed lymph nodes were sent for pathological examination using haematoxylin and eosin staining. Starting in May 2013, the immunohistochemical markers S-100, Melan-A and HMB-4 were used routinely. From the beginning, the SN was divided in two halves but this was changed in September 2012 when the SN was divided in 9 parts instead. Patients with a positive SN were planned for a CLND.

Statistical evaluation

As false negative (FN) were considered the patients that showed a nodal relapse during follow-up and the false negative rate (FNR), was calculated as the ratio between the false negatives and the total of false negative and true positives. Predictive factors for SN and NSN were calculated by univariate and multivariate logistic regression. Disease-free survival (DFS) was defined as the time between surgery and recurrence as detected with either clinical or radiological examination, radiology was not routinely used during follow-up. Survival was calculated from surgery to death, either from melanoma (melanoma-specific survival, MSS) or including other causes (overall survival, OS). Time-to-event analyses was performed using the Kaplan-Meier method and compared with the log rank test. Cox proportional hazard regression analysis using the enter method was used for multivariate analysis. A p-value of <0.05 was considered significant. Missing data were excluded from the analysis. All analyses were performed using IBM SPSS statistic version 22.0 (IBM Corp., Armonk, New York, USA).

Results

Out of the 769 patients, SN was detected in 764 of the patients (99%) and these patients were included in the analysis. There was 387 males (51%) and 377 females (49%) with a median age of 60.9 years (range 16.8–89.1). The median Breslow thickness of the primary lesions was 2.0 mm (range, 0.2–40 mm), and it decreased after 2004 when the guidelines for recommending SNB were changed (2.8 mm vs. 1.9 mm, $p < 0.001$) (Table 1). The number of procedures increased over the study period, from 13 per year in 2001 to 91 per year in 2013 (Fig. 1).

Sentinel node localization

All patients underwent preoperative lymphoscintigraphy and Patent Blue Violet was used in 732 patients (94%). The SN was localised to one nodal basin in 639 patients (84%), the axilla in 386 patients and inguinal in 253 patients. In 118 patients (15%) the SN was localised in two nodal basins and in 7 patients (1%) in three nodal basins. The localizations for two nodal basins were either both axillas (64%) or both inguinal regions (10%), axilla and inguinal (20%), inguinal and other region (3%), axilla and other region (3%). A SN in more than one nodal basin was rare for lesions localised on the extremities (1%), but for melanomas of the trunk the involvement of two (31%) or three (2%) different nodal basins were more common ($p < 0.001$).

Sentinel node status

A positive SN was found in 107 (14%) of the patients, of these 35 (33%) had a low metastatic load and 72 (67%) a high metastatic load. In 85 cases (79%) there was one positive SN, in 19 cases (18%) two positive SNs and in 3 patients (3%) there was three or more positive SNs. The rate of positive SN decreased after the first 4 years, and was then relatively stable at 13% (range 9–20%) (Fig. 1). In univariate analysis the predictive factors for sentinel node status were Breslow thickness, ulceration, Clark level and localization of the primary tumour. In multivariate analysis the only independent predictive factor was Breslow thickness (Table 2).

Table 1
Patient and primary tumour characteristics.

Characteristics	N (%)
Age, median (range)	60.9 (16.8–89.1)
Sex	
Male	387 (51%)
Female	377 (49%)
Breslow (T-status)	
≤1.0 mm (T1)	52 (7%)
1.01–2.0 mm (T2)	309 (41%)
2.01–4.0 mm (T3)	241 (32%)
>4.0 mm (T4)	153 (20%)
Missing	9
Ulceration	
Present	232 (34%)
Absent	461 (66%)
Missing	71
Primary tumour site	
Arm	153 (20%)
Trunk	372 (49%)
Leg	239 (31%)
Clark level	
II	34 (5%)
III	283 (40%)
IV	337 (48%)
V	50 (7%)
Missing	60

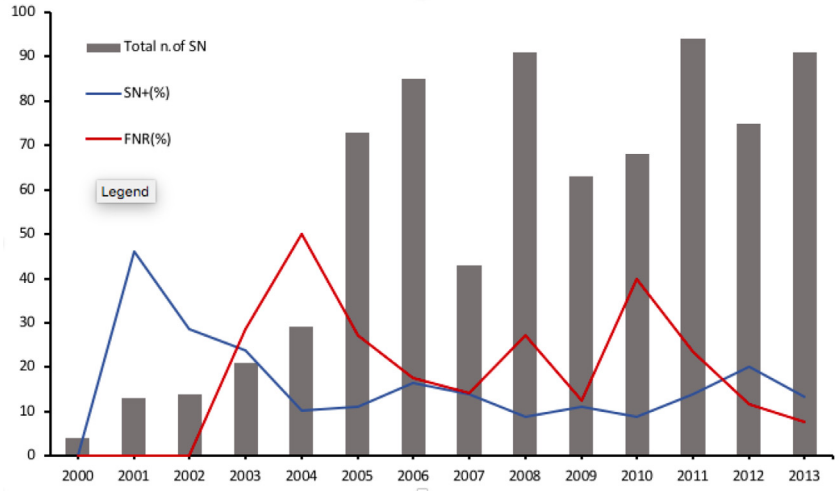

Fig. 1. SNB procedure trend in the time period 2000-2013.
During the analysed period we observed a reduction both in false negative rate (FNR), and in the SN positive rate (SN+), as well as a dramatic increase in the number of SNB procedures.

Non-sentinel node status

Among patients with a positive SN (n = 107), 86% underwent a CLND (n = 92), while 15 of the patients underwent clinical (n = 11) or ultrasound control (n = 4). After the CLND, 25 of the patients (27%) had additional metastatic non-sentinel nodes (NSN). There were no significant predictive factors for NSN in either univariate or multivariate analysis.

Recurrences

The first site of recurrence was in-transit metastasis in 44 patients (6%), nodal recurrences in 43 patients (6%) and general metastases in 72 patients (9%). The disease-free survival (DFS) at 5 years was 71% and at 10 years 64%, the median DFS was not reached. The false negative rate (FNR), based on nodal relapse after a negative SNB, was 20% for the whole period. The FNR varied over the studied period, but has showed a decreasing trend during the last years (Fig. 1).

Table 2
Predictive factors for positive LNS.

	Univariate analysis			*Multivariate analysis*		
	OR	*95% CI*	*p value*	*OR*	*95% CI*	*p value*
Age (per year)	1.0	0.9–1.0	0.513	1.0	0.9–1.0	0.069
Sex						
Female	1.0			1.0		
Male	1.2	0.8–1.8	0.429	1.2	0.7–1.9	0.517
T Status						
T1 + T2	1.0			1.0		
T3	3.0	1.7–5.1	< **0.001**	2.6	1.4–4.8	**0.002**
T4	6.2	3.6–10.8	< **0.001**	4.7	2.4–9.3	< **0.001**
Clark						
II + III	1.0			1.0		
IV	2.1	1.3–3.3	**0.003**	1.5	0.9–2.6	0.103
V	3.1	1.5–6.7	**0.003**	1.4	0.6–3.6	0.462
Localization						
Extremities	1.0			1.0		
Trunk	1.6	1.1–2.4	**0.024**	1.5	0.9–2.4	0.105
Ulceration						
No	1.0			1.0		
Yes	2.1	1.4–3.2	**0.001**	1.3	0.8–2.1	0.249

Melanoma-specific survival

The 5-year melanoma specific survival (MSS) was 81% and the 10-year MSS was 69%, the median MSS was not reached. For patients with a positive SN and high metastatic load (>1 mm) the median MSS was 84 months, while for low metastatic load (≤1 mm) the MSS was 71 months (p = 0.857). For patients with a negative SN, the median MSS was not reached (Fig. 2). Independent prognostic factors for MSS were lymph node status, Breslow thickness and ulceration (Table 3).

Overall survival

The 5-year overall survival (OS) was 74% and the 10-year OS was 44%, the median OS was 102 months. For patients with a positive SN with a low metastatic load (≤1 mm) the OS was 68 months, for high metastatic load (>1 mm) 65 months, and for patients with a negative SN the OS was 106 months (p < 0.001).

Complications

After SNB there were local complications recorded in 23 of the patients (3%), 14 patients with wound infections, seven patients with seromas, one patient with a large hematoma and one patient with a wound dehiscence.

Discussion

This is a single-centre experience reporting the outcome of all SNB procedures performed for melanoma between March 2000 and December 2013. During this time the number of procedures per year has increased almost ten times, and it is now routinely used for all T1b-T4 melanomas.

The rate of positive SN was 14% for the whole period, and in previous studies a positive SN rate between 13% and 31% has been reported [10,11]. Compared with these data our results are in the lower spectrum, and we also note that the rate of positive SN has decreased somewhat over time in our series. These findings are most probably due to the change in the Swedish national guidelines that initially recommended SNB for melanomas thicker than 1.5 mm, which in 2004 was changed to be recommended for all

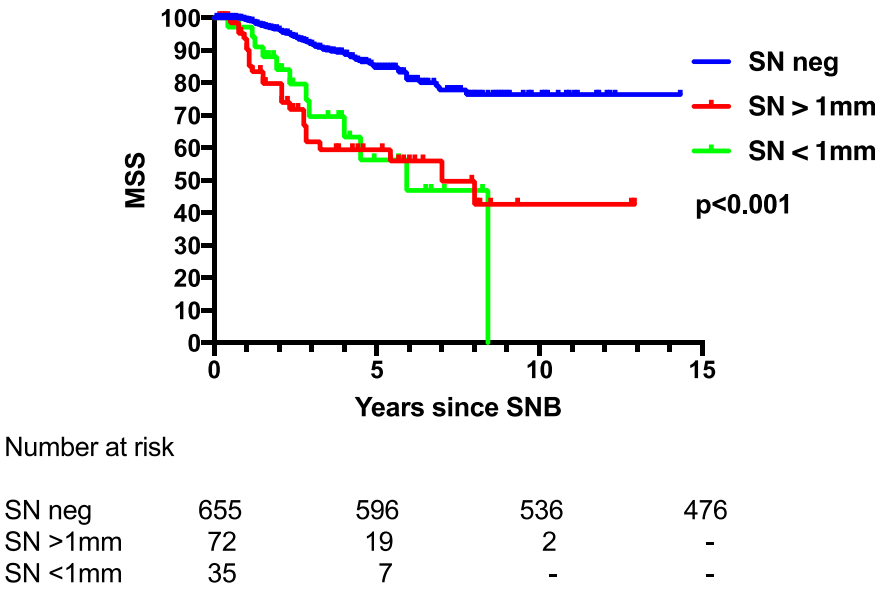

Fig. 2. Melanoma Specific Survival (MSS).
There was a significant difference in MSS between patients with negative SN, and patients with positive SN (p<0.001). There was no difference in median MSS between patient with positive SN with tumour load >1 (84 months) and positive SN with tumour load of ≤1mm (71 months) (p=0.857).

Table 3
Prognostic factors for melanoma specific survival.

	Univariate analysis			*Multivariate analysis*		
	HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Age (per year)	1.0	0.9–1.0	0.413	1.0	0.9–1.0	0.505
Sex						
Female	1.0			1.0		
Male	1.7	1.2–2.6	**0.007**	1.4	0.8–2.2	0.209
Sentinel Node						
Negative	1.0			1.0		
Metastatic load > 1 mm	3.8	2.4–6.1	< **0.001**	2.6	1.5–4.4	**0.001**
Metastatic load ≤ 1 mm	3.6	2.0–6.7	< **0.001**	2.7	1.4–5.5	**0.004**
T Status						
T1 + T2	1.0			1.0		
T3	2.2	1.3–3.7	**0.004**	2.1	1.1–4.1	**0.030**
T4	3.6	2.0–5.8	< **0.001**	2.8	1.3–5.8	**0.006**
Clark						
II + III	1.0			1.0		
IV	1.5	0.9–2.3	0.190	1.0	0.6–1.6	0.995
V	1.7	0.8–3.4	0.098	1.0	0.4–2.3	0.984
Localization						
Extremities	1.0			1.0		
Trunk	1.6	1.1–2.4	**0.018**	1.1	0.7–1.8	0.563
Ulceration						
No	1.0			1.0		
Yes	2.8	1.8–4.2	< **0.001**	1.9	1.2–3.0	**0.009**

melanomas thicker than 1.0 mm [9].

The FNR was 20% for the whole period, and compared to previous studies a FNR between 9% and 21% has been reported [12,13]. At our institution the FNR decreased over the years and was for the last time period similar to other large centres reporting a FNR of approximately 17% [14–16]. This shows that there is a learning curve for the SNB procedure, and this is a reason to centralize these procedures to high-volume centres [17].

Breslow thickness was the only independent predictive factor for a positive SN in our series, which is similar to several other studies. However, other predictive factors such as age, tumour site and ulceration could not be confirmed. Data concerning mitoses, lympho-vascular invasion and regression of the primary tumour was missed in our series, and could not be corrected for [6,7,14,18–20]. In approximately 20% of the patients with a positive SN undergoing CLND there are positive NSN. Predictive factors for positive NSN has previously been extensively analysed, and are summarized by Madu et al. [8]. The maximum diameter of the largest metastasis in the SN has been reported as the most reliable predictive factor, however we were not able to verify this, probably due to the low amount of patients with positive NSN in our group of patients.

In this series 67% of the SN positive patients had a tumour load larger than 1 mm. In a large multicentric study including 1539 patients with a positive SN, 47% of the patients had a tumour load larger than 1 mm [21]. In this study there was a mixed use of two different pathological examination protocols, the Melanoma Institute Australia (MIA) and the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group protocols. Several other studies, using various pathological protocols, have reported even lower ratios of metastases larger than 1 mm, ranging between 23% and 50% [22–27]. Rutkowski et al. presented 321 SNs evaluated with haematoxylin and eosin (H&E), and if negative tested also with S-100 and HMB-45, and in this series 65% had a tumour load larger than 1 mm [28], a finding similar to our data. The pathological technique at our institution changed during the last 16 months of the 13 year study period, a too short period to analyse any potential effect on the ratio between high and low tumour load.

For MSS the independent prognostic factors were SN status, Breslow thickness and the presence of ulceration. This verifies that these are the most important prognostic factor for stage I-II melanoma, which is also incorporated in the AJCC classification [29,30]. Interestingly, there was no difference in MSS between high or low tumour load in the SN, contrary to what has been reported earlier [22,23,31]. Possible limitations were the retrospective nature of this study and the lack of complete pathological data according to the Rotterdam criteria [23].

The MSLT-1 trial investigated the SNB technique and randomized patients into either WLE alone, with delayed LND if nodal recurrence developed or WLE and SNB, with immediate CLND for patients having a positive SN. There was no survival differences in

the overall population, but in a highly discussed sub-group analysis comparing the SN positive patients with patients having late recurrences in the observation arm, the study claimed that there was a survival benefit by using SNB and immediate CLND [7]. To further investigate this finding, the MSLT-2 trial randomized patients with positive SN to either CLND or observation with ultrasound of the nodal basin. The final results showed no difference in melanoma-specific survival (MSS), but a higher rate of nodal recurrences in the observation group [32].

Based on these studies there is still a debate whether an immediate CLND should be recommended in patients with a positive SN. Importantly the use of SNB is still recommended in most guidelines, but the interpretation is rather that SNB has to be seen as a biomarker for possible adjuvant therapies then as a therapeutic procedure [33]. Adjuvant phase III trials of both immunotherapy [34,35] and also targeted therapies [36] has now proven to prolong survival, which will dramatically change the treatment landscape for melanoma.

Even if SN status currently is regarded as the most important factor when guiding patients to these new adjuvant therapies, the development of new imaging techniques might in the future obviate the need for surgical excision of the sentinel node, especially if there is no therapeutic effect. Specific ultrasound patterns, like the "Berlin-morphology-criteria", can be employed to increase the imaging sensitivity during follow-up [37]. Another interesting concept has been shown using superparamagnetic iron oxide (SPIO)-enhanced MRI in eg. breast cancer to predict if there is metastases in the SN, and concepts like this might very well also be utilised for melanoma in the future [38].

Conclusion

SNB is a useful technique that reduced complications related to the previous elective lymph-node dissection, and SNB still stands as the best staging tool for malignant melanoma. In this study Breslow thickness was the only predictive factor for a positive SN. The independent prognostic factors for MSS were SN status, Breslow thickness and ulceration. Taken together, there is a learning curve for all involved specialities, with decreasing FNR over time. The SNB procedure is still the best technique to properly stage patients with melanoma, and since the introduction of the technique at our institution, it has resulted in a low morbidity procedure with reliable results comparable with other large international centres.

Declaration of interest

None.

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