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High positive sentinel node identification rate by EORTC melanoma group protocol
Prognostic indicators of metastatic patterns after sentinel node biopsy in melanoma

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ABSTRACT

Methods to work-up sentinel nodes (SN) vary considerably between institutes. This single institution study evaluated the positive SN-identification rate of the EORTC Melanoma Group (MG) protocol and investigated the prognostic value of the SN status regarding disease-free survival (DFS) and overall survival (OS) and evaluated the locoregional control after the SN procedure. Multivariate and univariate analyses using Cox's proportional hazard regression model was employed to assess the prognostic value of covariates regarding DFS and OS.

The positive SN-identification rate was 29% at a median Breslow thickness of 2.00 mm and the false-negative rate was 9.4%. Breslow thickness and ulceration of the primary correlated with SN status. SN status, ulceration and site of the primary tumour correlated with DFS. SN status and ulceration of the primary correlated with OS. The in-transit metastasis rate correlated with SN-positivity, Breslow thickness and ulceration. Projected 3-year OS was 95% in SN-negative and 74% in SN-positive patients. Transhilar bivalving of the SN with step sections from the central planes is simple and had a high SN-positive detection rate of about 30%. The SN status is the most important predictive value for DFS and OS. In-transit metastasis rates correlated with SN-positivity, Breslow thickness and ulceration of the primary.

1. Introduction

Of all the different types of cancer, melanoma has a share of 1% of all cases. Metastatic behavior and survival correlate with risk factors such as tumour thickness and the presence of ulceration of the primary, the presence and number of metastatic regional lymph nodes and non-visceral or visceral metastases [1]. A number of underpowered randomized trials have evaluated the impact of the adjuvant surgical procedure the elective lymph node dissection (ELND) in melanoma and have failed to demonstrate a survival advantage by ELND [2–5]. The most recent randomized trial, the WHO 14 demon-

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strated a potential benefit in patients with micrometastatic disease in the ELND specimen [5] and suggested that the Sentinel Node procedure might therefore be of benefit to patients in the management of primaries >1.5 mm. Also the long-term follow-up results of the USA Intergroup trial showed some potential benefit in patients with melanomas of intermediate thickness [4], as did a database matched paired analysis in patients with primary melanomas between 1.2 mm and 3.5 mm, by Morton and co-workers [6].

At the basis of these developments is the work of Morton in the late 1980's and early 1990's, who formulated the sentinel node (SN) procedure, which is based on the concept that a tumour will undergo an orderly progression of dissemination with the local lymphatic system as primary route of metastasis [7]. Whether this SN procedure, followed by complete lymph node dissection in case of a positive SN, results in survival benefit has been investigated in the Multicenter Selective Lymphadenectomy Trial (MSLT-I), which has not yet reached full maturity for final analysis.

Identification rates of positive SN in patients with primary melanomas thicker than 1.0 mm vary considerably in the literature. Usually rates of 15–20% are reported. Vulysteke [8] found 19% SN-positive patients in a total of 209 patients with a median Breslow thickness of 1.41 mm. Doubrovsky [9] and Gerschenwald [10] found 18% and 15% SN-positive patients in a total of 672 and 580 patients with a median Breslow thickness of 2.30 mm and 1.80 mm respectively. Balch [1] and Morton [11] found 13.9% and 19% SN-positive patients in a total of 3126 and 1159 patients respectively.

Methods to work-up SN vary considerably between institutes. This single institution study evaluates the positive SN-identification rate of the EORTC Melanoma Group (MG) protocol. This study also investigates the prognostic value of the SN status regarding disease-free survival and overall survival and it evaluates the locoregional control, specifically on recurrence patterns in the SN investigated lymph node basin(s) and on rates of in-transit metastasis after the SN procedure.

2. Patients and methods

2.1. *Patients*

From October 1997 to May 2004, 262 patients with malignant melanomas, with a Breslow thickness of at least 1.00 mm and/or at least a Clark level IV or if ulceration was present, underwent a sentinel lymph node bioposy (SLNB) at our institute (Erasmus Medical Center, Daniel den Hoed Cancer Center, Rotterdam, the Netherlands). Patient characteristics, operation notes and follow-up were all entered in a prospective database. The average age was 48 years (range 16–83 years). The mean Breslow thickness was 2.76 mm (range 0.60–15.00 mm). The baseline characteristics of these 262 patients are described in Table 1.

Table 1 – Patient characteristics of all 262 patients

	N	%
Gender		
Male	116	44
Female	146	56
Primary tumour location		
Arm	40	15
Leg	113	43
Trunk	91	35
Head/neck	18	7
Histology		
SSM	126	48
NM	90	34
ALM	4	2
Other	3	1
Unclassified	39	15
Clark level		
II	5	2
III	110	42
IV	121	46
V	10	4
Undeterminable	16	6
Ulceration		
Present	73	28
Absent	189	72

SSM = superficial spreading melanoma, NM = nodular melanoma, ALM = acrolentiginous melanoma.

2.2. *Triple technique*

To identify and retrieve the correct and all SN, the triple technique was used [12,13]. Firstly, a preoperative lymphoscintigraphy (LS) after four intradermal injections of 99m-labeled Tc-albumin nanocolloid (Nanocoll, Amersham Health, Gipharma, Saluggia, Italy) around the excision site of the primary tumour on the day of the surgery was performed. Scanning was carried out immediately after the injection and again after 2 h. Secondly, intraoperative use of handheld gamma detection probe (Europrobe, PI Medical Diagnostic Equipment B.V., Sneek, the Netherlands) was used to verify the location of SNs. And finally, shortly before surgery, patent blue dye (Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected intradermally next to the initial site of the melanoma, to help localize the SN visually during the operation.

A lymph node was considered to be a SN if it was stained blue, if it had an in situ radioactivity count of at least three times that of the background count, or if it had an ex vivo radioactivity count of at least ten times greater than that of the background count [14,15].

2.3. *Surgical procedure*

Most of the patients had already undergone (diagnostic) excision of the primary tumour elsewhere. They were treated by a local wide re-excision (with margins according to the guidelines of the Dutch Melanoma Workgroup), unless the diagnostic excision was considered wide enough or if the primary tumour was located in regions of the body where re-excision could not be performed with primary closure. During the same operation, the SN(s) were surgically removed with the help of the triple technique as described previously. In 10 patients re-excision had already taken place in another hospital and only removal of the SN(s) was performed.

2.4. Pathological analysis

All sentinel nodes after June 2002 ($n = 112$) were sent for pathological assessment according to the protocol by Cook [16], which is the EORTC MG guideline for pathological examination of SN. In brief, lymph nodes were fixed for 24 h in buffered formalin. After fixation they were cut in half through the hilum and its longest dimension and embedded in paraffin. In rare cases, exceptionally large nodes were sectioned parallel to the first cut in order to fit in the blocks. Five serial step sections of 4 μm each were cut from each face of the lymph node, and staining with H&E, S100 and HMB-45 was performed. There was a slight difference between the protocol by Cook [16] and that used before June 2002 ($n = 150$), in that serials sections were made with 50 μm intervals, which were 250 μm intervals before that time.

2.5. Follow-up

Patients were all followed at the outpatient clinic. Recurrences were scored as local recurrence, in-transit metastasis, regional lymph node recurrence, distant lymph node metastasis, subcutaneous metastasis or visceral metastasis. Patients with a negative SN who developed recurrence in the sentinel lymph node basin were further analyzed as false negative SN biopsy patients.

2.6. Statistical analysis

Categorical variables were tabulated by SN status and the imbalance of those groups was tested using the Fisher's exact test. Imbalances in continuous variables were tested using the Kruskal–Wallis test. Disease-free and overall survival was defined as time from SN biopsy till recurrence or death respectively. In-transit metastasis was defined as time from SN biopsy till in-transit recurrence. Patients without such an event on their last contact were censored at that time. Analysis of those endpoints was performed using the Kaplan–Meier approach. The log-rank test was used to evaluate a difference in survival between groups. Univariate and multivariate analyses using the Cox's proportional hazard regression model were performed to assess the prognostic value of covariates with respect to disease-free survival and overall survival. Few values for Clark and Breslow were missing. A single imputation algorithm was used in order to include those patients in the multivariate analysis. P-values of less than 0.05 were considered as significant. All statistical analyses were performed with Stata version 8.2 (Stata Corporation, College Station, Texas, USA).

3. Results

3.1. SN identification and status

In 262 patients, 256 underwent preoperative lymphoscintigraphy (LS), 6 did not have the preoperative lymphoscintigraphy due to logistical problems. In these 256 patients, a total of 334 lymph node basins were recognized through LS, with a total of 601 lymph nodes recognized. This resulted in an average of 1.80 lymph node per lymph node basin.

During all the operations a total of 510 lymph nodes were harvested (they were either stained blue and/or radioactive, see Patients and Methods), with an average of 1.95 lymph node per patient. It also yielded a rate of 85% of all the nodes found in the LS. However, at least one SN was found in all patients and therefore the procedure was considered to have a success rate of 100%.

In the 262 patients, 77 patients (29.4%) were considered to have a positive SN after the pathological examination of their nodes. There were no differences in SN-positivity between gender and age. Median Breslow thickness was 1.90 mm for SN-negative patients and 2.95 mm for SN-positive patients. The distribution pattern of tumour characteristics for SN-positive patients is summarized in Table 2.

Not shown in Table 2 is the analysis of the two different patient cohorts, for which two slightly different pathology protocols, as mentioned previously, were used. These two cohorts (250 μm versus 50 μm intervals) did not significantly differ from each other for mean Breslow thickness, 2.94 mm versus 2.54 mm, or ulceration, 27% versus 29%. Both cohorts also did not significantly differ from each other for positive SN identification rate, 30.7% versus 27.7%.

A total of 76 completion lymphadenectomies were performed in 77 SN-positive patients. One patient refused completion lymphadenectomy. Of the 76 patients who underwent completion lymphadenectomies, 61 did not reveal any further positive nodes (80%). Five patients (7%) had one

Table 2 – Characteristics for SN-positive patients

	n	%	P
Primary tumour location			
Arm	8	20	n.s.
Leg	35	31	
Trunk	31	34	
Head/neck	3	17	
Histology			
SSM	38	30	n.s.
NM	28	31	
ALM	1	25	
Other	1	33	
Unclassified	9	23	
Breslow thickness			
<1.00 mm	2	17	0.005
1.01–2.00 mm	25	21	
2.01–4.00 mm	27	34	
>4.00 mm	20	48	
Clark level			
II	2	40	n.s.
III	33	30	
IV	33	27	
V	4	40	
Undeterminable	5	31	
Ulceration			
Absent	47	25	0.015
Present	30	41	

SSM = superficial spreading melanoma, NM = nodular melanoma, ALM = acrolentiginous melanoma.

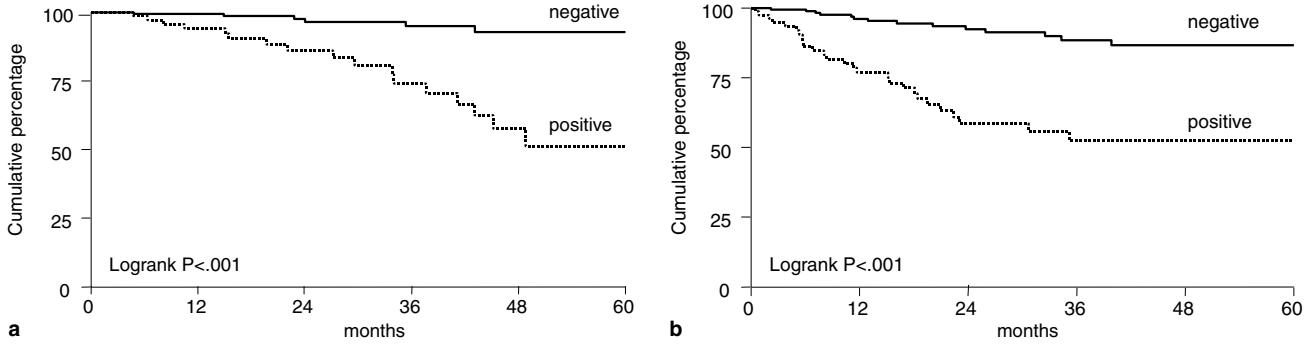

Fig. 1 – Kaplan–Meier estimated 5-year survival curves for: (a) overall survival and (b) disease-free survival.

additional metastatic node and ten patients (13%) had two or more additional metastatic nodes.

3.2. *Recurrences*

The median follow-up was 23.3 months (range: 0–82 months). The estimated 3-year overall recurrence-free survival for SN-negative patients was 88% and 52% for SN-positive patients ($P < 0.001$). The estimated 5-year overall recurrence-free survival for SN-negative patients was 87% and 51% for SN-positive patients ($P < 0.001$) (Fig. 1b). Table 3 shows the distribution of the first recurrence sites. SN-positive patients had a significantly increased risk of developing any form of recurrence compared to SN-negative patients.

3.3. *In-transit metastases*

The estimated 5-year in-transit metastasis rate was 8% for SN-negative patients versus 20% for SN-positive patients ($P < 0.001$) (Fig. 2a). The estimated 5-year in-transit metastasis rate was also significantly dependent upon the Breslow thickness ($P < 0.001$) (Fig. 2b) and ulceration status ($P = 0.03$) (Fig. 2c).

3.4. *False negative results*

Thus far, 8 false negative patients were seen (9.4% false negative rate). All these SN were retrospectively reviewed by a staff pathologist (M.K.) and remained node-negative. In three patients, fewer nodes were retrieved than seen on the lymphoscintigraphy. These nodes were possibly missed during the operation. These patients developed a nodal recurrence after 21, 24 and 8 months, respectively. Three patients developed distant ($n = 1$) or in-transit ($n = 2$) metastases and subsequently a positive node in the regional basin after 13, 11 and 9 months, respectively. Two patients were not treated according to the protocol. In one patient only blue dye was used and another patient SN biopsy was performed 5 months after re-excision. These were considered technical failures.

3.5. *Survival*

The estimated 3-year overall survival (OS) rate according to the SN status was 95% for SN-negative and 74% for SN-positive patients ($P < 0.001$). The estimated 5-year OS rate according to the SN status was 93% for SN-negative and 51% for SN-positive patients, respectively ($P < 0.001$) (Fig. 1a).

The estimated 5-year survival rates for four different categories of Breslow thickness, namely, <1.00 mm, 1.01–2.00 mm, 2.01–4.00 mm and >4.00 mm, were 100%, 86%, 77% and 65% respectively ($P = 0.11$) (Fig. 3a).

The estimated 5-year survival rates in the presence or absence of ulceration of the primary tumour, was 86% in the absence and 60% in the presence of ulceration, respectively ($P < 0.001$) (Fig. 3b).

The estimated 5-year survival rates according to the number of involved sentinel lymph nodes was 93% for no metastatic sentinel lymph nodes, 54% for one metastatic sentinel lymph node and 47% for multiple (two or more) metastatic sentinel lymph nodes ($P < 0.001$) (Fig. 4).

Table 4 shows an overview of Cox's univariate regression analyses for disease-free and overall survival. Also a Cox's

Table 3 – The distribution of all first recurrence sites

Type of 1st recurrence	SN−	%		SN+	%	
Locoregional failure						
Local recurrence	2	1.1		4	5.2	
In-transit metastasis	4	2.2	**6.5%**	7	9.1	**22.1%**
Regional lymph node	6	3.2		6	7.8	
Distant failure						
Distant lymph node	1	0.5		3	3.9	
Subcutaneous metastasis	2	1.1	**3.8%**	3	3.9	**27.3%**
Visceral metastasis	4	2.2		15	19.5	
Total	19	10.3		38	49.4	

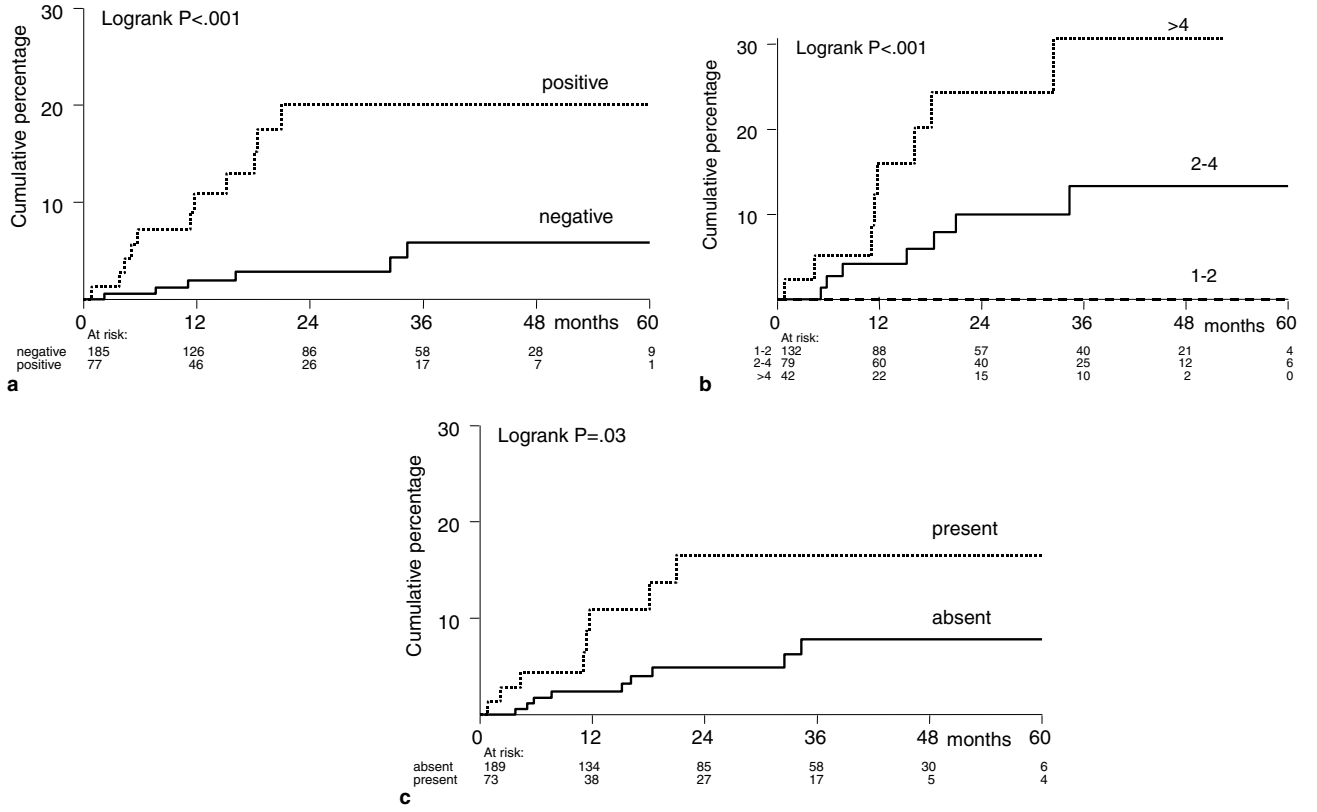

Fig. 2 – In-transit metastasis rate according to: (a) SN positivity, (b) Breslow thickness and (c) ulceration.

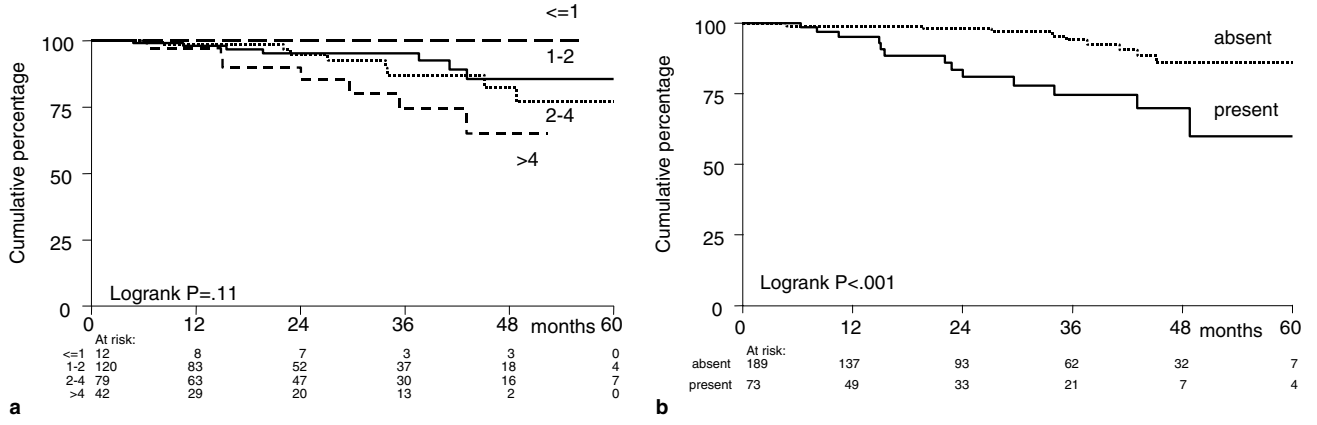

Fig. 3 – Kaplan–Meier estimated 5-year overall survival according to: (a) Breslow thickness and (b) ulceration status.

proportional hazard regression model was used to determine the influence of different covariates on the disease-free and overall survival rates (Table 5).

As seen in Table 5, the SN status, location, ulceration and a high Clark level (V) had a significant influence on the disease-free survival. SN status and ulceration had a significant influence on the overall survival. Breslow thickness was not a significant factor in this model, however Breslow thickness as a factor for disease-free survival approached significance ($P = 0.13$). The reason that Breslow thickness was not a significant factor might be due to the small patient population.

4. Discussion

In this single institution study we confirm the high detection rate of the EORTC MG protocol.

In the present study at least one SN was found in 100% of the patients during the surgical biopsy, this is comparable with other studies, which reported success rates between 98.5% and 100% [8,10,17,18]. The false negative rate found in the present study was 9.4%, this is also comparable with other studies, in which rates between 7% and 18% are reported [17–20].

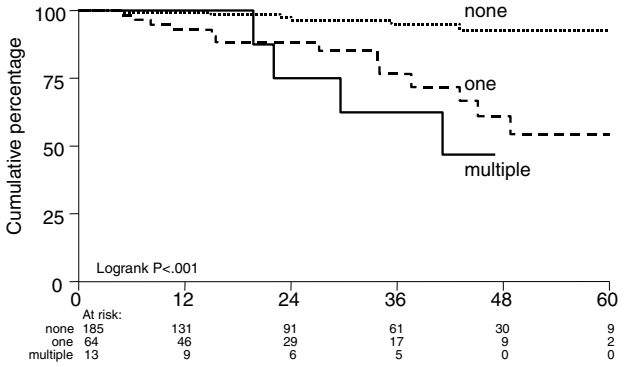

Fig. 4 – Overall survival according to the number of metastatic sentinel lymph nodes.

The Cook protocol [16] for the histopathologic work-up and examination of SN reported a higher positive SN identification rate (29.4%) than most other large studies [1,8–11,17,21,22], which all had detection rates between 14% and 20%. Our patient population did not differ from those studies with respect to the crucial prognostic factors (Table 6). The median Breslow thickness reported by Gerschenwald [10], Vuylsteke [8] and Doubrovsky [9] were 1.80 mm, 1.41 mm and 2.30 mm respectively. In this current study there was a median Breslow thickness of 2.00 mm and a SN-positive rate of 29.4% is the highest ever reported. The essential difference in the pathological work-up of the SN between the present study and other studies [1,8–11,17,21,22] is transhilar bivalving and taking most step-sections from the central hilar planes of the lymph node. Despite the higher rate of SN positivity, survival rates were similar to other studies (Table 6). The increase in SN positivity may reflect an increase in diagnosis of minimal and perhaps biologically less aggressive disease and therefore further research needs to be done on the clinical relevance of the increase in SN-positive detection rates.

The SN technique is based on the now well-supported hypothesis that melanoma lymphatic metastases follow an orderly progression through afferent lymphatic channels to SNs before spreading into other regional, non-SN [10,23]. The current study supports this hypothesis, as 80% of the patients, who had at least one positive SN and received a subsequent lymphadenectomy, did not reveal any other positive nodes in the nodes resected during the lymphadenectomy. The 5-year disease-free survival rates were 87% and 52% for SN-negative and positive patients, respectively in our study. These rates are comparable with several other studies, which report 5-year disease-free survival rates of between 78% and 88% and between 39% and 53% for SN-negative and positive patients, respectively [8–11,17,21,22]. Also the 5-year overall survival rates of the present study, 93% and 51% for SN-negative and SN-positive patients, respectively, are comparable with several other studies, which report similar overall survival rates of between 92% and 88% for SN-negative patients, and overall survival rates of between 54% and 67% for SN-positive patients [8–11,17,21,22].

Table 4 – Cox univariate regression analyses of disease-free and overall survival

Univariate	DFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
⩽50	1			1		
>50	1.09	0.59–2.02	0.77	0.76	0.33–1.77	0.53
SN status						
Negative	1			1		
Positive	5.51	2.89–10.53	<0.001	7.25	2.86–18.40	<0.001
Gender						
Female	1			1		
Male	1.14	0.62–2.10	0.68	0.91	0.40–2.08	0.82
Location						
Extremity	1			1		
Central	2.29	1.23–4.28	0.009	1.59	0.70–3.61	0.27
Ulceration						
Absent	1			1		
Present	2.72	1.47–5.02	0.001	3.76	1.65–8.59	0.002
Breslow						
⩽2 mm	1			1		
2–4 mm	3.23	1.46–7.14	0.004	1.69	0.63–4.53	0.30
>4 mm	5.28	2.26–12.36	<0.001	3.27	1.14–9.34	0.027
Clark						
2, 3	1			1		
4	1.27	0.65–2.50	0.49	0.57	0.23–1.40	0.22
5	5.00	1.92–13.03	0.001	2.44	0.69–8.67	0.17

DFS = disease-free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval.

Table 5 – Cox proportional hazard regression analyses of disease-free and overall survival

Covariate	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
Age						
⩽50	1			1		
>50	1.17	0.61–2.22	0.64	1.02	0.42–2.48	0.97
SN status						
Negative	1			1		
Positive	5.71	2.81–11.60	<0.001	7.29	2.65–20.10	<0.001
Gender						
Female	1			1		
Male	0.75	0.39–1.44	0.38	0.77	0.32–1.82	0.54
Location						
Extremity	1			1		
Central	3.31	1.66–6.60	0.001	2.13	0.89–5.10	0.09
Ulceration						
Absent	1			1		
Present	3.33	1.58–7.03	0.002	4.66	1.76–12.34	0.002
Breslow						
⩽2 mm	1			1		
2–4 mm	1.94	0.82–4.56	0.13	0.94	0.32–2.74	0.91
>4 mm	1.15	0.38–3.52	0.81	0.58	0.13–2.57	0.47
Clark						
2, 3	1			1		
4	1.38	0.67–2.87	0.39	0.71	0.26–1.92	0.28
5	11.63	2.96–45.76	<0.001	5.43	0.94–31.27	0.06

DFS = disease-free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval.

Table 6 – Review of other SN studies

Name	%SN+	Pt.	Mean	Median	Ulc. (%)	SN + DFS	SN + OS	SN − DFS	SN − OS
Morton [11]	19.8	1159			29		70.6%		88.4%
Gerschenwald [10]	15	580	2.40	1.80	23.7	56% (3 years)	70% (3 years)	89% (3 years)	97% (3 years)
Vuylsteke [8]	19	209	1.78	1.41	17	50%	67%	88%	92%
Doubrovsky [9]	18	672	2.90	2.30	31.8		59%		87.5%
Balch [1]	13.9	3126					58		
Carlson [22]	17.7	592			13	59% (3 years)	77% (3 years)	86% (3 years)	92% (3 years)
Estourgie [17]	24	250	2.70		31.6	53%	64%	80%	89%
Kretschmer [21]	29.1	244		2.30	34.8	38.6%	54.4%	77.7%	90.1%
DDHCC	29.4	262	2.76	2.00	28	52% (3 years)	74% (3 years)	88% (3 years)	95% (3 years)

DDHCC = Daniel den Hoed Cancer Centre, DFS = disease-free survival, OS = overall survival.

Whether SN staging will have an impact on overall survival remains to be seen: a recent study by Doubrovsky [9] shows that the reason SLNB is superior to ELND is due to the difference in histopathological protocols used to examine the lymph nodes, however SLNB patients had no survival advantage compared to ELND patients in this retrospectively matched control study. More importantly the interim analysis of the MSLT-I trial does not suggest any survival benefit for the overall population with high-risk primary melanomas. Survival rates at 5 years are virtually identical at 87% and 86% irrespective of whether or not a SN procedure has been performed [11]. Whether a complete lymph node dissection at the time of the identification of a positive SN has an impact on survival is unclear at the moment as well. But, survival rates at 5 years are reported significantly higher in the SN-positive patient population than in patients that did not undergo an SN-staging and underwent a delayed lymph node dissection at a later stage, because of positive nodal disease. However, this is not a strictly randomized comparison and it may well be that patients who develop clinically positive disease represent a biologically unfavorable selection amongst the patients, as compared to the complete set of SN-positive patients [11]. Since the overall outcome in the overall population is not different between patients that have or have not undergone a SN procedure it is clear that the data thus far presented are incomplete, as they have not provided insight in the curves of SN-negative patients (including the SN-false-negative patients), which may well be significantly

worse than the Observation patients that never developed nodal disease, just has been observed in the WHO-1 trial [2]. The present study can not address this dilemma, as there is no group of patients that did not undergo a SN procedure, but only had a local wide excision or only had an ELND.

Another important issue is the alleged increased rate of in-transit metastasis after the SN procedure. Thomas [24] reported a higher rate of in-transit metastasis after SN biopsy plus lymphadenectomy (20.9%). Another recent study by Estourgie [25] reported a rate of 23% in-transit metastasis in SN-positive patients. The present study shows an estimated 5-year in-transit metastasis rate of 20% in SN-positive patients (who subsequently underwent a lymph node dissection). However, the theory that the SN procedure itself leads to more in-transit metastases can be refuted. The study by Estourgie [25] shows a major unbalance in prognostic tumour characteristics Breslow thickness and ulceration of the primary between the two groups that were compared. These were 3.8 mm versus 2.9 mm and 48% versus 22% ulceration present for the SN and palpable lymph node groups, respectively.

The present study shows that both in the SN-negative and in the SN-positive patient groups the ulceration status and Breslow thickness of the primary tumour influences the in-transit metastasis rate. This correlation is significant for the Breslow thickness ($P < 0.001$) and ulceration ($P = 0.03$). Recent publications with large patient populations concur with this observation [26,27]. SN-positive patients have a significantly increased risk of developing any form of recurrence compared to SN-negative patients. Studies with much larger case numbers seem to demonstrate that the increase in the in-transit metastasis rate is not real, but due to a prolonged recurrence-free interval, since the SN procedure avoids nodal recurrences, thereby increasing the chance of in-transit metastases to manifest as a first recurrence site. The overall in-transit probability however remains unchanged; independent of whether early or delayed excision of nodal metastases is performed [21,28]. Many comments [28–32] by international authors point out that the presumption by Thomas [24] and by Estourgie [25] that sentinel lymph node biopsy would lead to an increased rate of in-transit metastasis is not true. Therefore, the suggestion that SN biopsy should be abandoned, because of the supposed risk, is unjustified.

In spite of the absence of proof of a survival benefit associated with SN staging, the procedure is quite useful for stratifying patients in randomized phase III systemic adjuvant therapy trials, to create more homogeneous patient populations to determine whether adjuvant systemic trials are of benefit [33].

Moreover SN-staging may well improve long term locoregional control in the lymph node basin compared to the patients who underwent a delayed lymph node dissection [11]. At the same time it is clear that ultrasound of the regional lymph nodes may also be able to achieve this by detecting very small non-palpable lymph node metastases, thus offering an alternative to a SN procedure [34,35].

In conclusion, this study confirms that the EORTC MG protocol performs well in detecting a high rate of nearly 30% of positive SN in patients with cutaneous melanomas >1 mm. Essential is transhilar bivalving and step-sectioning from the central hilar planes of each face of the lymph node. SN-status is the strongest predictive factor for disease-free and overall survival. Breslow thickness and ulceration influence SN status. The SN status is the most important predictive value for disease-free and overall survival. Ulceration is the single most predictive factor for survival. In-transit metastasis rates correlate with SN-positivity, Breslow thickness and ulceration of the primary. The SN status is currently the most powerful prognostic tool available and is a mandatory stratification tool for every prospective adjuvant systemic therapy trial.

Conflict of interest statement

None declared.

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