Effects of Time Interval between Primary Melanoma Excision and Sentinel Node Biopsy on Positivity Rate and Survival

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Abstract

Background Sentinel node biopsy is essential for adequate melanoma staging. Most melanoma guidelines advocate to perform wide local excision and sentinel node biopsy as soon as possible, causing time pressure. Objective: To investigate the role of time interval between melanoma diagnosis and sentinel node biopsy on sentinel node positivity and survival.

Methods This is a retrospective observational study concerning a cohort of melanoma patients from four European Organization for Research and Treatment of Cancer Melanoma Group tertiary referral centers from 1997-2013. 4,124 melanoma patients underwent sentinel node biopsy. Patients were selected if date of diagnosis and follow-up information were available, and sentinel node biopsy was performed in <180 days. A total of 3,546 patients were included. Multivariable logistic regression and cox regression analyses were performed to investigate how baseline characteristics and time interval until sentinel node biopsy are related to positivity rate, disease free survival and melanoma specific survival.

Findings Median time interval was 43 days (interquartile range (IQR) 29–60 days), 705 (19·9%) of 3,546 patients had a positive sentinel node. Sentinel node positivity was equal for early surgery (≤43 days) vs. late surgery (>43 days): 19·7% vs. 20·1% (p=0·771). Median follow-up was 50 months (IQR 24–84 months). Sentinel node metastasis (hazard ratio (HR) 3·17, 95% CI 2·53–3·97), ulceration (HR 1·99, 95% CI 1·58–2·51), Breslow thickness (HR 1·06, 95% CI 1·04–1·08), and male gender (HR 1·58, 95% CI 1·26–1·98) (all p<0·00001) were independently associated with worse MSS and DFS, time interval was not.

Interpretation No effect of time interval between melanoma diagnosis and sentinel node biopsy on five year survival or sentinel node positivity rate was found for a time interval of up to three months. This information can be used to counsel patients and remove strict time limits from melanoma guidelines.

Introduction

Worldwide, sentinel node biopsy (SNB) has become essential for adequate staging of melanoma patients. It is the current gold standard to detect early lymph node involvement, as recommended by the American Joint Committee on Cancer (AJCC), the American Society of Clinical Oncology (ASCO), the Society of Surgical Oncology (SSO) as well as the European Society of Medical Oncology (ESMO)[1-3].

Currently no uniform recommendation exists on the maximum allowable time interval between melanoma diagnosis (i.e. date of excisional biopsy), and wide local excision (WLE) combined with SNB. Most melanoma guidelines advise to perform WLE and SNB as soon as possible, within an acceptable time frame. The Dutch national melanoma guideline for instance advocates a strict maximum time interval of six weeks after primary melanoma diagnosis[4]. Promoting a relatively short time frame for performing WLE and SNB suggests a detrimental effect if not adhered to.

Advising a short time frame for WLE and SNB negatively affects the referral system, as it forms an incentive for general practitioners (GP's) and dermatologists to perform high urgency referrals. High urgent referral implies influence of time interval (i.e. a longer interval may be detrimental) and therefore wait time to surgery can increase patient anxiety.

However, most melanoma specialists will not be expecting a link between SNB time interval and prognosis for two main reasons: first of all, to date SNB has been a strong predictor of prognosis, but whether the procedure has a prognostic effect itself remains subject to debate[5], let alone, the interval to the procedure. Second, the time interval between diagnosis and SNB is likely to be very short as compared to the duration of melanoma development pre-diagnosis. Variation in SNB timing of a few weeks (30 to 60 days) will probably represent only a fraction in the whole melanoma development story, and thus is unlikely to be of any effect on melanoma course.

The aim of this study is to investigate if time interval until WLE and SNB is associated with sentinel node (SN) positivity rate, disease free survival (DFS) and melanoma specific survival (MSS) in a large European melanoma population.

Methods

Patients

For purposes of the current study a retrospective cohort was collected of melanoma patients undergoing SNB in one of four European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group centers. The study was approved and performed in accordance with local ethics committee guidelines and national legislation.

Between 1997 and 2013, 4,124 patients underwent SNB in one of four EORTC Melanoma Group centers. In total, 3,546 patients were selected with known date of primary melanoma diagnosis (i.e. diagnostic excisional biopsy) and SNB within 180 days, and available follow-up information. Collected data included: gender, age, diagnosis date, date of SNB, primary tumor characteristics; i.e. location, Breslow thickness, ulceration, histological subtype, outcome of SNB, details on completion lymph node dissection (CLND), and follow-up (FU).

Diagnosis

Diagnosis of the primary melanoma was based on histopathologic examination of an excisional biopsy in all cases. Excisional biopsy was performed with total thickness excision and a narrow circumferential margin, as described in the European Consensus-based Interdisciplinary Guideline, American Association of Dermatology Guidelines and the National Cancer Comprehensive Network Clinical Practice Guidelines[6-8]. Melanoma diagnosis was defined as the date of excisional biopsy.

Surgical Procedure and Pathology:

In all centers, eligibility for SNB was assessed according to international guideline criteria; i.e. Breslow thickness of >1·0mm or presence of risk factors ulceration, Clark level IV or V (AJCC staging 6th edition for patients operated up to 2009[9]), regression or mitosis >1/mm^2 (AJCC staging 7th edition for patients from 2009 up to 2013[1]). Generally, WLE (with a margin of 1-2 cm depending on the Breslow thickness) and SNB were performed in the same setting. SNB was performed according to the triple technique; i.e. pre-operative lymphoscintigraphy within 24 hours prior to the surgical procedure; perioperative intradermal injection of patent blue near the primary tumor site; and intraoperative use of a handheld gamma detection probe to locate the sentinel node(s) (SN)[10, 11]. A lymph node was defined as SN, if it was blue and / or hot (in situ: Geiger teller count of at least more than three times the background count, ex situ: Geiger teller count of at least ten times the background count) as described in detail elsewhere [12, 13]. Histopathological analysis of the SN was conducted according to the EORTC Melanoma Group Pathology Protocol[14].

Statistics

Time interval was defined as the time between the date of melanoma diagnosis and the date of WLE and SNB in days. FU was calculated from date of SNB to date of last FU or death. DFS was calculated from date of SNB to date of first recurrence (any site) or until death (unrelated cause) or end of FU. Overall survival (OS) was calculated from date of SNB to death (any cause) or last FU. MSS was calculated from date of SNB until death by melanoma or last FU, deaths by other causes were censored (considered

as withdrawal from the population). Primary tumor characteristics including Breslow thickness, ulceration, histological subtype, SN tumor burden, gender, and location of the primary tumor, as well as time interval were analyzed using X^2-tests or Mann-Whitney U tests, as appropriate. Survival was estimated with the Kaplan-Meier method and compared per time interval category (<median vs. >median, <first quartile vs. >first quartile, <fourth quartile vs. >fourth quartile, respectively) using the log-rank test.

To reduce bias due to missing values, we imputed missing covariates using multiple imputation[15]. Briefly, ten datasets were created that differed only in the imputed values and analyses were performed on each of the sets. The derived effect estimates were pooled using Rubin's rules[16] to obtain the final results that we report here. All univariable and multivariable binominal logistic regression and cox regression models were performed with the multiply imputed data sets (10 imputations).

Binominal logistic regression analysis was performed to identify predictors for SN-positivity with adjustment for: gender, age, primary tumor location, histologic subtype, Breslow thickness, ulceration status, Clark level, number of removed SNs, center, and time interval. Cox proportional hazard multivariable analysis was performed to identify prognostic factors for survival, with adjustment for all the variables used for multivariable binominal logistic regression as mentioned in the above, and SN status. All tests were performed two-sided. To correct for multiple testing we used the Bonferroni correction and considered p-values of less than 0·0005 to be statistically significant. All statistical analyses were performed using SPSS Version 21·0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21·0. Armonk, NY: IBM Corp.).

Role of the funding source No funding was obtained for the current study.

Results

Patients

For the current study 3,546 patients with a SNB within 180 days after diagnosis were selected. Data were available for patients with a SNB performed from 1997 up to 2013 in center one, from 1997 up to 2004 in center three and from 2000 up to 2012 in center two and four. Of all patients, 1,849 were women (52·1%), and 1697 (47·9%) were men. The median age was 54 years (interquartile range (IQR) 43 – 66 years) and median FU was 50 months (IQR 24 - 84 months). **Table 1** summarizes the baseline characteristics of the study population.

Table 1. Baseline characteristics (N=3,546)

Characteristic	N (%) or Median [IQR]
Center	
1	563 (15·9)
2	1,005 (28·3)
3	1,033 (29·1)
4	945 (26·6)
Gender	
Female	1,849 (52·1)
Male	1,697 (47·9)
Age in years	54 [43 – 66]
Location	
Extremity	1,666 (47·0)
Trunk	1,541 (43·5)
Head/neck	338 (9·5)
Missing	1 (0·0)
Histology	
SSM	1,880 (53·0)
NM	1,072 (30·2)
ALM	96 (2·7)
LMM	135 (3·8)
Other	47 (1·3)
Unspecified/missing	316 (8·9)
Breslow in mm	2·00 [1·20 – 3·30]
Missing	52 (1·5)
Tumor thickness	
T1 <1·0mm	632 (17·8)
T2 1·1 – 2·0mm	1,294 (36·5)
T3 2·1 – 4·0mm	991 (27·9)
T4 >4·0 mm	577 (16·3)
Missing	52 (1·5)
Ulceration	
Absent	2,420 (68·2)
Present	996 (28·1)
Missing	130 (3·7)
Time Interval	43 [29 – 60]
SN status	
Negative	2,841 (80·1)
Positive	705 (19·9)
No. SNs removed	1 [1 – 2]
Missing	119 (3·4)

Table 1. Baseline characteristics (N=3,546) (continued)

Characteristic	N (%) or Median [IQR]
No. SNs positive	1 [1 – 1]
Rotterdam Criteria	705 (100)
<0·1mm	65 (9·2)
0·1-1·0mm	212 (30·1)
>1·0mm	291 (41·3)
Missing	137 (19·4)
CLND	705 (100)
No	94 (13·3)
Yes	578 (82·0)
Missing	33 (4·7)
Additional positive LNs	578 (100)
No	458 (79·2)
Yes	118 (20·4)
Missing	2 (0·3)
Recurrence	
No	2,810 (79·2)
Yes	736 (20·8)
First recurrence	736 (100)
Local	54 (7·3)
In transit	140 (19·0)
Regional LN	156 (21·1)
Distant	237 (32·2)
Missing	149 (20·2)
FU	50 [24 – 84]

Distribution of patient and tumor characteristics per N and % or median and interquartile range. Abbreviations: IQR, inter quartile range; SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acrolentiginous melanoma; LMM lentigo maligna melanoma; SN, sentinel node; CLND, completion lymph node dissection; LNs, lymph nodes; FU, follow-up.

Time interval

The median time interval between melanoma diagnosis and SNB was 43 days (IQR 29 - 60 days) for all patients. There was significant variation between centers: 44 days (IQR 35 – 57 days) in center one; 25 days (IQR 17 – 34 days) in center two; 48 days (IQR 35 – 61) in center three; and 58 days (IQR 44 – 71 days) in center four (p<0·00001) (**Figure 1**).

In a multivariable logistic regression analysis treatment in center two (odds ratio (OR) 0·14, 95% confidence interval (95% CI) 0·11 – 0·18, p<0·00001) and in center four (OR 3·06, 95% CI 2·43 – 3·84 p<0·00001) were relevant predictors for early SNB (data not shown). Breslow thickness, ulceration status, location, histologic type, Clark level, and age were not.

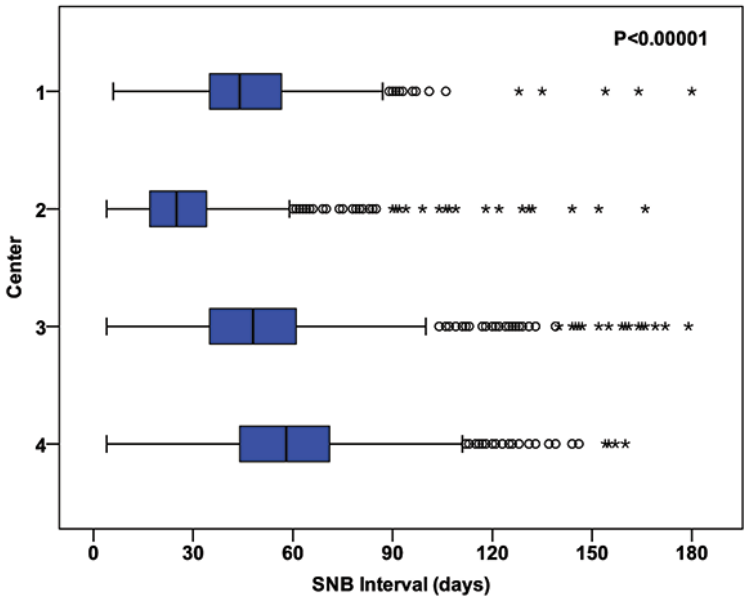

Figure 1. Distribution of Sentinel Node Biopsy Time Interval per Center. Boxplots indicating median (vertical line) and interquartile range (Box) of sentinel node biopsy (SNB) time interval in days per center. ○ (circles) indicate outliers >1.5 Box lengths (>1.5 SD), * (asterisks) indicate outliers >3 Box lengths (>3 SD).

SN Positivity

Distribution of SN positive patients per center was as follows: center one: 30·2% (170/563), center two: 17·3% (174/1005), center three: 15·3% (158/1033), and center four: 21·5% (203/945) (p<0·00001). The proportion of patients with a low, intermediate or high SN tumor burden (<0·1mm, 0·1-1mm, and >1·00mm respectively according to the Rotterdam criteria[17]) did not differ between patients undergoing SNB in ≤43 days vs. patients undergoing SNB after 43 days (p=0·122).

Table 2 displays the unadjusted and adjusted OR and 95% confidence interval for SN positivity per risk factor. Time interval was no relevant predictor for a positive SN (Table 2).

Overall, 6% (170/2806) of SN negative patients developed regional lymph node recurrence. The proportion of SN negative patients with regional lymph node recurrence did not differ significantly between early and late SNB: 6·3% (90/1438) vs. 5·8% (80/1368) (p=0·648).

Survival

The estimated 5-year DFS and MSS were not significantly different for early (≤43 days) vs. late (> 43 days) SNB: 76·8% (standard error (SE) 1·2%) vs. 76·8% (SE 1·1%) (p=0·729); and 86·4% (SE 1·0%) vs. 87·2% (SE 0·9%) (p=0·617) respectively **(Figure 2)**. Patients with a time interval of less than 29 days (first quartile) did not have a different survival from

Table 2. Univariable and Multivariable Binary Logistic Regression Analysis Positive SN Status (N=3,546).

Factor	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Center						
1	Ref			Ref		
2	0·48	0·38 – 0·62	<0·001*	0·54	0·41 – 0·71	<0·001*
3	0·42	0·33 – 0·53	<0·001*	0·41	0·31 – 0·54	<0·001*
4	0·63	0·50 – 0·80	<0·001*	0·58	0·45 – 0·75	<0·001*
Gender						
Female	Ref			Ref		
Male	1·27	1·08 – 1·50	0·005	1·07	0·89 – 1·29	0·46
Age, cont.	0·99	0·98 – 0·99	0·012	0·99	0·98 – 0·99	0·001*
Location						
Extremity	Ref			Ref		
Trunk	1·45	1·22 – 1·72	<0·001*	1·42	1·16 – 1·74	<0·001
Head/neck	2·25	1·73 – 2·94	<0·001*	2·12	1·57 – 2·88	<0·001*
Histology						
SSM	Ref			Ref		
NM	1·49	1·25 – 1·79	<0·001*	0·95	0·77 – 1·18	0·63
ALM	1·65	1·04 – 2·61	0·03	1·62	0·98 – 2·66	0·06
Other	0·56	0·27 – 1·18	0·12	0·54	0·25 – 1·19	0·12
Breslow, cont.	1·20	1·16 – 1·24	<0·001*	1·16	1·11 – 1·20	<0·001*
Ulceration						
No	Ref			Ref		
Yes	2·12	1·79 – 2·52	<0·001*	1·65	1·36 – 2·01	<0·001*
Clark level						
I-III	Ref			Ref		
IV-V	2·24	1·87 – 2·68	<0·001*	1·60	1·31 – 1·96	<0·001*
# SNs, cont.	1·20	1·14 – 1·27	<0·001*	1·12	1·06 – 1·19	<0·001*
Interval, cont.	1·00	0·99 – 1·00	0·58	1·00	0·99 – 1·00	0·92

Pooled coefficients from multiply imputed data (10 imputations). The multivariable models were adjusted for gender, age, primary tumor location, histologic subtype, Breslow thickness, ulceration status, Clark level, number of removed SNs, center, and time interval. A p-value of <0·0005 was considered statistically significant (marked with an *). Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; cont., continuous; SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acrolentiginous melanoma; # SNs, number of removed sentinel nodes.

patients with a time interval of more than 29 days, and patients with a time interval of less than 60 days did not have a different survival from patients with a time interval of more than 60 days (fourth quartile) (data not shown). Patients operated within 29 days also did not have a different survival from patients with a time interval of more than 60 days (first quartile vs. fourth quartile, data not shown). After stratification for SN status

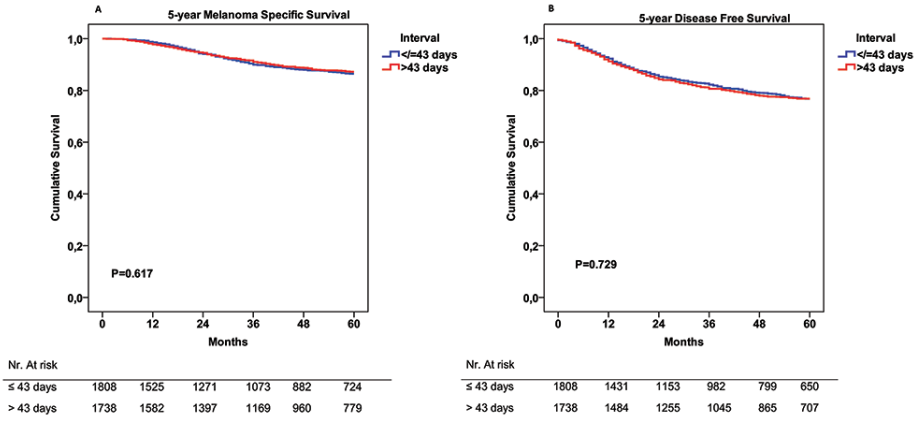

Figure 2. 5-year estimated survival curves per time interval. Kaplan-Meier curve of melanoma specific survival (A) and disease free survival (B) in months for a time interval ≤median (blue line) and >median (red line).

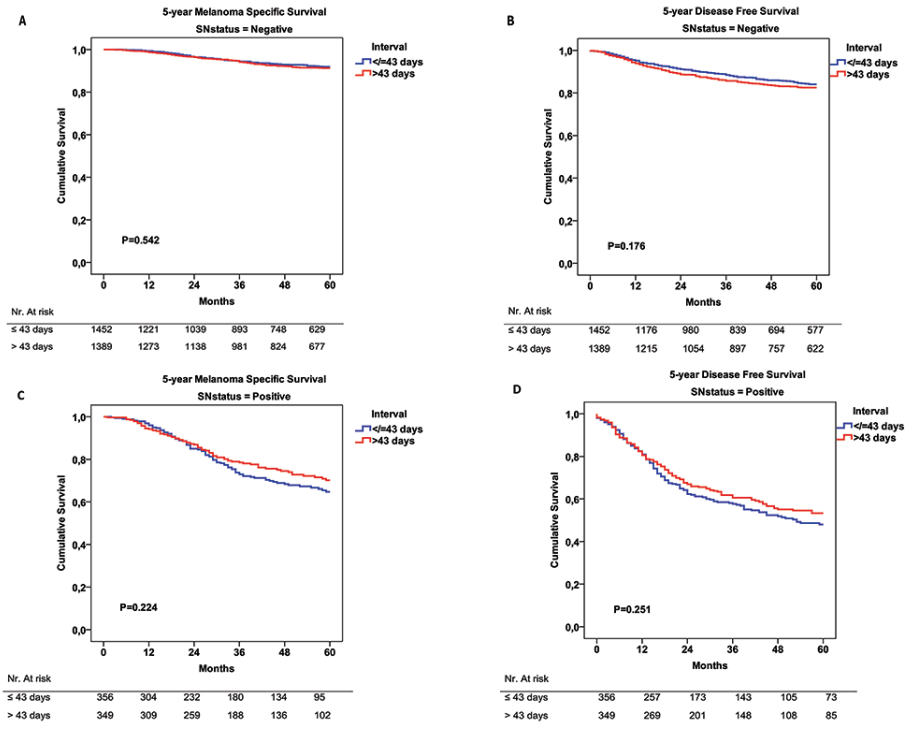

Figure 3. 5-year estimated survival curves per time interval and SN status. Kaplan-Meier curve of SN negatives (A,B) and SN positives (C,D) showing Melanoma Specific Survival MSS (A,C) and Disease Free Survival DFS (B,D) in months for a time interval < median (blue line) and > median (red line).

again no significant difference in survival was observed for median time interval as cut-off value **(Figure 3).** Univariable and multivariable Cox regression analyses were carried out to detect effects of time interval on survival **(Table 3).** Time interval as continuous variable predicting survival was neither significant in univariable analysis, nor after adjustment for known prognostic and confounding factors.

Discussion

In the current study we investigated if time interval from diagnosis until SNB had an effect on SN positivity rate and survival in a retrospective European melanoma cohort from four leading Melanoma centers. In the included 3,546 SNB patients no significant relationship between time interval and SN positivity rate **(Table 2)**, 5-year DFS nor 5-year MSS **(Figure 2 and Figure 3)** was found. There also was no significant difference between SN tumor burden categories and early vs. late time interval.

SN Positivity

Younger age, head & neck melanomas, higher Breslow thickness, ulceration, high Clark level, and a higher number of SNs removed were found to be predictors for a positive SN, which is in line with previous reports[18, 19]. Overall SN positivity rate was 19·9%, which is in line with previous studies as well, and the 15% to 30% SN positivity rate for each center also lies within previously reported SN positivity rates[18, 20-23]. It is known that there can be a wide variety in SNB positivity due to differences in expertise of surgeons, nuclear physicists and pathologists, as well as differences in patient characteristics according to volume and referral population[24]. Since all centers are EORTC Melanoma Group Centers with a high level of experience and expertise, a uniform approach to the work up and treatment of patients undergoing SNB can be expected, and any remaining differences between centers will probably be due to a different case mix as well as inevitable minor variations in execution of the same protocols.

As indicated in the above no significant difference in SN tumor burden categories was found between early and late SNB. Whether there may have been a minimal increase in tumor burden during the time interval between excisional biopsy and WLE plus SNB can neither be confirmed nor denied with the current study.

Time Interval and Survival

The only covariate influencing interval until SNB (<43 days) was center of treatment. This implies that primary tumor characteristics (e.g. high-risk melanoma features or an irradical excisional biopsy) were no significant factor for more urgent WLE and SNB in the process of scheduling patients for surgery.

Table 3. Univariable and Multivariable Cox Regression Analysis 5-Year Melanoma Specific Survival (MSS). (N=3,546)

Factor	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
SN status						
Negative	reference			reference		
Positive	4·45	3·61 – 5·49	<0·001*	3·17	2·53 – 3·97	<0·001*
Center						
1	reference			reference		
2	0·73	0·53 – 1·01	0·06	0·82	0·59 – 1·16	0·26
3	0·92	0·70 – 1·22	0·56	0·99	0·73 – 1·34	0·94
4	0·58	0·42 – 0·79	<0·001	0·61	0·44 – 0·86	0·003
Gender						
Female	reference			reference		
Male	1·85	1·49 – 2·29	<0·001*	1·58	1·26 – 1·98	<0·001*
Age, cont.	1·01	1·00 – 1·02	0·03	1·01	0·99 -1·02	0·08
Location						
Extremity	reference			reference		
Trunk	1·75	1·56 – 1·97	<0·001*	1·53	1·19 – 1·96	<0·001
Head/neck	2·22	1·68 – 2·94	<0·001*	1·57	1·08 – 2·28	0·018
Histology						
SSM	reference			reference		
NM	2·54	2·02 – 3·20	<0·001*	1·53	1·19 – 1·96	<0·001
ALM	1·98	1·04 – 3·75	0·04	1·74	0·89 – 3·39	0·10
Other	0·85	0·42 – 1·71	0·65	0·93	0·46 – 1·90	0·85
Breslow, cont.	1·10	1·09 – 1·12	<0·001*	1·06	1·04 – 1·08	<0·001*
Ulceration						
No	reference			reference		
Yes	3·29	2·66 – 4·07	<0·001*	1·99	1·58 – 2·51	<0·001*
Clark level						
I-III	reference			reference		
IV-V	1·97	1·57 – 2·48	<0·001*	1·44	1·12 – 1·85	0·004
# SNs, cont.	1·05	0·97 – 1·12	0·23	0·97	0·90 – 1·05	0·50
Interval, cont.	0·99	0·99 – 1·00	0·35	1·00	0·99 – 1·01	0·74

Pooled coefficients from multiply imputed data (10 imputations). The multivariable models were adjusted for SN status, gender, age, primary tumor location, histologic subtype, Breslow thickness, ulceration status, Clark level, number of removed SNs, center, and time interval. A p-value of <0·0005 was considered statistically significant (marked with an *). Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; cont., continuous; SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acrolentiginous melanoma; # SNs, number of removed sentinel nodes.

To date, the effects of a longer time interval until SNB on survival have only been reported by three studies; Parrett et al.[21] and more recently Tejera-Vaquerizo et al[23] and Oude Ophuis et al[25]. The median time interval of 43 days (six weeks) found in the current study is in line with these studies[21, 23, 25]. Parrett et al. did not find any significant difference in DFS, OS and MSS, nor SN positivity rates[21]. Oude Ophuis et al. reported that interval had no effects on survival in a SN positive cohort of 1,015 patients[25]. The current study confirms these findings in both SN positive and SN negative patients, and demonstrates that SN positivity rate was not influenced by time interval either. Tejera-Vaquerizo et al. did find a *detrimental effect of a short time interval* on survival for 1,498 SN negative patients[23]. The current study contained 2,841 SN negative patients: no effects of time interval are found in this relatively low risk melanoma population. It could be that local differences in population or a selection bias favoring more aggressive melanomas caused the survival differences found by Tejera-Vaquerizo et al., but we can only speculate on the true cause of these contradictive findings. The fact that no survival differences were found in a larger group of SN negative patients in this study is reassuring.

It is the question whether performing WLE and SNB as soon as possible is necessary considering the above. Tejera-Vaquerizo et al. suggest to wait *longer* before performing SNB based on their theory that removal of the primary melanoma enables the start/continuation of an immunologic reaction in the SN, which would be disrupted by early removal of the SN[23]. Our findings do not confirm the findings of Tejera-Vaquerizo et al. that SN negative patients with a shorter time interval have a worse prognosis. The fact that a different interval does not change SN positivity rate or survival outcome in the current study is in fact compatible with the hypothesis that SNB could just be of no therapeutic impact.

Limitations

The SNB time intervals in the current study ranged between 4 and 180 days, with 50% of patients being operated between 29-60 days (IQR), and the variance of time interval is low between centers (**Figure 1**). This small range limits the possibility to study effects of a wider time interval; no conclusions can be drawn on a time interval beyond the maximum range. Potentially there could be an effect when comparing the outlier time intervals, but investigating this was not possible due to the design of the study where the majority of patients was operated around the IQR of 29-60 days.

This is a retrospectively collected cohort from four leading tertiary referral centers across North-East Europe. Inevitably, this can cause a selection bias, due to differences in case-mix, patient selection and protocol execution per center as reported in the above.

Median time interval varied significantly per center, depending on local referral systems and wait lists. SN positivity rate varied as well. This was not due to the time interval

to SNB, as was shown with logistic regression analysis. Considering that each center will have had a different population, and thus a different a priori risk of a positive SN, we cannot be sure that minor differences in surgical procedure and pathology review have occurred despite the adherence to the melanoma guidelines active at the time of surgery. To overcome these potential biases multivariable regression analyses have been performed with adjustment for center and primary tumor characteristics, as well as SN status.

There are generally two motives for high urgency referral; expedited performance of SNB, and expedited performance of WLE (for instance in case of a narrow excisional biopsy margin). The first has been addressed in the current study; early timing of SNB was found to have no effect on SN positivity rate or survival. On WLE only limited data was available; namely that it generally was performed in the same setting as SNB and a clinical margin of 1-2cm was applied depending on Breslow thickness. No data were available on the exact width of the margin of the excisional biopsy or the WLE, nor whether either one of these margins was tumor positive. Data were also lacking on whether any additional WLE had been performed in order to achieve a tumor negative margin. This could have affected survival outcomes, as Haydu et al.[26] demonstrated an association between excision margins <1cm and higher risk of recurrence for T2 melanomas. More recently Hayes et al.[27] reported the long term FU results of a RCT with T3 and T4 melanomas undergoing 1cm excision margin vs. 3cm excision margin[28] showing a worse MSS for patients with 1cm margin vs >1cm margin at a median FU of 8·8 years. Concerning the timing of WLE; McKenna et al. reported on 986 patients with an adequate diagnostic excisional biopsy followed by WLE (with a >1cm margin in 80%), no effects on recurrence free survival or OS were seen for any time interval[29].

This is in line with the current study, although lack of margin data is a definite drawback.

Conclusion

This is the largest SNB population to date to report on effects of time interval to WLE and SNB on SN positivity rate and survival. The current study sought to investigate possible effects of time interval to WLE and SNB on SN positivity rate and survival and found none in the 3,546 patients investigated. As expected a short change in time interval (up to +/- 1 months) has no obvious impact on SN positivity rate and prognosis. Whether intervals longer than 3 months may have an effect cannot be determined by this study. This reassuring information supports the removal of strict time intervals for WLE and SNB from melanoma guidelines, and can be used in daily clinical practice to counsel patients and reduce the number of high urgency referrals.

Research in context

Evidence before this study

An extensive search was performed in Embase, Medline, Cochrane Central, and Web-of-Science for studies describing timing of sentinel node biopsy in melanoma patients and the influence on survival. Search terms were: "melanoma AND sentinel node biopsy OR lymph node dissection OR lymphadenectomy AND timing OR wait list OR wait time OR delay OR delayed OR prognosis OR survival OR positivity rate". No date or language restrictions were applied to the search. Case reports were excluded. Two retrospective, non-randomized studies reported data regarding this subject. The findings of the first study are in line with our analyses. The second study reported a significant adverse effect on survival for early operated sentinel node negative patients. Our group has recently published a third relevant article focusing on sentinel node positive patients, results are in line with the current study.

Added value of this study

To our knowledge, this is the largest cohort study investigating the effects of sentinel node biopsy timing on SN positivity rate and survival. As opposed to the study describing adverse survival outcome for SN negative patients undergoing early surgery, which suggests that SNB timing can play a role in survival, no adverse effects on SN positivity rate, disease free survival, or melanoma specific survival were found.

Implications of all the available evidence

Overall, these findings did not show an influence of SNB timing on SN positivity rate or survival. The findings of the study reporting a worse survival for SN negative patients have not been validated in this largest cohort of SN melanoma patients, which confirms the assumption that the effect of SNB timing on survival, if at all existing, is very limited,. Based on all studies, it appears to be safe to delay SNB for more than six weeks. This information can be used to adapt current melanoma guidelines and counsel patients.

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