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To cite this version:

M. de Vries, M.J. Speijers, E. Bastiaannet, J.Th.M. Plukker, A.H. Brouwers, et al.. Long-term follow-up reveals that ulceration and sentinel lymph node status are the strongest predictors for survival in patients with primary cutaneous melanoma. EJSO - European Journal of Surgical Oncology, 2011, 37 (8), pp.681. 10.1016/j.ejso.2011.05.003 . hal-00715500

HAL Id: hal-00715500

https://hal.science/hal-00715500v1

Submitted on 8 Jul 2012

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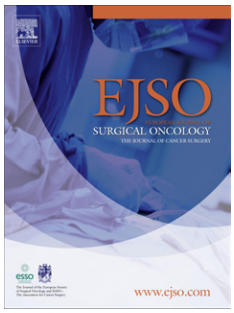

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PII: S0748-7983(11)00287-3

DOI: 10.1016/j.ejso.2011.05.003

Reference: YEJSO 3162

To appear in: *European Journal of Surgical Oncology*

Accepted Date: 5 May 2011

Please cite this article as: de Vries M, Speijers MJ, Bastiaannet E, Plukker T, Brouwers AH, van Ginkel RJ, Suurmeijer AJH, Hoekstra HJ. Long-term follow-up reveals that ulceration and sentinel lymph node status are the strongest predictors for survival in patients with primary cutaneous melanoma, European Journal of Surgical Oncology (2011), doi: 10.1016/j.ejso.2011.05.003

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LONG-TERM FOLLOW-UP REVEALS THAT ULCERATION AND SENTINEL LYMPH NODE STATUS ARE THE STRONGEST PREDICTORS FOR SURVIVAL IN PATIENTS WITH PRIMARY CUTANEOUS MELANOMA

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Presented at SSO 2010 – 63rd Annual Cancer Symposium of the Society of Surgical Oncology, March 3-7, St. Louis, Missouri, United States of America.

Synopsis

Long-term follow-up data show that tumor-positive SLN melanoma patients have a worse DFS, DSS and OS than tumor-negative SLN patients after 10 years. Ulceration and SLN status are the strongest prognostic factors for long-term DFS and DSS.

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ABSTRACT

Purpose: To assess the long-term outcome after sentinel lymph node biopsy (SLNB) in melanoma patients.

Methods: Between 1995-2009 450 melanoma patients underwent SLNB in a single center. Survival and prognostic factors were analyzed for 429 patients.

Results: Median age was 53 (range 11-84) years. Median Breslow thickness was 2.4 (range 1-20) mm and 36% were ulcerated melanomas. Median follow-up time was 64.8 (range 2-174) months. A tumor-positive SLN was present in 140 patients (31%). Completion lymph node dissection (CLND) was performed in 119 patients and these patients were analyzed for recurrence and survival.

124 Patients (29%) relapsed during follow-up; 55 in the node-positive group who underwent CLND (55/119;46%) and 69 in the node-negative group (69/310;22%;p<0.001). In the node-negative group 17 patients developed recurrence in the regional node field; false-negative rate 11%.

On multivariate analysis strongest prognostic factors for disease free survival (DFS) were primary melanoma ulceration and SLN positivity (Hazard Ratio (HR) of 2.2 and 2.3; p<0.001). For disease specific survival (DSS) the same was found to be true with a HR of 2.1 for ulceration and 2.0 for SLN positivity (p=0.001 and p=0.002 respectively). 10-Year DFS was 71% for node-negative patients compared with 48% for node-positive patients (p<0.001). 10-Year DSS was 77% for node-negative patients compared to 60% for node-positive patients (p<0.001).

Conclusions: This study shows a remarkably high percentage of tumor-positive SLN. The long-term follow-up data confirm that tumor-positive SLN patients have a worse DFS and DSS than tumor-negative SLN patients. Ulceration and SLN status proved to be the strongest prognostic factors for long-term DFS and DSS.

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INTRODUCTION

With sentinel lymph node (SLN) status being a prognostic factor, the sentinel lymph node biopsy (SLNB) has a definitive role in staging melanoma patients presenting with clinically uninvolved regional lymph nodes. As such, SLNB is nowadays implemented in the new American Joint Committee on Cancer (AJCC) staging system.[1] Recent data from the fourth interim analysis of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I) showed significantly higher disease specific survival rates for intermediate thickness melanomas after immediate completion lymph node dissection (CLND) for occult nodal metastases confirmed by SLNB compared to nodal observation and therapeutic lymph node dissection in case of nodal recurrence. Moreover, disease free survival rates are higher in patients who underwent SLNB compared to patients with wide local excision (WLE) and nodal observation alone.[2]

Published data with respect to the long term results of the SLNB in melanoma patients in a single center, surpassing a median follow-up of 5 years, are rare.

In 1995 the SLNB procedure has been introduced at the University Medical Center Groningen.[3] The aim of the study was to gain insight in the long-term results of the SLNB staging procedure regarding detection, complication rates, patient survival rates and prognostic factors using the 7th American Joint Committee on Cancer melanoma staging manual.

PATIENTS AND METHODS

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In the period may 1995-december 2009 a total of 450 patients, 231 female (51%) and 219 male patients (49%), median age 53.2 (mean 52.5, range 11-84) years, presenting with stage I/II cutaneous melanoma (≥ 1.0 mm) were treated by WLE and SLNB as a staging procedure at the University Medical Center Groningen. The study protocol was approved by the hospital's Institutional Review Board.

SLNB technique

All patients were admitted to the hospital to undergo a SLNB, wide local excision and, if indicated, a CLND. The SLNB procedure at our institution has been described in detail previously.[3] Excision specimens were sent for routine histopathological analysis with haematoxylin-eosin (HE) staining. Specific immunohistochemical staining was performed on HE-negative specimens for the protein S100, the melanoma-associated monoclonal antibody HMB45 and antibodies targeted to the MART -1/Melan-A antigen on melanoma cells. If histopathological examination of the sentinel lymph node revealed metastatic melanoma tissue, then all those patients were advised to undergo a CLND of the involved regional lymph node basin. Axillary lymph node dissection comprised Level I-III axillary dissection with preservation of the pectoralis minor muscle. In the case of a tumor-positive SLN in the groin, superficial and deep groin lymph node dissections were performed, in which the femoroinguinal lymph nodes and the lymph nodes along the iliac artery and vein were excised, together with the obturator lymph nodes. After superficial lymphadenectomy, the sartorius muscle was freed from its attachment to the anterior superior iliac spine, moved in a medial direction, and fixed to the ligament of Poupart. Since 2002, patients with HE-negative and immunohistochemical-positive sentinel lymph nodes underwent superficial lymphadenectomy alone. If additional positive lymph nodes were found in the resection specimen, deep groin dissection (iliac and obturator nodal dissection) was performed. Neck dissections comprised cervical or posterior lymph node dissection

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with the standard surgical procedure. Since 2005 the UMCG participates in the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), which randomizes patients between CLND or nodal observation by ultrasonography of the involved nodal basin in case of a tumor-positive SLN.[4]

Statistical analysis

Disease Free Survival (DFS), Overall Survival (OS) and Disease Specific Survival (DSS) were calculated using any recurrence (DFS), death due to any cause (OS) and death due to melanoma (DSS) as events. Follow-up time was defined as the time interval between excision of the primary melanoma and either recurrence or death or last day of clinical follow-up. Univariate and multivariable Cox Proportional Hazard Analyses were used to assess factors associated with survival. Any variable with $p<0.05$ in the univariate analyses was entered in the multivariable model. Proportional hazard assumption was tested, as well as tests for interaction. Kaplan Meier (KM) curves were constructed according to SN status for each survival analysis. Besides, follow-up was truncated at 1, 3, 5, 7 and 10 years to assess Hazard Ratio's (HR) for SLN status for each of those years, adjusted for age, sex, ulceration, Breslow thickness, Clark level and localization of the primary melanoma. P-values <0.05 were considered statistically significant.

RESULTS

Clinical and pathological features

The clinical and pathological characteristics are summarized in Table 1. Notably, in the tumor-positive sentinel lymph node group the primary melanomas were significantly thicker. There was a trend

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towards male predominance in this group (p=0.07). The median follow-up duration for all patients in this study was 64.8 (range 2.4-173.8) months with a mean of 75.3 months.

SLN identification

At least one sentinel lymph node could be located in 447 out of the 450 patients (99.3%) and a total number of 1008 nodes were harvested in the whole group (mean 2.24, median 2.00, range 0-7). These nodes were identified in 536 basins, mean 1.20 per patient. The sentinel lymph nodes were identified by both blue dye and probe in 425 basins, in 107 basins by probe alone and in 4 basins by dye alone.

SLNB mortality and morbidity

None of the patients undergoing WLE and SLNB died as a result of the procedure. Post-operative complications occurred in 31 patients (6.9%). Most complications were minor, e.g. wound infections, post-operative bleedings and seromas. Two anaphylactic reactions to blue-dye were reported (0.4%).

SLN status

A tumor-positive SLN was found in 140 patients (31.1%). In 100 cases (71.4%) the HE-stained slides accounted for de diagnosis and the remainder of tumor-positive SLN was provided by IHC in 34 cases and by RT-PCR in 6 patients. In 85% of SLN positive patients (n=119) CLND was performed and additional positive non-sentinel lymph nodes were found in 22.7% of cases (n=27).

The remaining 21 SLN tumor-positive patients had no CLND; eleven patients were randomized for observation in the MSLT-II, eight patients refused surgery (five patients refused because of very small

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tumor load in the SLN; RT-PCR positivity or isolated tumor cells) and in two patients an interval node was tumor-positive, making CLND technically impossible.

These 21 patients were excluded from the analysis of recurrences and prognostic factors for survival. DFS, OS and DSS were therefore calculated on 429 patients as well as the univariate and multivariable Cox Proportional Hazard Analyses, KM curves and HR for SLN status. However, the false-negative rate was calculated over the whole group (450 patients).

Recurrences

Recurrent disease occurred in 124 patients (28.9%) during a median follow-up of 68.4 (range 2.4-173.8) months; 55 patients in the SLN positive group (55/119; 46.2%) and in 69 patients in the SLN negative group (69/310; 22.3%; p<0.001). The distribution of first recurrences in this patient cohort is shown in Table 1. In the SLN positive group (n=119) there were initially 10 local recurrences, 18 in-transit metastases and 7 regional lymph node recurrences. Sixteen of these 35 patients (45.7%) progressed to distant metastases. Another 20 patients presented with distant metastases as first recurrence.

In the SLN negative group 17 patients developed recurrence in the regional node field, resulting in a false-negative rate of 11% (17/(17+140)). Nine patients presented with local recurrent disease and 9 patients developed in-transit metastases as first type of recurrence. Twenty of these 35 patients (57.1%) progressed, in the course of the disease, to distant metastases. Another 34 patients had distant metastases as first recurrence.

Six patients (28.6%) recurred from the 21 SLN tumor-positive patients who did not undergo CLND. The sites of first recurrences of these patients were as follows: one patient with in-transit metastases, three patients with nodal relapses, and two patients with distant metastases.

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Survival

SLN tumor status was significantly associated with all aspects of survival (Table 2). The median follow-up time of DFS was 4.9 (0.2-14.5) years. DFS at 10 years was 71% for SLN negative patients compared with 48% for SLN positive patients (p<0.001). The median follow-up time of OS and DSS was 5.7 (0.2-14.5) years. DSS at 10 years was 77% for SLN negative patients compared with 60% for SLN positive patients (p<0.001), for OS the 10-year survival percentages are 70% and 55% respectively (p=0.003). Median follow-up time for deceased patients was 40.5 months (5.5-147.3) and for the survivors 93.4 months (2.4-173.8). Survival curves are shown in Figure 1.

Prognostic factors

Prognostic factors were calculated for DFS, DSS and OS and are shown in Table 2. On multivariate analysis the strongest prognostic factors for DFS were presence of ulceration of the primary cutaneous melanoma and SLN positivity (HR of 2.2 and 2.3, p<0.001 respectively). The same results were observed for DSS, with a HR associated with presence of ulceration of 2.1 (p=0.001) and a HR associated with SLN positivity of 2.0 (p=0.002). For OS the strongest independent prognostic factor was age above 50 years (HR 2.2, p<0.001), followed by presence of ulceration (HR 1.9, p=0.001) and SLN positivity (HR 1.7, p=0.009). Breslow tumor thickness groups (1-2mm; 2-4 mm and >4mm) could only be identified as an independent prognostic factor for DFS in this cohort. There was a trend towards significance for OS. Table 3 shows that over time the HR for events remains high for SLN positive patients.

DISCUSSION

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Prognostic factors and survival

This long term follow-up study of prognostic factors in cutaneous melanomas reveals that a tumor-positive SLN is a strong prognostic factor for DFS, OS and DSS even after 10 year follow-up. Regional lymph node status has been recognized as one of the most powerful indicators of patient outcome. On multivariate analysis we observed that ulceration, lymph node status, and age were predictive of DFS, OS and DSS. Ulceration and SLN status were the strongest predictive factors in this study. This finding is comparable with a recently report from Mays et al[5]. We found that patients with increased age have a worse prognosis than younger patients. Recently published data by Rutkowski et al. also show that melanoma patients $\geq$ 65 years of age are characterized by a higher primary tumor stage and worse prognosis in the presence of regional lymph node metastases than younger patients.[6] Tumor mitotic rate of cutaneous melanoma was not included in the analyses because of a lack of data in referral cases.

SLN identification and false-negative rate

In the present study we found a sentinel lymph node detection rate of 99.3%. This is comparable with other studies which reported success rates between 95.3% and 100%.[7-9] Failure to detect the SLN occurred in the early years of practice and in only three patients with all head and neck melanomas.[10]

The false-negative rate for SLNB is defined as the proportion of node-positive patients who had a tumor-negative SLN. However, the number of patients who have a tumor-negative sentinel node result, who subsequently develop clinically positive nodes in the dissected regional lymph node basin, are in fact reported in the literature. These rates vary between 5-9%. The false-negative rate is

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actually higher using a more proper definition: {patients with negative SLN with recurrent nodal disease}/{patients with negative SLN with recurrent nodal disease + patients with tumor-positive SLN}.[11] Amongst other investigators, we have found comparable results in earlier studies: in line with other studies using this definition and an earlier report from our hospital the false-negative rate in the current study is 11%.[3,12] Remarkably, however, the false-negative rate recently dropped to 2% in our center. Recently data from the Sunbelt Melanoma Trial by Scoggins et al. show no OS difference between patients with a false-negative SLN and patients with a true-positive SLN result.[12] However, the authors discuss that their finding is also somewhat at odds with the MSLT, which showed that the survival of patients who developed clinically detected nodal metastases in de wide local excision-only group was worse than those who had nodal metastases detected by the SLNB.

Tumor metastases in the SLN

This single center study shows a remarkably high percentage (31%) of SLN positive patients. In comparison with the earlier report based on our database, this percentage has risen from 24% to 31%. One explanation for this higher rate of tumor-positive SLNs might be the increased experience with and the improved knowledgement of the SLNB procedure for both the surgical oncologist and the pathologist. Median Breslow thickness has decreased from 2.5 to 2.4. The presence of ulceration has also fallen from 40% to 36%. Median age has dropped from 57 to 53 years. This last factor may be another possible explanation for the increase in tumor-positive SLNs because the older patients have altered lymphatic function.[13] This 'lymphatic dysfunction' may modify metastatic patterns and can possibly play a role in the reduced nodal positivity rate in the elderly.

Compared to other studies, the high Breslow thickness and ulceration rate in our study group are explanatory factors for the high percentage of tumor-positive SLNs. These two variables are significantly associated with the likelihood of detecting metastases in the SLN: the higher the Breslow

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thickness and ulceration rate the more tumor-positive SLNs are found.[14] Several studies even show that the percentage of tumor-positive SLN may reach 35-47% in patients with T4 tumors (Breslow > 4.0 mm).[15-17]

However, as reported by Mocellin, these variables (Breslow thickness and ulceration rate) do not address the issue of whether or not this association is of any clinical relevance or practical value (i.e., whether this statistical association translates into a combination of negative predictive value, error rate, and sentinel node reduction rate of clinical relevance). As mentioned earlier, the final results of the MSLT-I play an important role in these predictive models: the intermediate thickness (1.2-3.5 mm) SLNB group had a better survival.

In this study group 21 patients did not undergo CLND despite of a tumor-positive SLN. Hopefully, the MSLT-II will finally answer the question whether observation after tumor-positive SLN has the same DFS and DSS rates as tumor-positive SLN followed by CLND. Meanwhile, the Rotterdam criteria (<0.1mm, 0.1-1.0mm and >1.0mm for the largest diameter of the largest metastasis in the SLN) showed that a CLND might not be indicated when the tumor load in the SLN is < 0.1 mm.[18] These data need to be supported by other, larger studies which are currently underway.

SLNB morbidity

The complication rate of SLNB (6.9%) in our institution is comparable with the literature. Although much research on SLNB in melanoma has been published, little focus has been on complication rates. The well known large studies have been reporting percentages of 4.6% (by the Sunbelt Melanoma trial) and 10.1% (by the Multicenter Selective Lymphadenectomy Trial I).[8,19] Major complications did not occur, except for anaphylactic reaction to blue dye in two patients (0.4%). A recent study observed a comparable incidence of patent blue reactions of 0.5% in SLNBs in patients with breast cancer.[20] In the past years we have performed studies on morbidity after axillary and inguinal SLNB

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with or without CLND. There were more wound infections in the SLNB group followed by CLND and it was therefore recommended using prophylactic antibiotic treatment in the case of CLND after tumor-positive SLN.[21,22] Although there is a slight risk of limb edema, the lymphedema after CLND is less than therapeutic lymph node dissection for palpable nodal disease according to data from the MSLT Cooperative Group.[23] Hospital length of stay was also significant longer in the delayed CLND compared to the early CLND. So early CLND, in addition to a tumor-positive SLN, is not only of prognostic value and beneficial in staging regional nodes, selecting patients for adjuvant therapy or clinical trials and above all, improving melanoma-specific survival, it also decreases both lymphedema and hospital length of stay. At our center we have studied quality of life (QoL) in melanoma survivors who underwent SLNB. It was found that QoL after axillary or inguinal SLNB with or without CLND was better than that in a norm group of the general population. Patients who underwent CLND in the axilla after SLNB reported most QoL-related problems.[24]

In conclusion, the SLNB, which is now incorporated in the latest AJCC Melanoma staging manual (7th edition), is a safe procedure with a low short- and long-term morbidity with an acceptable low false-negative rate. Long-term follow up after 10 years show that tumor-positive SLN patients have a worse DFS, DSS and OS than tumor-negative SLN patients. Ulceration and SLN status are the strongest prognostic factors for long-term DFS and DSS. SLNB will provide patients with information regarding their disease status. Early CLND might improve DSS and reduce treatment related morbidity compared to delayed CLND according to recently published MSLT-I data.[2,23] Participation of patients with primary melanoma and tumor-positive SLNs in the MSLT-II (which randomizes SLN positive patients to undergo CLND or not) and the European Organisation for Research and Treatment of Cancer melanoma group registration trial (MINITUB, which aims for patients with identified minimal SLN tumor burden to not undergo CLND) is essential to make any further progress in the treatment of primary melanomas.[4,25]

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Acknowledgements

The authors thank Mrs. C. Lemstra, nuclear medicine technician from the Department of Nuclear Medicine and Molecular Imaging, and the melanoma nurse practitioners Mrs. A. Prozee and Mr. K.M. Meijer from the Department of Surgical Oncology for their dedicated care for the melanoma patients at the UMCG.

The authors declare no conflicts of interest.

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Figure 1: Kaplan-Meier survival estimates for Disease Free Survival (p<0.001), Overall Survival (p=0.003) and Disease Specific Survival (p<0.001) according to sentinel lymph node (SLN) status (N=429).

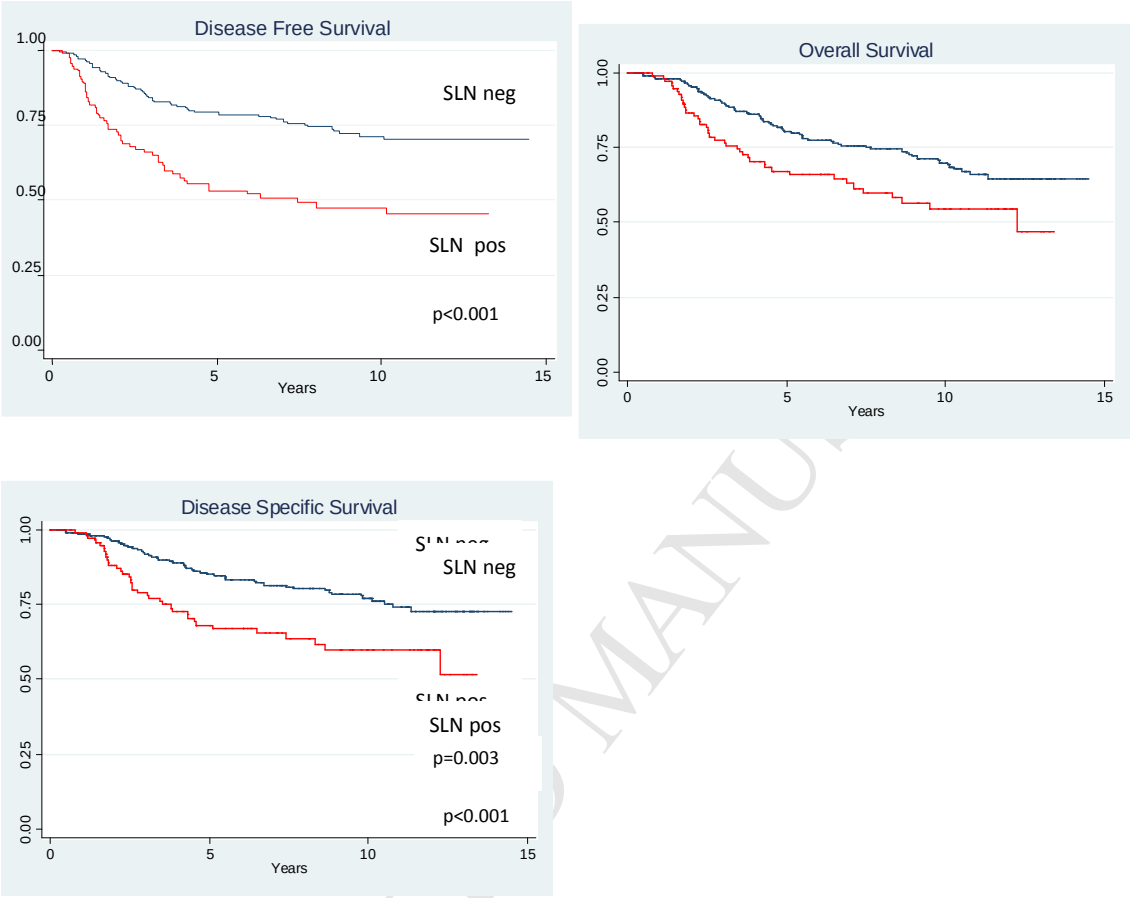

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Table 1: Clinical and pathological features and distribution of first recurrences (N=429). Percentages in brackets.

Characteristics		All patients N = 429	SLN positive N=119	SLN negative N = 310	p-values
Sex	Male	208 (48.5)	66 (55.5)	142 (45.8)	0.07
	Female	221 (51.5)	53 (44.5)	168 (54.2)	
Age	Mean/median	52.6/53.8	53.1/52.4	52.4/54.4	0.67
	<50 years	182 (42.4)	51 (42.9)	130 (41.9)	
	≥50 years	247 (57.6)	68 (57.1)	180 (59.1)	
Breslow (mm)	Mean/median	3.0/2.4	3.4/3.0	2.9/2.2	0.03
	1.00-2.00	167 (38.9)	25 (21.0)	142 (45.8)	
	2.01-4.00	187 (43.6)	69 (58.0)	118 (38.1)	
	>4.00	75 (17.5)	25 (21.0)	50 (16.1)	
Clark level	II+III	81 (18.9)	18 (15.1)	64 (20.6)	0.37
	IV+V	342 (79.7)	99 (83.2)	242 (78.1)	
	Unknown	6 (1.4)	2 (1.7)	4 (1.3)	
Ulceration	Present	155 (36.1)	49 (41.2)	106 (34.2)	0.13
	Absent	274 (63.9)	70 (58.8)	204 (65.8)	
Histologic subtype	SSM	239 (55.7)	65 (54.6)	174 (56.1)	0.13
	NM	145 (33.8)	39 (32.8)	106 (34.2)	
	ALM	12 (2.8)	4 (3.4)	8 (2.6)	
	Others	28 (6.5)	9 (7.6)	19 (6.1)	
	Unknown	5 (1.2)	2 (1.7)	3 (1.0)	
Localization	Axial	209 (48.7)	62 (52.1)	147 (47.4)	0.39
	Extremities	220 (51.3)	57 (47.9)	163 (52.6)	
SLN status	Positive	119 (27.7)	NA	NA	NA
	Negative	310 (72.3)			
Type of first recurrence	Local recurrence	19 (15.3)	10 (18.2)	9 (13.0)	
	In-transit metastases	27 (21.8)	18 (32.7)	9 (13.0)	
	Regional lymph node	24 (19.4)	7 (12.7)	17 (24.6)	
	Distant	54 (43.5)	20 (36.4)	34 (49.3)	
	Total	124 (100)	55 (100)	69 (100)	<0.001

SLN = Sentinel Lymph Node

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Table 2: Disease Free Survival, Overall Survival and Disease Specific Survival analysis for the 429 patients at 5 and 10 years. Hazard Ratios (HR) are shown and 95%-Confidence Interval in brackets.

	Disease Free Survival						Overall Survival						Disease Specific Survival					
	Univariate				Multivariable		Univariate				Multivariable		Univariate				Multivariable	
	5yr	10yr	HR (95%CI)	p	HR (95%CI)	p	5yr	10yr	HR (95%CI)	p	HR (95%CI)	p	5yr	10yr	HR (95%CI)	p	HR (95%CI)	p
Age																		
<50 yrs	76.3	70.5	1	***0.04***	1	***0.03***	82.8	78.8	1	***<0.001***	1	***<0.001***	83.9	79.8	1	***0.02***	1	***0.007***
≥50 yrs	68.7	59.9	1.5 (1.0-2.1)		1.5 (1.0-2.2)		72.0	56.3	2.2 (1.5-3.3)		2.2 (1.5-3.4)		77.8	66.4	1.7 (1.1-2.6)		1.9 (1.1-2.9)	
Sex																		
Female	78.7	71.0	1	***0.003***	1	0.1	84.2	74.1	1	***<0.001***	1	***0.03***	86.5	77.8	1	***0.004***	1	***0.07***
Male	64.0	57.1	1.7 (1.2-2.5)		1.4 (0.9-2.0)		67.3	56.0	2.0 (1.4-2.9)		1.6 (1.0-2.4)		72.9	65.6	1.8 (1.2-2.8)		1.5 (1.0-2.3)	
Ulceration																		
No	81.2	74.4	1	***<0.001***	1	***<0.001***	85.5	73.8	1	***<0.001***	1	***0.001***	88.8	80.9	1	***<0.001***	1	***0.001***
Yes	55.9	48.2	2.5 (1.7-3.6)		2.2 (1.5-3.2)		63.5	53.5	2.1 (1.4-3.0)		1.9 (1.3-2.8)		66.4	58.8	2.3 (1.5-3.5)		2.1 (1.4-3.2)	
Breslow																		
1.00-2.00	87.0	76.9	1	***0.001***	1	***0.03***	85.2	76.3	1	***0.001***	1	0.06	89.7	82.4	1	***0.003***	1	0.1
2.01-4.00	66.1	58.9	2.2 (1.4-3.4)		1.6 (1.0-2.5)		76.4	62.2	1.5 (1.0-2.4)		1.2 (0.7-1.8)		77.5	68.1	1.9 (1.2-3.2)		1.3 (0.8-2.4)	
>4.00	54.7	52.4	2.9 (1.8-4.9)		2.0 (1.2-3.4)		59.5	51.5	2.5 (1.5-4.0)		1.8 (1.1-2.9)		68.0	60.9	2.6 (1.5-4.7)		1.9 (1.0-3.4)	
Clark level																		
II+III	81.2	75.5	1	0.2			83.4	71.9	1	0.2			84.5	78.5	1	0.2		
IV+V	69.9	61.9	1.6 (1.0-2.7)				74.8	63.9	1.6 (1.0-2.7)				79.4	70.4	1.6 (0.9-3.0)			
Unknown	60.0	60.0	1.5 (0.3-6.5)				80.0	80.0	0.8 (0.1-5.8)				80.0	80.0	1.0 (0.1-7.7)			
Localization																		
Extremities	75.9	67.1	1	0.2			82.3	71.6	1	***0.02***	1	0.2	85.0	74.5	1	0.1		
Axial	67.4	61.9	1.3 (0.9-1.7)				69.8	58.9	1.7 (1.1-2.5)		1.3 (0.8-2.0)		74.9	70.2	1.4 (0.9-2.0)			
SLN*																		
Negative	79.4	71.3	1	***<0.001***	1	***<0.001***	80.3	70.1	1	***0.003***	1	***0.009***	85.2	77.0	1	***<0.001***	1	***0.002***
Positive	53.2	47.6	2.5 (1.8-3.6)		2.3 (1.6-3.3)		67.1	54.5	1.8 (1.2-2.6)		1.7 (1.1-2.5)		68.1	59.9	2.1 (1.4-3.2)		2.0 (1.3-3.1)	

***SLN = Sentinel Lymph Node**

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Table 3: Development of Hazard Ratio (HR) for time after diagnosis according to positive SLN status (adjusted for age, sex, Breslow, Clark, localization and ulceration). 95%-Confidence Interval in brackets (N=429).

	1 Year	3 Year	5 Year	7 Year	10 Year
DFS	4.1 (1.8-9.1) P=0.001	2.2 (1.4-3.4) P=0.001	2.4 (1.6-3.6) p<0.001	2.4 (1.6-3.5) p<0.001	2.3 (1.6-3.3) p<0.001
OS	No estimation* p=0.4	2.2 (1.2-3.9) p=0.008	1.8 (1.1-2.9) p=0.01	1.7 (1.1-2.6) p=0.02	1.8 (1.2-2.6) P=0.005
DSS	No estimation* p=0.6	2.5 (1.3-4.6) p=0.004	2.2 (1.4-3.6) P=0.002	2.1 (1.3-3.3) p=0.003	2.1 (1.3-3.3) P=0.001

*no estimation of the HR due to less than 5 events

DFS = Disease Free Survival

OS = Overall Survival

DSS = Disease Specific Survival

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