Chapter 1

Nodular histologic subtype and ulceration are tumor factors associated **with high risk of recurrence in sentinel node negative melanoma patients**

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Abstract:

Background: Since its introduction, the sentinel lymph node biopsy (SLNB) has become the standard staging procedure in clinical node negative melanoma patients. A negative SLNB however, does not guarantee a recurrence-free survival. Insight in metastatic patterns and risk factors for recurrence in SLNB negative melanoma patients can provide patient tailored guidelines.

Methods: Data concerning melanoma patients who underwent SLNB between 1996 and 2015 in a single center, were prospectively collected. Cox regression analyses were used to determine variables associated with overall recurrence and distant first site of recurrence in SLNB negative patients.

Results: In 668 patients, SLNB's were performed between 1996 and 2015. Of these patients, 50.4% was male and 49.6% female with a median age of 55.2 (range 5.7-88.8) years. Median Breslow thickness was 2.2 (0.3-20) mm. The SLNB was positive in 27.8% of patients. Recurrence rates were 53.2% in SLNB positive and 17.9% in SLNB negative patients p:<0.001. For SLNB negative patients, the site of first recurrence was distant in 58.5%. Melanoma located in the head and neck region (HR4.88, p:0.003) and increasing Breslow thickness (HR1.15, p:0.013) were predictive for distant first site of recurrence in SLNB negative patients. SLNB negative patients with a nodular melanoma and ulceration had a recurrence rate of 43.1%, the site of recurrence was distant in 64% of these patients.

Conclusions: The recurrence rates of SLNB negative nodular ulcerative melanoma patients, approach those of SLNB positive patients. Stringent follow-up is recommended in this subset of patients.

Introduction:

Cutaneous melanoma mainly spreads through the lymphogenic route, from the sentinel lymph nodes to the adherent lymph node basin. After decades of experience we now know that in negative sentinel lymph node biopsy (SLNB), skip metastases are very rare.[1, 2] Since its introduction in the early nineties by Donald Morton, the SLNB has become a widely accepted staging procedure and has become one of the most important prognostic variables in predicting outcome in cutaneous melanoma.[3-7] At time of primary staging, approximately 20% of melanoma patients are SLNB positive with a false negative rate less than 5%.[1, 8-10]

SLNB positivity is associated with several clinicopathological characteristics, such as Breslow thickness, mitosis and the presence of ulceration.[11-13] The risk for recurrent disease is associated with this SLNB status, resulting in higher recurrence rates of up to 47 % in SLNB positive patients[14, 15] and lower recurrence rates of 24% in SLNB negative patients.[15-17] Some of these SLNB negative patients have a distant first site of recurrence and even seem to skip the lymphogenic metastatic route.[15] These patients with direct hematogenous recurrences may either have different clinicopathological characteristics, or more aggressive tumor biology.

The purpose of this study was to evaluate risk factors for recurrent disease and distant first site of recurrence in SLNB negative melanoma patients.

Methods:

The study population consists of all consecutive melanoma patients who underwent a wide excision with a 1-2 cm margin according to the international melanoma guidelines and a SLNB at the University Medical Center Groningen (UMCG) between 1996 and 2015. The SLNB technique used at the UMCG has been described elsewhere in detail.[18] Patient and tumor related clinicopathological characteristics were prospectively collected in a database. Data concerning patient and tumor clinicopathological characteristics, follow-up, recurrence and survival were retrieved from the database for analysis.

Statistics were performed by IBM SPSS 22.0 (IBM SPSS, Chicago, IL, USA). Differences between groups were analysed by the Chi square test for nominal variables; for continuous variables, the one-way ANOVA or the Kruskall-Wallis test was used. Cox regression analyses were used to determine variables associated with overall recurrence in all patients, and distant first site of recurrence, in SLNB negative patients. Overall recurrence was defined as any recurrence besides recurrence in the same basin as the SLNB. On the basis of our data, the following were included in the analysis: patient demographics, histologic type, location of primary lesion, Breslow thickness, Clark level, ulceration, mitosis, regression, lymphangioinvasion, use of immunosuppressant medication and whether the primary excision was radical. Variables were checked for correlation with Pearson's or Spearmans's rho. Variables on a 20% significance level in the univariate cox regression were entered in the multivariate cox regression analysis. In the multivariate analysis, variables were checked for multicollinearity and confounding. Confounding limit was set at 10%. Confounders and variables with a multicollinear association were excluded from multivariate analysis. Variables with a $p < 0.05$ in the multivariate analysis were identified as significant factors.

Melanoma specific survival (MSS), disease free survival (DFS), and time to death from moment of first recurrence were analyzed by the Kaplan-Meier test. SLNB was defined as falsely negative if the first site of recurrence was in the same basin as the SLNB, and also when combined with systemic recurrence. To determine whether a SLNB was falsely negative in case of systemic recurrence, all positron emission tomography/computed tomography scans performed at the moment of systemic recurrence were reviewed to check for nodal involvement in the same basin as the SLNB. Because of the 100 % recurrence rate in the same basin in falsely negative SLNB patients, they were not included in the cox regression analysis.

In case of multisite recurrence, the recurrence site with the worst prognosis was scored as the first site of recurrence. For example: in case of recurrence in retro-peritoneal lymph nodes and brain metastases, brain metastases were scored as first site of recurrence. Follow-up was conducted in the UMCG. We received institutional review board approval, and the study was conducted according to the declaration of Helsinki.

Results:

During the study period a SLNB was performed in 668 patients. Baseline clinicopathological characteristics of all patients are displayed in Table 1.

Table 1. Clinicopathological characteristics overall, in SLNB negative patients and in SLNB positive patients (n=668)

Characteristic	Overall n=668(%)	SLNB negative n= 458	SLNB positive n= 186	p
Sex, n (%)				0.070
Male	337 (50,4)	220	104	
Female	331 (49,6)	238	82	
Agea, median (range)	55,2 (5,7-88,8)	55.3(11.5-88.8)	53.5 (5.7-88.8)	0.890

Site of primary, n (%)				0.003
Lower extremity	228 (34,1)	149	68	
Head and neck	95 (14,2)	75	16	
Trunk	256 (38,3)	166	86	
Upper extremity	89 (13,3)	68	16	
Histological typing, n (%)				0.705
Superficial Spreading	414 (62)	291	110	
Nodular	192 (28,7)	128	56	
Acral lentiginous	21 (3,1)	12	7	
Other b	28 (4,2)	20	8	
Breslow thickness c, median (range)	2,2 (0,30-20,0)	1.9 (0.3-20.0)	3.00 (0.8-13.0)	<0.001
T-stage, n (%)				<0.001
T1: <1,00 mm	38 (5.7)	7	0	
T2: 1,01-2,00 mm	271 (40.6)	155	34	
T3: 2,01-4,00 mm	244 (36.5)	114	83	
T4: >4,00 mm	114 (17.1)	52	37	
Clark level, n (%)				0.035
II	7 (1.0)	5	2	
III	137 (20.5)	109	26	
IV	472 (70.7)	312	141	
V	40 (6.0)	23	14	
Ulceration, n (%)				0.001
Yes	223 (33.4)	133	80	
No	435 (65.1)	319	103	
Mitosis				0.055
Yes	561 (84)	380	159	
No	45 (6.7)	37	7	

Data are presented as n(%) or median (range)

SLNB sentinel lymph node biopsy

[a] *Age at diagnosis of primary melanoma.*

[b] *Other histological typings are: verrucus, spitzoid, epitheloid, desmoplastic melanoma and lentigo maligna melanoma.*

Median age at diagnosis of primary melanoma was 55.2 (5.7-88.8) years, and superficial spreading melanoma was the most common histological subtype (62%). Median overall Breslow thickness was 2.2 (0.30-20.0) mm. The median Breslow thickness in the different histological subtypes was as follows: superficial spreading melanoma (n=414):

1.8 (0.30-9.0) mm, nodular melanoma (n=192): 3.4 (0.9-20) mm, acral lentiginous melanoma (n=21): 3.6 (1.1-11) mm, other melanomas (n=28) 3.3 (0.85-17.00) mm and unknown histological subtype (n=13): 3.00 (1.0-7.0) mm. SLNB was positive in 27.8% of patients. In SLNB-negative patients, 24 patients experienced a nodal recurrence in the same basin as the SLNB, resulting in a SLNB false-negative rate of 3.6%. In Table 1 the differences between the baseline clinicopathological characteristics are displayed by SLNB status. During the median follow-up of 58.8 (range 1.8-190) months a recurrence was diagnosed in 82 of the truly SLNB-negative patients (17.9%) and in 99 SLNB positive patients (53.2 %).

Multivariate cox regression analysis revealed the following variables to be associated with overall recurrence in SLNB negative patients: male sex (HR1.78, p:0.025), increasing age (HR1.02, p:0.0085) per year, melanoma located in the head and neck region (HR2.16, p:0.024), nodular melanoma (HR 1.82,p:0.028) and the presence of ulceration (HR2.11, p:0.002). In SLNB positive patients, excisional biopsy decreased the risk for recurrence (HR 0.49, p:0.005) as well as melanoma located on the upper extremity (HR0.37, p:0.045). Male sex (HR1.10, p:0.048), increasing Breslow thickness (HR1.09, p:0.048) and the presence of ulceration (HR2.15, p:<0.001) was associated with recurrence in this group. Mitosis and Clark level were not included in both multivariate analyses because of multicollinearity with Breslow thickness (Table 2). In SLNB negative patients with a nodular melanoma the recurrence rate was 38 of (29.7%) 128; if ulceration was also present in the primary melanoma, the recurrence rate was increased to 43.1 %. The site of recurrence was distant in 64% of these patients. Of all SLNB negative patients, 12.7% had nodular ulcerated melanoma. In the entire group of SLNB negative patients with nodular melanoma 25% eventually progressed to distant disease, 34.5% if ulceration was also present.

Table 3 shows the distribution of recurrence patterns for both SLNB negative and positive patients. The most common site of first recurrence was distant in all SLNB categories. In SLNB negative patients this was 58.5% of all first recurrence sites. Of all the 181 patients with a recurrence, 77% developed overall distant disease at some point

in the course of their disease. If patients progressed to stage IV during the course of their disease, the largest portion of these distant recurrences was American Joint Committee on Cancer stage M1c (82.5%).

Table 2 Univariate and multivariate cox regression analysis of clinicopathological characteristics associated with overall recurrence in all patients and by SLNB status (n=668)

Characteristic	Recurrence overall	n= 205	Univariate SLNB - (n=82)	Multivariate SLNB -	Univariate SLNB + (n=99)	Multivariate SLNB+
	n/205	(%)	HR, p	HR, p (95% CI)	HR, p	HR, p (95% CI)
Sex, n (%)						
Male	126	61.5	2.34,<0.001	1.78, 0.025(1.08-2.94)	1.34, 0.156	1.10, 0.048(1.01-1.20)
Female	79	38.5				
Age [a], median (range)	58.66 (19.2-81.4)		1.03, 0.001	1.02,0.008(1.01-1.04)	1.02, 0.036	1.01, 0.127(0.99-1.03)
Site of primary, n (%)						
Lower extremity	71	34.6	1.00, 0.010	1.00,0.006	1.00, 0.100	1.00, 0.035
Head/Neck	34	16.6	2.20, 0.011	2.16,0.024(1.11-4.21)	1.48, 0.264	1.79, 0.144(0.82-3.92)
Trunk	84	41	1.47, 0.156	1.34,0.346(0.73-2.64)	0.93, 0.600	0.89, 0.687(0.53-1.52)
Upper extremity	16	7.8	0.56, 0.206	0.43,0.068(0.17-1.07)	0.39, 0.046	0.37, 0.045(0.14-0.98)
Histological typing, n (%)						
Superficial Spreading	106	51.7	1.00, 0.002	1.00,0.164	1.00, 0.840	
Nodular	74	36.1	2.50, <0.001	1.82, 0.028(1.07-3.09)	0.91, 0.669	
Acral lentiginous	11	5.4	3.45, 0.019	2.76, 0.080(0.89-8.59)	1.46, 0.418	
Other [b]	10	4.9	1.82, 0.257	1.02, 0.978(0.30-3.50)	1.31, 0.534	
Excision radical						
Yes	153	74.6	0.93, 0.786		0.49, 0.001	0.49, 0.005(0.30-0.81)
No	52	25.4				
Breslow thickness [c], median (range)	3.00 (1.05-20.00)		1.16, <0.001	1.06, 0.151 (0.98-1.16)	1.11, 0.007	1.09, 0.048(1.00-1.20)
Clark level, n (%)						
II	1	0.5	1.91, 0.524			
III	27	13.2	0.79, 0.443		0.60, 0.133	
IV	150	73.2	1.00, 0.042		1.00, 0.311	

V	23	11.2	2.39, 0.012		1.39, 0.333	
Ulceration, n (%)						
Yes	110	53.7	3.02, <0.001	2.11,0.002(1.31-3.39)	2.28, <0.001	2.15, <0.001(1.40-3.29)
No	92	44.9				
Mitosis, n (%)						
Yes	178	86.8	5.58, 0.088		2.32, 0.240	
No	4	2.0				
Regression						
Yes	22	10.7	0.99, 0.840		0.97, 0.206	
No	111	54.1				
Lymphangioinvasion						
Yes	18	8.8	1.14, 0.081	1.16,0.172(0.94-1.43)	0.92, 0.641	
No	184	89.8				
Immunosuppressant meds						
Yes	7	3.4	2.37, 0.143		1.12, 0.819	1.97, 0.193(0.71-5.43)
No	198	96.6				

Data are presented as n(%) or median (range)

SLNB sentinel lymph node biopsy, NA not applicable

** p <0.05. All variables with significance level of p<0.2 in the univariate cox regression analysis were entered in the multivariate cox regression analysis.*

[a] Age at diagnosis of primary melanoma.

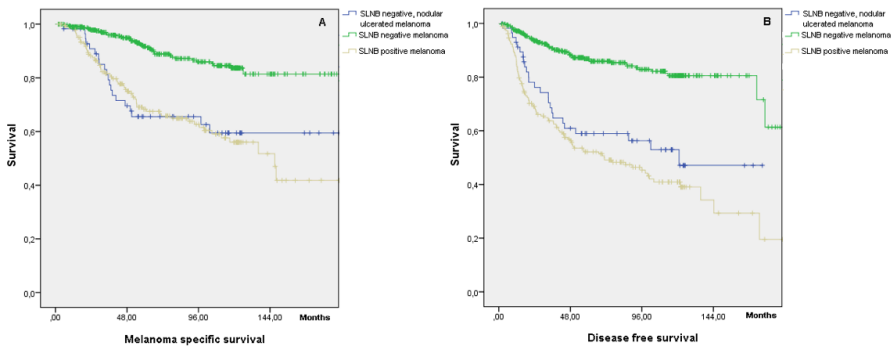
[b] Other histological typings are: verrucus, spitzoid, epitheloid, desmoplastic melanoma and lentigo maligna melanoma.

Table 3 Recurrence rates and site of first recurrence in SLNB negative patients and SLNB positive patients.

	Overall n(%)	SLNB negative n	SLNB positive n	p
Recurrence, n (%)				<0.001
Yes	205 (30.7)	82	99	
No	463 (69.3)	376	87	
Type 1st recurrence				0.053
Loco-regional	30 (14.7)	14	16	
In transit	43 (21.1)	18	25	
Basin of SLNB/CLND	30 (14.7)	0	9	
Lymphatic	3 (1.5)	1	2	
Distant	98 (48)	49	46	
M-stage distant recurrence				0.278
M1a	4 (4.1)	3	1	
M1b	12 (12.4)	4	8	
M1c	80 (82.5)	42	37	
Unknown	1			

SLNB sentinel lymph node biopsy, CLND completion lymph node dissection

Figure 1 Survival split by sentinel lymph node biopsy negativity or positivity with nodular subtype and ulceration



A: Melanoma specific survival, B: Disease free survival

MSS and DFS was significantly worse for SLNB positive patients compared to SLNB negative patients p<0.001. If a recurrence had occurred, survival did not differ between SLNB negative and SLNB positive patients. There was a significant difference between MSS and DFS in SLNB negative patients with ulcerated and nodular melanoma compared to the overall SLNB negative group p:<0.001 (Figure 1).

Multivariate cox regression analysis revealed melanoma located on the head and neck (HR4.88, p:0.003), trunk (HR:3.33, p:0.012) and upper extremity (HR:6.60, p:0.008) to be associated with distant first site of recurrence in SLNB negative melanoma patients as well as increasing Breslow thickness (HR1.15, p:0.013). The absence of mitosis (HR:0.06, p:0.035) is protective for distant first site of recurrence in SLNB negative patients (Table 4).

Table 4 Univariate and multivariate cox regression analysis of clinicopathological characteristics associated with distant first site of recurrence in SLNB negative patients.

Characteristic	1st recurrence= distant	n=48	Univariate	Multivariate
	n/48	(%)	HR, p	HR, p (95% CI)
Sex, n (%)				
Male	32	66.7	1.43, 0.243	
Female	16	33.3		
Age [a], median (range)	60.2 (19.4-79.6)		1.03, 0.009	1.02, 0.160 (0.99-1.04)
Site of primary, n (%)				
Lower extremity	11	22.9	1.00, 0.113	1.00, 0.011
Head/Neck	13	27.1	2.79, 0.015	4.88, 0.003(1.74-13.73)
Trunk	20	41.7	1.68, 0.169	3.33, 0.012 (1.31-8.48)
Upper extremity	4	8.3	1.68, 0.374	6.60, 0.008(1.63-26.74)
Histological typing, n (%)				
Superficial Spreading	19	39.6	1.00, 0.124	1.00, 0.103
Nodular	24	50	2.06, 0.022	1.91, 0.079(0.93-3.93)
Acral lentiginous	2	4.2	2.32, 0.266	2.05, 0.437(0.34-12.54)
Other [b]	3	6.3	1.18, 0.795	0.13, 0.107(0.01-1.56)
Breslow thickness [c], median (range)	3.00 (1.05-20.0)		1.12, 0.008	1.15, 0.013(1.03-1.29)

Clark level, n (%)				
II	0			
III	9	18.8	1.59, 0.650	
IV	29	60.4	1.00, 0.581	
V	7	14.6	0.77, 0.548	
Missing	3	6.2		
Ulceration, n (%)				
Yes	27	41.7	1.42, 0.231	
No	20	56.3		
Missing	1	2.1		
Mitosis, n (%)				
Yes	42	87.5		
No	1	2.1	0.03, 0.004	0.06, 0.035(0.01-0.82)
Missing	5	10.4		
Regression				
Yes	21	43.8	0.99, 0.777	
No	7	14.6		
Missing	20	41.7		
Lymphangioinvasion				
Yes	4	8.3	1.03, 0.766	1.04, 0.880 (0.63-1.71)
No	43	89.6		
Immunosuppressant meds				
Yes	1	2.1		
No	47	97.9	0.82, 0.843	

Data are presented as n(%) or median (range)

SLNB sentinel lymph node biopsy

** p <0.05. All variables with significance level of p<0.2 in the univariate cox regression analysis were entered in the multivariate cox regression analysis.*

a Age at diagnosis of primary melanoma.

b Other histological typings are: verrucus, spitzoid, epitheloid, desmoplastic melanoma and lentigo maligna melanoma.

Discussion:

The current study reveals that in SLNB negative patients, recurrence rates approach the recurrence rates of SLNB positive patients (43.1% VS 53.2%) if the unfavorable variables nodular histologic subtype and ulceration are accounted for. These pathological characteristics are present in 12.7% of SLNB negative melanoma patients. As displayed by the Kaplan-Meier curves in Figure 1, DFS and MSS is significantly worse for SLNB negative nodular and ulcerated melanoma patients, compared to the overall SLNB negative group.

Risk factors for recurrent disease in SLNB negative patients were increasing age, male sex, melanoma located on the head and neck region, nodular melanoma and the presence of ulceration (Table 2). Except for nodular melanoma, the significance of these variables in predicting recurrent disease in SLNB negative melanoma patients was previously illustrated by several authors.[17, 19, 20] O'Connell et al. recently stated that nodular histologic subtype approached significance in predicting recurrence in SLNB negative melanoma patients.[17] Obviously a negative SLNB might create the impression of a less aggressive melanoma; however, one cannot be so sure when it concerns a nodular subtype. Because the recurrence percentage of SLNB negative patients with ulcerated nodular melanoma approaches the recurrence percentage of SLNB positive melanoma patients, primary tumor characteristics are apparently more relevant for recurrence in these patients than the status of the sentinel node. In absence of a lymphogenous recurrence and/or positive SLNB, risk factors for distant first site of recurrence were melanoma located on the head and neck, increasing Breslow thickness and the presence of ulceration. In SLNB negative patients distant first site of recurrence occurred in 58.8% of all recurrences. In this subset of patients the melanoma seems to skip the lymphogenic metastatic route and metastasizes directly hematogenously. Overall, it is expected that unfavorable tumor clinicopathological characteristics should be more frequent in the SLNB positive group.[6, 12, 13, 21] Previous publications on SLNB negative patients revealed increasing Breslow thickness, ulceration, head and neck melanoma and unexpected lymph drainage patterns to be predictors for distant recurrence.[14-16,

19, 20] Unexpected or aberrant lymph drainage patterns are expected in head and neck melanomas more than melanomas located on the upper and lower extremity. An affinity for hematogenous spread is suggested in this subset of melanomas.[22, 23] This might be an explanation for our findings.

The recurrence percentages were increased by more than twofold in the group of SLNB negative patients with a nodular ulcerated melanoma compared to the whole group, suggesting a higher likeliness of hematogenous spread in these patients. Morton et al. posed two dissemination theories, the incubator hypothesis and the marker hypothesis. According to the first hypothesis, melanoma metastasizes to lymph nodes mostly and in approximately 10%, directly via the hematogenous route. Tumor cells may grow in the SLNB but might incubate before spreading tot distant sites. Removal of the SLNB and adherent lymph nodes can prevent further spread. The marker hypothesis however, implicates a simultaneous spread. Tumor load in the SLNB merely is a marker for the ability of the tumor to spread. According to both hypotheses, absence of melanoma cells in the SLNB indicates a primary melanoma unlikely to disseminate to distant sites.[24] Perhaps the 10% direct distant spread posed in the incubator hypothesis is caused by melanomas with unfavorable prognostics such as nodular subtype and ulceration. This hematogenous dissemination route was also described by Gerschenwald et al., who suggested a subset of patients with a pure hematogenous dissemination route, without nodal involvement.[16] Nodular melanoma is usually detected at a higher Breslow thickness than superficial spreading melanoma, even though the duration of change in a lesion before treatment is shorter in nodular melanoma than the superficial spreading type, which is suggestive for aggressive biologic behavior.[25] Lin et al published results where a significantly lower amount of tumor infiltrating lymphocytes (TIL) were found in nodular melanoma compared to superficial spreading melanoma, suggesting a different immunogenicity between the different histological subtypes. [26] Unfortunately, we do not routinely look for tumor-infiltrating-lymphocytes in our institution, so we were not able to cross-reference this to our data.

The presented data on increased recurrence rates in patients with ulcerated nodular melanoma, increasing Breslow thickness melanoma and head and neck localization is crucial for clinicians involved in melanoma care, as these findings can not only alter decisions on the duration and frequency of follow-up but also increase the awareness of the likelihood of distant recurrence in these patients. Therefore we propose to distinguish a high risk for recurrence in the SLNB negative subgroup.

SLNB positive patients have a worse DFS in comparison to SLNB negative patients. However, when a recurrence occurs, survival is similar. Survival was shorter in patients with a distant first site of recurrence compared to other recurrent sites, which has been extensively described in the literature.[15, 27]

Patients with unfavorable primary clinicopathological characteristics such as positive SLNB, are already considered for adjuvant targeted- or immunotherapy trials. It might also be worth considering high risk SLNB negative patients for inclusion. First, however, adjuvant studies have yet to show a beneficial effect in SLNB positive patients with respect to MSS. Before expanding inclusion criteria, the risk-benefit ratio should be properly assessed.

Although many researchers have focused on recurrence patterns of melanoma, we are still unable to accurately predict the course of the disease in many patients. We believe that most of the biological behavior in the end can be explained by possible unrevealed genetic mutations with distinctive biological behavior. Today, melanoma is characterized and staged by clinicopathologic features. There might be a role for genetic profiling aiming to identify the melanoma patients with a misleadingly favorable SLNB pathologic prognosis whose disease is likely to recur in the future.

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