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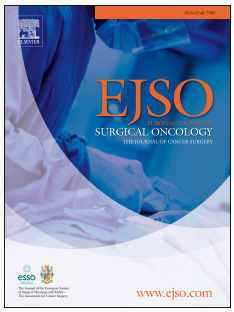

The Interval Between Primary Melanoma Excision and Sentinel Node Biopsy Is Not Associated with Survival in Sentinel Node Positive Patients - *An EORTC Melanoma Group study*

Charlotte M.C. Oude Ophuis, MD, Cornelis Verhoef, MD PhD, Piotr Rutkowski, MD PhD, Barry W.E.M. Powell, MD PhD, Jos A. van der Hage, MD PhD, Paul A.M. van Leeuwen, MD PhD, Christiane A. Voit, MD PhD, Alessandro Testori, MD PhD, Caroline Robert, MD PhD, Harald J. Hoekstra, MD PhD, Dirk J. Grünhagen, MD PhD, Alexander M.M. Eggermont, MD PhD, Alexander C.J. van Akkooi, MD PhD

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Title: The Interval Between Primary Melanoma Excision and Sentinel Node Biopsy Is Not Associated with Survival in Sentinel Node Positive Patients - *An EORTC Melanoma Group study*

Authors:

Charlotte M.C. Oude Ophuis, MD[a,#], Cornelis Verhoef, MD PhD[a], Piotr Rutkowski, MD PhD [b], Barry W.E.M Powell, MD PhD [c], Jos A. van der Hage, MD PhD[d], Paul A.M. van Leeuwen, MD PhD [e], Christiane A Voit, MD PhD[f], Alessandro Testori, MD PhD [g], Caroline Robert, MD PhD[h], Harald J. Hoekstra, MD PhD [i], Dirk J. Grünhagen, MD PhD [a], Alexander M.M. Eggermont, MD PhD [j], Alexander C.J. van Akkooi, MD PhD [d]

[#] Family name is a double name.

[a] Department of Surgical Oncology, Erasmus MC Cancer Institute, Groene Hilledijk 301 3075 EA Rotterdam, the Netherlands

c.oudeophuis@erasmusmc.nl, c.verhoef@erasmusmc.nl, d.grunhagen@erasmusmc.nl

[b] Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, ul. W.K. Roentgena 5, 02-781 Warsaw, Poland

rutkowskip@coi.waw.pl

[c] Melanoma Unit, St. George's Foundation University Hospital, Blakshaw Road, Tooting, London, SW17 0QT, United Kingdom

bpowell@sgul.ac.uk

[d] Department of Surgery, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands

j.vd.hage@nki.nl, a.v.akkooi@nki.nl

[e] Department of Surgical Oncology, Vrije Universiteit Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands

pam.vleeuwen@vumc.nl

[f] *In memoriam.* Department of Dermatology, Charité, University of Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany

no e-mail address.

[g] Division of Dermato Oncological Surgery, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy

alessandro.testori@ieo.it

[h] Department of Dermatology, Cancer Institute Gustave Roussy, 114 rue Édouard-Vaillant, 94805 Villejuif, France

caroline.robert@igr.fr

[i] Department of Surgical Oncology, Groningen University, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands

h.j.hoekstra@umcg.nl

[j] Direction, Cancer Institute Gustave Roussy, 114 rue Édouard-Vaillant, 94805 Villejuif, France

alexander.eggermont@igr.fr

Corresponding Author:

Alexander C.J. van Akkooi

The Netherlands Cancer Institute

Department of Surgery

Plesmanlaan 121

1066 CX Amsterdam

The Netherlands

Phone: 0031 20 512 2551

Fax: 0031 20 512 2459

Email: a.v.akkooi@nki.nl

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Synopsis

This study examines >1000 sentinel node (SN) positive melanoma patients. Time interval between primary excision and SN biopsy (SNB) is no prognostic factor for disease free and melanoma specific survival. Guidelines advocating SNB <6 weeks should be reconsidered.

Abstract

Background: Worldwide, sentinel node biopsy (SNB) is the recommended staging procedure for stage I/II melanoma. Most melanoma guidelines recommend re-excision plus SNB as soon as possible after primary excision. To date, there is no evidence to support this timeframe. Aim: To determine melanoma specific survival (MSS) for time intervals between excisional biopsy and SNB in SNB positive patients.

Methods: Between 1993-2008, 1 080 patients were diagnosed with a positive SNB in nine Melanoma Group centers. We selected 1 015 patients (94%) with known excisional biopsy date. Time interval was calculated from primary excision until SNB. Kaplan-Meier estimated MSS was calculated for different cutoff values. Multivariable analysis was performed to correct for known prognostic factors.

Results: Median age was 51 years (Inter Quartile Range (IQR) 40-62 years), 535 (53%) were men, 603 (59%) primary tumors were located on extremities. Median Breslow thickness was 3.00mm (IQR 1.90-4.80mm), 442 (44%) were ulcerated. Median follow-up was 36 months (IQR 20-62 months). Median time interval was 47 days (IQR 32-63 days). Median Breslow thickness was equal for both <47 days and ≥47 days interval: 3.00mm (1.90-5.00mm) vs 3.00mm (1.90-4.43mm) (p=0.402). Sentinel node tumor burden was significantly higher in patients operated ≥47 days (p=0.005). Univariate survival was not significantly different for median time interval. Multivariable analysis confirmed that time interval was no independent prognostic factor for MSS.

Conclusions: Time interval from primary melanoma excision until SNB was no prognostic factor for MSS in this SNB positive cohort. This information can be used to counsel patients.

Keywords: Cutaneous Melanoma, Melanoma, Sentinel Lymph Node Biopsy, Melanoma Specific Survival, Prognosis, Waiting List.

Manuscript Text

Introduction

Parallel to the increasing incidence of primary cutaneous melanomas, sentinel node biopsies (SNB) are being performed more often. This is the current standard to detect early lymph node micrometastases[1-3].

As recommended by the American Joint Committee on Cancer (AJCC), as well as the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO), by performing a SNB, it is possible to provide accurate staging of intermediate thickness (Breslow 1.0 – 4.0mm) primary cutaneous melanoma[4, 5]. This way, patients can be provided more information about their prognosis [4, 6, 7]. Sentinel node (SN) status can help to select patients who might benefit from completion lymph node dissection (CLND) and / or adjuvant systemic therapies in trial setting, for instance the EORTC 18991 study on pegylated interferon alfa and the EORTC 18071 study on ipilimumab[8, 9]. Currently no uniform recommendation exists on the maximum allowed time interval between primary melanoma excision and wide local excision (WLE) combined with SNB. Most national melanoma guidelines advise to perform WLE and SNB as soon as possible within an acceptable time frame. The Dutch national melanoma guideline advocates a strict maximum time interval of six weeks[10]. This suggests a detrimental effect on survival if not adhered to. To date, only two studies have reported on this topic. Parrett et al. found no adverse effects on survival for a time interval of <40 days vs. > 40 days, while Tejera-Vaquerizo et al. reported a detrimental effect of a time interval of <40 days at the expense of SN negative patients[11, 12]. These contradicting findings are not sufficient to answer the question which effects, if any, time interval may have on survival.

One of the negative aspects of advising a short time frame for SNB is the incentive for general practitioners (GP's) and dermatologists to perform high urgency referrals. The potentially increased patient anxiety due to longer wait times (depending on the country's healthcare system) may also play a considerable role in this. Altogether this poses the need to objectively describe the possible influences of the time interval between primary diagnosis and WLE plus SNB on survival. We hypothesize that this time interval may be associated with a difference in survival. Aim of the study is to investigate if time interval between primary diagnosis and WLE plus SNB is associated with survival differences in a SN positive melanoma population.

Methods

Patients

For purposes of this current study, a retrospective cohort of SN positive patients, previously collected and described, was used[13]. In brief, this cohort contained 1 080 SN positive patients from nine European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group centers, undergoing SNB between 1993 and 2008. The study was performed in accordance with local ethics committee guidelines. In total, 1 015 patients (94%) were selected with known date of primary melanoma excision. Collected data included: gender, age, date of primary excision, date of SNB, primary tumor characteristics i.e. location, Breslow thickness, ulceration, CLND data i.e. performed yes/no, positive non-SNs yes/no, and follow-up (FU).

Melanoma 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 margin, as described in the American Association of Dermatology Guidelines and the National Cancer Comprehensive Network Clinical Practice Guidelines[14, 15]. Date of diagnosis was defined as the date of excisional biopsy. All patients treated at the participating centers were worked up for SNB in line with the recommendations stated by the European Society of Medical Oncology [16].

Surgical Procedure and Pathology:

SNB was performed if Breslow thickness was > 1.0 mm or if risk factors were present such as ulceration or high Clark level (IV or V), regression, or high mitotic rate (>1 count/field). Generally, WLE (with a margin of 1-2 cm depending on the Breslow thickness) and SNB were performed in the same setting. In all centers the triple technique was used for SNB; consisting of pre-operative lymphoscintigraphy within 24 hours prior to the procedure; perioperative injection of patent blue near the primary tumor site and use of an intraoperative handheld gamma detection probe to locate the SN(s) [17, 18]. A lymph node was defined as SN, if it was blue and / or hot (in situ: intraoperative gamma detector count of at least 3x background count, ex situ: intraoperative gamma detector count of at least 10x background count)[13]. Pathology review and reports were conducted according to the EORTC Melanoma Group Pathology Protocol, including scoring of SN tumor burden according to the Rotterdam criteria [19-21].

Outcome measures:

Time interval until SNB was the variable of interest (dependent variable) in this study. The primary endpoint was melanoma specific survival (MSS). Secondary endpoints were disease free survival (DFS); overall survival (OS); and SN tumor burden.

Statistics

Time until SNB was calculated from date of diagnosis until SNB date. FU was calculated from SNB date to last FU date or death. DFS was calculated from SNB date until date of first recurrence (any site). OS was calculated from SNB date until death (any cause) or last FU. MSS was calculated from SNB date until death by melanoma or last FU, deaths by other causes were censored (considered as withdrawal from population).

Patients were divided into two categories based on time interval: early SNB (< median) vs, late SNB (≥ median). Additionally, the first (Q1) and third quartile (Q3) of time interval were tested as binominal categories, and first (Q1) and last quartile (Q4) were tested against each other to detect differences between both outer quartiles. Breslow thickness, ulceration, SN tumor burden, gender and location of the primary tumor were analyzed per time interval category in order to investigate the possibility of differences in distribution indicating a selection bias in favor of early or late SNB. Kaplan-Meier estimated MSS was calculated per time interval category. Cox proportional hazard multivariable analysis was performed adjusting for age, gender, Breslow thickness, histology type, ulceration, Clark level, SN tumor burden, CLND category (performed/not performed), additional positive non-SNs and time interval as continuous variable. The maximum allowed degrees of freedom in the model were based on the number of events, not exceeding one tenth of the number of events.

A p-value of <0.05 was considered 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.).

Results

In total 1 015 patients (93.9%) were selected of whom diagnosis date was known and time interval was less than 154 days (22 weeks). Median age at diagnosis was 51 years (IQR 40-62 years). Median FU was 36 months (IQR 20 -62 months), median DFS was 27 months (11 – 57 months). **Table 1** summarizes the baseline characteristics of the study population per time interval category.

Regression and mitotic rate were only recorded in a minority of patients, hence these variables were not included for further analysis. Median Breslow thickness was 3.00 mm (IQR 1.90 – 4.80mm). Median time interval per center is shown in **table 2.** The proportion of patients undergoing SNB early (<47 days) differed significantly per center, due to more early surgical procedures in Center 2 and Center 9 (operated within 47 days: 95.3% and 60.9% vs. 23.9% - 56.6% in the remaining centers) (**table 1, table 2)**. Median FU did not differ between patients operated at <47 days (37 months, IQR 19 – 62 months) vs. patients operated at ≥47 days (35 months, IQR 21 – 62 months) (p=0.632).

5-year Estimated Kaplan-Meier MSS showed no significant difference in survival for early SNB (<47 days) vs. late SNB (≥ 47 days) **(Figure 1)**. For time interval categories Q1 and Q3 respectively, also no significant difference in MSS or DFS was seen (data not shown). Survival was not different between both outer quartiles; 5-yr MSS for Q1 (<32 days) was 70% vs. 72% for Q4 (>63 days), p=0.574 **(Figure 2).**

Univariable logistic Cox regression analyses showed a significant difference in 5-year estimated MSS for the following variables: older age (as continuous variable), gender, histological subtype, Clark level, ulceration, Breslow thickness, SN tumor burden, and positive

non-SNs at CLND **(table 3)**. Non-significant on univariable analyses were: primary tumor location, center, CLND category and time interval (as continuous variable).

A Cox proportional hazard multivariable analysis was performed with inclusion of the significant factors on univariable analyses as mentioned above, CLND category and time interval to adjust for any possible occult selection bias on univariable analysis. Only male gender, presence of ulceration, higher Breslow thickness, SN tumor burden >0.1mm and positive non-SNs at CLND remained as independent prognostic factors for 5 year MSS **(table 3)**. Time interval from primary excision to SNB was no independent prognostic factor for 5 year MSS after adjustment for potential confounding factors on multivariable analysis. DFS and OS were calculated for the entire cohort and each co-variable per time interval category (results not shown). Results were similar to the MSS data, namely that time interval was not a prognostic factor. For DFS, the following additional prognostic indicators were found: increasing age (HR 1.01, 95% CI 1.00 – 1.01, p=0.050), center 2 (HR 0.59, 95% CI 0.35 – 0.98, p=0.040), center 4 (HR 0.51, 95% CI 0.31 – 0.83, p=0.006), center 5 (HR 0.47, 95% CI 0.29– 0.77, p=0.002), 8 (HR 0.33, 95% CI 0.17 – 0.62, p=0.001) and 9 (HR 0.24, 95% CI 0.12 – 0.48, p=0.001), and Clark level IV (HR 2.07, 95% CI 1.01 – 4.24, p=0.048) and V (HR 2.21, 95% CI 1.03 – 4.76, p=0.042).

Discussion

The MSLT 1 final report showed no difference in 10-year MSS for WLE and SNB followed by immediate CLND versus WLE alone and nodal observation followed by delayed therapeutic lymph node dissection if necessary [22]. Sub analyses in node positive patients with intermediate-thickness melanoma (1.2-3.5mm) showed a significantly improved 10-year distant DFS and MSS in favor of SNB. Considering this, any potential impact of the time interval until SNB on survival might more likely become detectable in patients with nodal disease, i.e. a positive SN. This formed the rationale to perform the current study with *SN positive patients.*

In this study, 5-year estimated MSS is not significantly different for short versus longer time intervals **(Figure 1, figure 2).** SN tumor burden according to the Rotterdam criteria [13, 20] is significantly more often high in those patients undergoing SNB after a time interval of 47 days or more. Thus it may seem that late performance of SNB might have an adverse effect on tumor burden. Oppositely of the increase of SN tumor burden with a longer time interval, the risk of additional positive non-SNs at CLND was higher in patients with early SNB (≤47 days). In multivariable logistic regression (data not shown), time interval was not correlated to CLND outcome, but Center was. This has been addressed by van der Ploeg et al[23]. Since time intervals are different between centers **(table 2),** there is a strong correlation between center and time interval. This could explain why it would seem that time interval has influence on the proportion of patients with positive non-SNs at CLND while in truth proportion of positive non-SNs is associated with the center of treatment.

After correcting for tumor burden, CLND outcome, and other known prognostic factors in a multivariable model time interval cannot be identified as a detrimental prognostic factor for MSS. This is in line with the study of Parrett et al. which concerned 491 SN positive and negative

patients from a single institution[12]. With a median time interval of 40 days, no differences in DFS, OS and MSS were found, nor any significant difference in SN positivity rates.

Importantly, the current study consists of SN positive patients only. Since SN positive patients have a worse prognosis, the outcome of this study strengthens the findings of Parrett et al. SN negative patients have not been investigated in the current study, but effect of time interval on survival is not expected in these low-risk patients. Interestingly, Tejera-Vaquerizo et al. did find a detrimental effect of a short time interval on survival for SN negative patients[11]. They hypothesized that a shorter time interval and worse prognosis were associated due to surgeons prioritizing patients for surgery when primary tumor features were worrisome. Validation of these data is needed, as the described findings are counterintuitive.

The phenomenon that high SN tumor burden was more frequently observed in those patients undergoing SNB at a later time interval might cause one to consider a correlation between SN tumor burden and time interval.

When stratifying for SN tumor burden in Kaplan-Meier estimated survival analyses, no significant differences in MSS are seen for time interval (data not shown). After stratification for time interval <47 days vs. >47 days, SN tumor burden did distinguish clearly between good, intermediate and poor prognosis (**Figure S1**). The fact that there was no unadjusted survival difference between the group with a time interval of <47 days versus the group with a time interval of ≥ 47 days while the proportion of patients with a high SN tumor burden was slightly larger in the latter may be explained by the fact that survival is influenced by many variables and that the net effect canceled out the slightly more frequent high SN tumor burden in the latter group. The fact that survival for high SN tumor burden found with early SNB versus high SN

tumor burden found with late SNB is not different confirms that SN tumor burden is a prognostic factor regardless of SNB timing.

It is remarkable that there are differences in DFS across centers and not in MSS. Due to the retrospective nature of this study, the exact timing of follow-up visits is not known for all centers. It could be that more frequent follow-up visits in these centers led to a lead-time bias effect. Another possibility could be that these centers treated more patients with low risk primaries. This was not the case, since centers with a low median Breslow thickness had more ulcerated tumors and vice versa. As detailed follow-up information including date and site of first recurrence was not known for all patients, the lower HR for DFS in five out of nine participating centers may also be explained by a selection bias due to missing data.

There is sparse literature with regard to the maximum allowable time interval for SNB. Two large prospective trials have included a maximum time interval as inclusion criterion. These are the MSLT I trial, with a maximum allowed time interval to SNB of 12 weeks [24], and the SUNBELT trial, where the maximum allowed time interval was 90 days (=13 weeks) [25]. This maximum time interval is at least two times as high as the median time interval found in the current cohort. These time intervals seem to be reasonable in the light of providing treatment within a timely manner, and at the same time allowing an adequately broad window for scheduling SNB. As for WLE, which is often combined with SNB: McKenna et al. reported long term survival data of a large retrospective cohort showing no differences in recurrence free survival and OS regardless of the time interval until WLE [26]. While time interval until SNB is not prognostic for survival in the current study, it can be used as a quality measure for hospitals performing SNB. This could form an addition to registration of SN positivity rate per hospital, another recently proposed quality measure[27].

There are limitations in the current study. It is a retrospectively collected cohort from nine tertiary referral melanoma institutes across Europe. Inevitably, this can cause a selection bias, due to differences in local patient population, patient selection and protocols per center. As all centers are EORTC Melanoma Group centers, there is much expertise in work up and treatment of melanoma patients. Uniform work up of patients eligible for SNB, surgery and histopathological analysis of the SN was already applied in all these centers prior to implementation into European consensus guidelines. Local differences will have mainly consisted of referral policies, wait lists and case-mix rather than technical approaches to melanoma patients.

In the current cohort adjuvant interferon therapy was not used as a covariate, as only a minority of patients received interferon in adjuvant trial setting (n=36), and for one third of all patients no information was available on trial participation. Primary melanomas in the head and neck region seem to be underrepresented, and median Breslow thickness varies considerably per center**.** Also the number of thick melanomas is high **(Table 1).** One possible explanation for this may be the fact that all participating centers are EORTC Melanoma Group referral centers, with a corresponding high risk case-mix. Considering this, the current cohort may not be entirely representative for the general population that would normally be offered a SNB. To overcome this, multivariable analyses have been performed to correct for known prognostic and potential confounding factors. The FU is limited, and an update of follow up data would definitely improve the value of the current study. During the median FU of 36 months (3 years) DFS and MSS were not affected by time interval, which is considerable. As this cohort consists of SN positive patients only, it is by definition not representative for the entire population undergoing SNB. It does reflect a wide variety of SN positive patients, including patients with thin melanomas and patients with thick melanomas.

Since no differences in survival are found for different time intervals in this high risk SN group, survival differences for the more beneficial SN negative patient population are unlikely. One has to take into account that although no effects on survival were seen for SN positive patients, SN-positivity rate might be adversely influenced by a longer time interval. No conclusions can be drawn on this aspect with the current SN positive cohort alone.

Finally, although a fixed maximum time interval based on survival does not seem to be necessary, minimizing the amount of wait time to surgery is still important to ease patient anxiety, as it affects the daily life of most patients. A survey by Eskander et al. in patients undergoing elective malignant thyroid surgery showed that anxiety levels significantly decreased after surgery, suggesting that stress and anxiety levels can be minimalized by performing surgery timely [28]. Another study by Oudhoff et al. concerning surgery for benign disorders, reported an increase in negative emotional reactions to waiting, significantly associated with wait time, which decreased significantly after surgery[29].

Taking all of the above into consideration, the need to perform early SNB as advised by specific melanoma guidelines should be reconsidered. As there is no solid base to adhere to a maximum time interval between WLE and SNB as stated in the above, maintaining a time interval falsely suggests that there still is a clinicopathological ground for performing SNB as soon as possible. This may facilitate unnecessary patient anxiety for patients on waiting lists. We therefore suggest that international melanoma guidelines should revise the need of a timeframe for SNB after primary melanoma excision in order to reduce patient anxiety and pressure on surgeon's schedule.

Conclusions

Time interval between primary melanoma excision and wide local excision (WLE) combined with Sentinel Node Biopsy (SNB) did not influence 5-year estimated DFS and MSS in a population of SN positive patients. Patients who got their SNB later had a slightly larger disease deposit and although this may have implications for prognosis this study did not detect any difference. These findings indicate that it is safe and equally informative to perform SNB after a prolonged interval of >9 weeks(4^{th} quartile). This information can be used to counsel patients.

Conflict of interest statement

The authors reported no conflicts of interest.

Acknowledgements

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Figure Captions

Figure 1. 5 Year Estimated Melanoma Specific Survival (MSS) for Median Sentinel Node Biopsy (SNB) Time Interval.

5-year estimated melanoma specific survival (MSS) in months for time interval <47 days (blue line) and ≥47 days (red line).

Figure 2. 5 Year Estimated Melanoma Specific Survival (MSS) for Sentinel Node Biopsy (SNB) Time Interval Outer Quartiles.

5-year estimated melanoma specific survival (MSS) in months for first quartile Q1, <32 days (blue line) and fourth quartile Q4, >63 days (red line).

Supplementary:

Figure S1 5 Year Estimated Melanoma Specific Survival (MSS) for Sentinel Node (SN) Tumor Burden Stratified for Time Interval.

5-year estimated melanoma specific survival (MSS) in months stratified for a time interval until SN biopsy of <47 days (A) and a time interval of ≥ 47 days (B) for sentinel node (SN) tumor burden categories <0.1 mm (yellow line), 0.1-1.0mm (blue line), and >1.0mm (red line)

Tables

Table 1. Baseline Characteristics of Sentinel Node Positive Patients (N = 1 015)

Characteristic	< 47 days	≥ 47 days	All	p
N (%)	507 (50)	508 (50)	1 015 (100)	
Center				
1	53 (10.5)	62 (12.2)	115 (11.3)	
2	82 (16.2)	4 (0.8)	86 (8.5)	
3	101 (19.9)	120 (23.6)	221 (21.8)	
4	102 (20.1)	102 (20.1)	204 (20.1)	
5	22 (4.3)	70 (13.8)	92 (9.1)	
6	25 (4.9)	41 (8.1)	66 (6.5)	
7	60 (11.8)	46 (9.1)	106 (10.4)	
8	20 (3.9)	36 (7.1)	56 (5.5)	
9	42 (8.3)	27 (5.3)	69 (6.8)	0.005*
Gender				
Female	228 (45.0)	252 (49.6)	480 (47.3)	
Male	279 (55.0)	256 (50.4)	535 (52.7)	0.139
Age, years				
≤ 51	255 (50.3)	264 (52.0)	520 (51.1)	
> 51	252 (49.7)	244 (48.0)	496 (48.9)	0.594

Table 1. Baseline Characteristics of Sentinel Node Positive Patients (N = 1 015), continued

Location				
Extremity	314 (61.9)	289 (56.9)	603 (59.4)	
Trunk	177 (34.9)	204 (40.2)	381(37.5)	
Head/neck	16 (3.2)	15 (3.0)	31 (3.1)	0.122
Histology				
SSM	179 (35.3)	197 (38.8)	376 (37.0)	
NM	172 (33.9)	157 (30.9)	329 (32.4)	
Other	25 (4.9)	15 (3.0)	40 (4.0)	
Unknown	131 (25.8)	139 (27.4)	270 (26.6)	0.538
Breslow Thickness, mm				
T1 (</= 1.00)	29 (5.7)	20 (3.9)	49 (4.8)	
T2 (1.01-2.00)	118 (23.3)	139 (27.4)	257 (25.3)	
T3 (2.01-4.00)	201 (39.6)	210 (41.3)	411 (40.5)	
T4 (>4.00)	159 (31.4)	137 (27.0)	296 (29.2)	
Missing	-	2 (0.4)	2 (0.2)	0.236
Clark level				
II	12 (2.4)	20 (3.9)	32 (3.2)	
III	120 (23.7)	133 (26.2)	253 (24.9)	
IV	309 (60.9)	276 (54.3)	585 (57.6)	
V	48 (9.5)	52 (10.2)	100 (9.9)	
Unknown	18 (3.6)	27 (5.3)	45 (4.4)	0.567

Table 1. Baseline Characteristics of Sentinel Node Positive Patients (N = 1 015), continued

Ulceration				
Absent	249 (49.1)	262 (51.6)	511 (50.3)	
Present	229 (45.2)	213 (41.9)	442 (43.5)	
Unknown	29 (5.7)	33 (6.5)	62 (6.1)	0.550
SN tumor burden				
<0.1mm	60 (11.8)	52 (10.2)	112 (11.0)	
0.1 – 1.0mm	238 (46.9)	199 (39.2)	437 (43.1)	
>1.0mm	209 (41.2)	257 (50.6)	466 (45.9)	0.005*
CLND performed				
No	24 (4.7)	22 (4.3)	46 (4.5)	
Yes	468 (92.3)	482 (94.9)	950 (93.6)	
Unknown	15 (3.0)	4 (0.8)	19 (1.9)	0.276
Positive non SNs				
No	380 (75.0)	415 (81.7)	795 (78.3)	
Yes	110 (21.7)	87 (17.1)	197 (19.4)	
Unknown	17 (3.4)	6 (1.2)	23 (2.3)	0.009*
Time interval, median (IQR)	32 (26 – 40)	63 (54 – 75)	47 (32 – 63)	0.331

N, number of patients; IQR, inter quartile range; SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acrolentiginous melanoma; CLND, completion lymph node dissection; SN, sentinel node. * significance reached at $p<0.05$.

Table 2. Time Interval Between Melanoma Diagnosis and Sentinel Node Biopsy per Center

Center	Time interval in days: median, (inter quartile range)
1	48 (36 – 61)
2	9 (0 - 30)
3	49 (36 – 63)
4	47 (33 – 61)
5	63 (48 – 73)
6	53 (37 – 69)
7	41 (29 – 62)
8	50 (41 – 64)
9	37 (21 – 59)

Table 3. Univariable and Multivariable Analysis on 5 Year Melanoma Specific Survival (MSS) (N = 1 015)

	Univariable			Multivariable		
Covariate	HR	95% CI	*P*	HR	95% CI	*P*
Age, continuous	1.01	1.00 – 1.02	0.043*	1.01	0.99 – 1.01	0.322
Gender						
Female	1			1		
Male	1.31	1.00 - 1.72	0.046*	1.37	1.04 – 1.81	0.024*
Histology						
SSM	1			1		
NM	1.40	1.01 - 1.93	0.042*	0.96	0.68 – 1.35	0.959
Other	2.04	1.10 - 3.76	0.023*	1.75	0.92 – 3.34	0.088
Unknown	1.39	0.98 - 1.99	0.065	1.32	0.89 – 1.95	0.170
Clark level						
II	1			1		
III	1.34	0.48 - 3.75	0.576	1.61	0.57 - 4.57	0.372
IV	1.98	0.73 - 5.36	0.178	2.09	0.77 - 5.73	0.150
V	3.84	1.37 - 10.8	0.011*	2.42	0.84 - 6.96	0.101
Unknown	2.70	0.86 - 8.47	0.090	2.21	0.67 - 7.28	0.194
Ulceration						
Absent	1			1		
Present	2.19	1.65 - 2.91	<0.0001*	1.67	1.24 - 2.26	0.001*

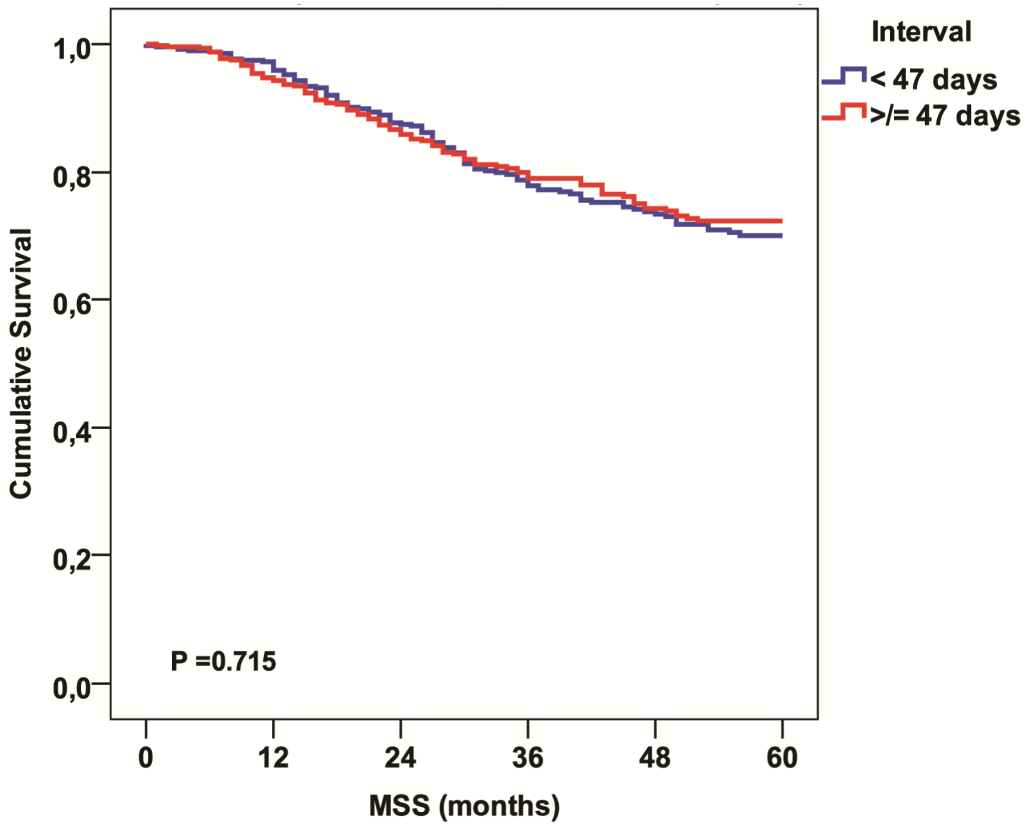
Table 3. Univariable and Multivariable Analysis on 5 Year Melanoma Specific Survival (MSS) (N = 1 015), Continued

Unknown	1.73	0.98 - 3.05	0.059	1.44	0.77 – 2.70	0.254
Breslow, continuous	1.07	1.06 – 1.09	<0.0001*	1.05	1.02 – 1.07	0.0002*
Tumor burden						
< 0.1 mm	1			1		
0.1 – 1.0 mm	3.20	1.48 - 6.93	0.003*	2.85	1.31 - 6.21	0.008*
> 1.0 mm	5.96	2.79 - 12.7	<0.0001*	4.14	1.91 – 9.00	0.0003*
CLND done						
No	1			1		
Yes	1.12	0.53 – 2.37	0.775	0.63	0.29 – 1.37	0.244
Unknown	1.99	0.58 – 6.81	0.271	0.61	0.06 – 6.29	0.674
Positive non-SNs						
No	1			1		
Yes	2.47	1.86 – 3.28	<0.0001*	2.27	1.68 – 3.05	<0.0001*
Unknown	2.37	0.97 – 5.79	0.058	2.51	0.34 – 18.4	0.366
Time interval, continuous	1.00	0.99 – 1.01	0.721	1.00	0.99 – 1.01	0.567

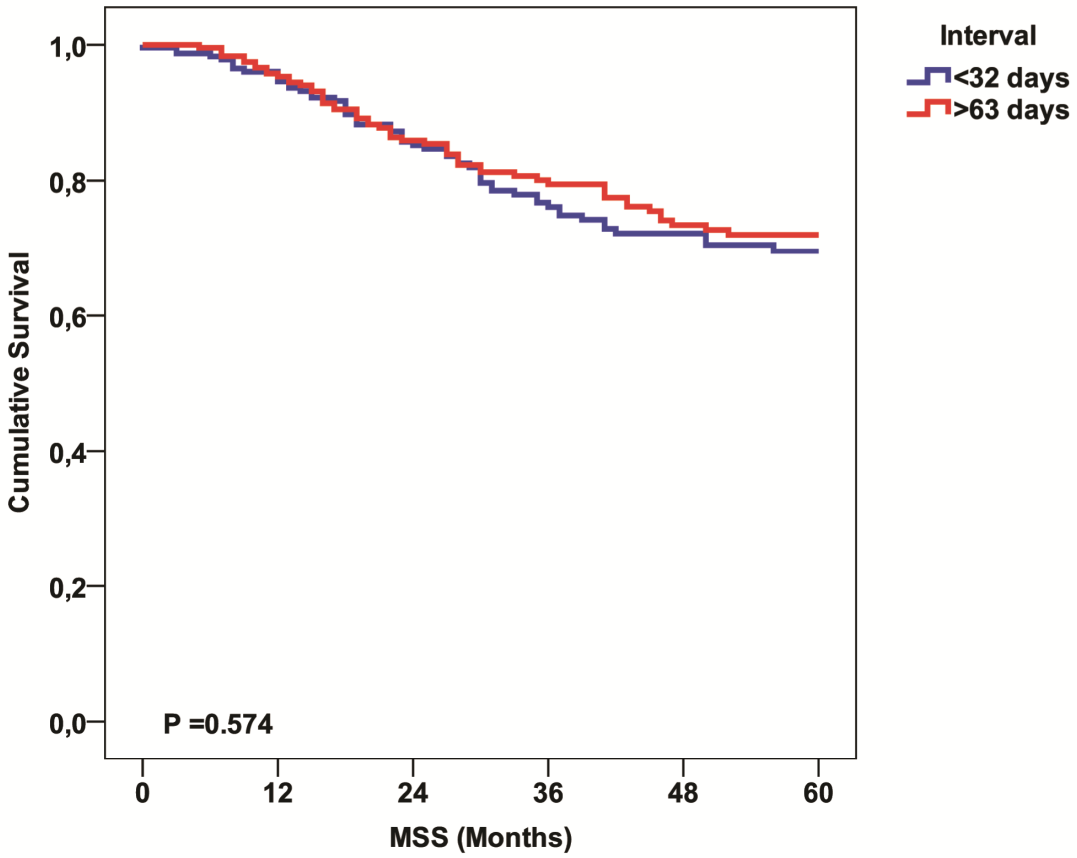
Abbreviations: MSS, melanoma specific survival; N, number of patients; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; *, significant at p<0.05; SSM, superficial

Table 3. Univariable and Multivariable Analysis on 5 Year Melanoma Specific Survival (MSS) (N = 1 015), Continued

spreading melanoma; NM, nodular melanoma; n.s., not significant; CLND, completion lymph node dissection; SN, sentinel node.



Nr. at risk						
< 47 days	507	435	353	261	194	136
≥ 47 days	508	445	354	253	198	142



Nr. at risk						
≤ 32 days	246	204	166	124	89	62
> 63 days	254	224	177	130	107	81