Timing of Completion Lymphadenectomy after Positive Sentinel Node in Melanoma Patients

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Abstract

Background Nodal staging with sentinel node biopsy (SNB) and completion lymphadenectomy (CLND) informs melanoma patients and physicians on their prognosis. It is not known whether CLND timing is associated with survival outcome/CLND tumour load. The aim was to investigate if CLND timing is associated with CLND tumour load, disease free survival (DFS) and/or melanoma specific survival (MSS).

Methods A retrospective cohort of SNB positive melanoma patients from 9 EORTC Melanoma Group Centres undergoing surgery from 1993-2009 was examined. Patients were selected based on availability of CLND and follow-up data. CLND interval was defined as the number of days between diagnosis and CLND. Patient and tumour characteristics were collected. 5-year DFS and MSS were calculated. Cox and logistic regression analysis were performed adjusting for known prognostic/predictive indicators.

Results 784 patients were selected. Median age was 51 years (interquartile range (IQR) 40-62 years), 418 (53.3%) patients were male. Median Breslow thickness was 3.00mm (IQR 2.00-5.00mm), 148 patients (18.9%) had residual tumour load. Median CLND interval was 84 days (IQR 65-105 days). 5-year DFS and MSS were not significantly different for patients operated <84 days and ≥84 days: 54.2% vs. 53.3%, and 66.9% vs. 65.1%. In a multivariable Cox model, CLND interval was not a significant prognostic indicator. CLND interval was negatively correlated with positive non-SNs, after adjustment for known risk factors this effect was no longer found.

Conclusions The time interval between diagnosis and CLND did not influence CLND tumour load, DFS or MSS. This information can be used to counsel patients.

Introduction

A positive sentinel node biopsy (SNB) is generally followed by a completion lymph node dissection (CLND) as suggested by most current melanoma guidelines[1-3]. With a CLND any potential additional occult nodal metastases are removed, which can potentially improve survival. Moreover, the detailed pathological information on the extent of nodal disease can be used for adequate N-staging according to the AJCC Melanoma Staging System (7th edition) [1]. This can inform patients and their physicians more precisely on their prognosis, can select patients for adjuvant radiotherapy and allow inclusion of patients into adjuvant therapy trials.

Previously, several studies have reported on the timing of SNB and its potential association with survival, results are conflicting: Parrett et al. found no effect[4], Tejera-Vaquerizo et al. found a negative effect of early SNB for SN negative patients[5], while more recently Fortes et al. stated that early SNB had a positive effect on survival for SN positive patients[6]. Oude Ophuis et al. have investigated this topic as well, finding no difference in survival in a larger series of 1,015 SN positive patients[7]. Nor did SNB timing influence SN positivity in a group of 3,546 SN positive and SN negative patients[8].

The MSLT-2, Minitub and DeCOG studies[9-11] examine if a CLND has any therapeutic effect. Besides this question, is not known whether timing of the CLND after a positive SN can affect tumour burden and subsequent survival outcomes.

Previous retrospective studies report only on immediate CLND after a positive SN versus delayed therapeutic LND (in case of a false negative SNB or if no SNB was performed at all)[12-16]. Since the first group includes not only the patients with positive non-SNs but also up to 80% of patients with no additional positive nodes, while the latter group includes only the 20% of patients with occult positive lymph nodes at the time of diagnosis that have developed into clinically evident lymph nodes, these two heterogeneous groups cannot be compared one to one.

Aim of this study was to investigate if timing of CLND after a positive SNB is associated with tumour burden in CLND, disease free survival (DFS) and/or melanoma specific survival (MSS) differences in a large European cohort of melanoma patients.

Patients and Methods

Patients

A retrospective cohort described previously consisting of SN positive melanoma patients from 9 EORTC Melanoma Group Centres undergoing a SNB between 1993 and 2009 was used for this study[17]. For the current study additional information was gathered on date of CLND, number of excised lymph nodes and number of tumour positive non-SNs.

An update of follow-up data up to 2016 was performed in order to achieve long term follow-up results. Date of diagnosis and date of SNB were previously collected[7].

In brief, this cohort consisted of 1,080 patients with a melanoma of at least 1.0 mm Breslow thickness, or presence of at least one risk factor such as ulceration or Clark level IV/V (according to the 6th edition of the AJCC staging system used at the time of diagnosis)[18]. All patients had undergone a SNB and SN was considered positive after regular pathological work-up of the SN according to the EORTC protocol (see below). Patients were selected based on availability of detailed information on CLND: i.e. date of CLND, number of excised lymph nodes and number of additional positive non-SNs, and sufficient follow-up. Patients without CLND; with a CLND more than 180 days after diagnosis; or with a CLND more than 100 days after SNB were excluded, as this was considered to be aberrant from standard practice in our opinion.

Sentinel Node Biopsy

All patients underwent SNB according to the triple technique as described in detail previously [17, 19]. Histopathological examination of the removed SNs was performed according to the EORTC Melanoma Group pathology protocol[20]. Microscopic tumour burden and localization was scored according to the combined Rotterdam-Dewar Criteria[17, 21].

Completion lymphadenectomy

CLND consisted of either an axillary, inguinal, ilio-inguinal or a cervical lymphadenectomy, depending on the localization of the positive SN. The total number of surgically removed lymph nodes and the number of involved lymph nodes was registered for each patient.

Statistics

CLND interval was defined as the time between diagnostic excision of the primary melanoma and CLND in days. Separately the time interval between diagnosis and SNB, and the time interval between SNB and CLND were explored. As the time interval between diagnostic excision of the primary melanoma and SNB has been described previously[7] the current study will focus only on the SNB-CLND interval; defined as the time between SNB and CLND in days. Follow-up was calculated from date of diagnosis (i.e. date of diagnostic excision) until last follow-up or death of any cause. DFS was calculated from the date of diagnosis until first recurrence, deaths due to other cause and patients without recurrence at last follow-up were censored. MSS was calculated from date of diagnosis until the date of death due to melanoma, deaths due to other cause and patients alive at last follow-up were censored. Kaplan-Meier estimated 5 year DFS and MSS were calculated and the log rank test was applied for comparison between early and late (<median vs. >median / Q1 vs Q4) CLND interval and SNB-CLND interval. As maximum SN tumour

diameter (Rotterdam Criteria) was the most prognostic SN tumour burden factor[17] this was chosen for further evaluation in the current series. Logistic regression analysis and Cox regression analysis were performed univariable and multivariable, adjusting for: centre, gender, age, location of the primary, histology type, Breslow thickness, ulceration status, SN tumour burden, number of positive SNs/ SN ratio, number of removed lymph nodes at CLND, number of positive lymph nodes (non-SNs) in CLND resection specimen, and CLND interval. A two-sided p-value of less than 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

Of the 1,080 patients in the initial database, 296 patients were excluded for various reasons. Sixty-three patients had not undergone CLND, 200 patients had incomplete CLND data or FU data, 28 patients had a CLND > 180 days after diagnosis, and 5 patients had a CLND > 100 days after SNB. A total of 784 patients from 8 centres remained for the current study. Baseline patient, tumour and CLND features are displayed in **Table 1.**

Median follow-up was 65 months (IQR 28-113 months). All CLNDs were performed within a range of 0 - 178 days (median 84 days, IQR 65 – 105 days) after diagnosis, and median 37 days (IQR 27 – 48 days, range 0 - 97) after SNB. Again, none of them because of palpable nodes.

Non-SN Positivity

Positive non-SNs were found in 83/384 (221.6%) patients with a CLND <84 days after diagnosis (<median), and in 65/400 (16.3%) patients with a CLND ≥84 days (≥median) after diagnosis, which was not significantly different (p=0.055). The median number of positive non-SNs was similar between patients undergoing CLND <84 days and patients undergoing CLND ≥84 days after diagnosis (p=0.103). The proportion of patients with positive non-SNs was higher for patients operated within 65 days (Q1) than for patients operated more than 105 days (Q4) after diagnosis: 25.9% vs. 15.8% (p=0.014). Binominal logistic regression analysis was performed to investigate whether CLND interval was predictive for positive non-SNs; unadjusted OR was 0.99 (95% CI 0.985-0.997, p=0.003). After adjustment for: centre of treatment, gender, Breslow thickness, Ulceration, SN tumour burden and positive SN ratio (all p<0.05univariate), CLND interval was not a significant predictor (**Table 2**).

Table 1. Baseline Features (N = 784)

		N(%) or median [IQR]
Centre	1	102 (13.0)
	2	55 (7.0)
	3	228 (29.1)
	4	114 (14.5)
	5	110 (14.0)
	6	63 (8.0)
	7	55 (7.0)
	8	57 (7.3)
Gender	Female	366 (46.7)
	Male	418 (53.3)
Age	cont.	51 [40 – 62]
Location	Extremity	380 (48.5)
	Trunk	376 (48.0)
	Head/neck	28 (3.6)
Histology	SSM	330 (42.1)
	NM	300 (38.3)
	LMM	13 (1.7)
	ALM	29 (3.7)
	Other	4 (0.5)
	Unknown	108 (13.8)
Breslow	cont.	3.00 [2.00 – 5.00]
T Stage	T1	35 (4.5)
	T2	180 (23.0)
	T3	314 (40.1)
	T4	254 (32.4)
	Unknown	1 (0.1)
Ulceration	Absent	370 (47.2)
	present	379 (48.3)
	Unknown	35 (4.5)
# of SNs	cont.	2 [1 – 3]
# of positive SNs	cont.	1 [1 – 1]
Positive SN ratio	Cont.	1 [0.50 - 1]
SN tumour burden	<0.1mm	73 (9.3)
	0.1-1.0mm	334 (42.6)
	>1mm	377 (48.1)
SN tumour localisation	Subcapsular	138 (17.6)
	Non-subcapsular	534 (68.1)
	Unknown	112 (14.3)
CLND location	Axillary	375 (47.8)

Table 1. Baseline Features (N = 784) (continued)

		N(%) or median [IQR]
	Inguinal	291 (37.1)
	Ilio-inguinal	50 (6.4)
	Cervical	34 (4.3)
	multiple sites	33 (4.2)
	Unknown	1 (0.1)
# removed LN at CLND	cont.	14 [10 – 20]
# positive non-SNs	cont.	0 [0 – 0] (range 0 - 3)
CLND tumour load	Negative	636 (81.1)
	Positive	148 (18.9)
Interval diagnosis - CLND (days)	cont.	84 [65 – 105]
Interval diagnosis - SNB (days)	cont.	47 [33 – 62]
Interval SNB – CLND (days)	cont.	37 [27 - 48]

Baseline features of all 784 patients as number (%) or median [IQR]. Positive SN ratio was calculated as the number of positive SNs divided by the number of retrieved SNs. Abbreviations: IQR, inter quartile range; cont., continuous; SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acrolentiginous melanoma; SN, sentinel node; CLND, completion lymph node dissection; LN, lymph node(s); SNB, sentinel node biopsy.

Survival

Survival rates were not significantly different for patients undergoing CLND within 84 days (<median) after diagnosis and after 84 days or more (≥median); 5-year DFS was 53.3% (SE 2.6%) vs. 54.2% (SE 2.7%), 5-year MSS was 66.9% (SE 2.5%) vs. 65.1% (SE 2.5%) (**Figure 1 and Figure 2**). Different cut-off values for CLND time interval (Q1 vs Q2-4, <Q1-3 vs Q4, Q1 vs. Q4) did not show significant differences in survival either (data not shown). Five-year DFS and MSS were also calculated for the time interval between SNB and CLND with the median of 37 days as cut-off: DFS was 55.0% (SE 2.7%) vs. 52.6% (SE 2.6%) (p= 0.913), and MSS was 68.5% (SE 2.5%) vs. 63.8% (SE 2.5%) (p=0.479) respectively.

Prognostic Indicators

Results of univariable and multivariable Cox regression analysis for all patients are displayed in **Table 3.** CLND interval was not significant as prognostic indicator on univariable analysis. In order to adjust for a potential occult effect masked by other covariates, CLND interval was also included in the multivariable model, along with significant covariates at univariable analysis. Centre 4, Higher Breslow thickness, ulceration, SN tumour burden 0.1-1.0mm and >1.0mm, and number of positive non-SNs in the CLND resection specimen were significant prognostic indicators for 5-year MSS, time interval until CLND was not.

Table 2. Uni- and Multivariable Binominal Logistic Regression Analysis for Positive non-SN Status

			Univariable			Multivariable		
		n	OR	95% CI	p	OR	95% CI	p
Centre	1	102	ref			ref		
	2	55	2.56	1.06 - 6.19	0.037*	2.18	0.83-5.74	0.114
	3	228	2.69	1.34 - 5.39	0.005*	2.00	0.97 - 4.14	0.061
	4	114	1.16	0.50 - 2.68	0.732	1.32	0.55 - 3.17	0.530
	5	110	1.21	0.52 - 2.80	0.662	1.13	0.48 - 2.69	0.779
	6	63	1.38	0.54 - 3.54	0.504	1.61	0.61 - 4.26	0.333
	7	55	1.84	0.73 - 4.65	0.198	2.65	1.02 - 6.92	0.047*
	8	56	4.83	2.11 - 11.0	<0.0001*	5.20	2.21 - 12.3	<0.0001*
Gender	Female	366	Ref			ref		
	Male	418	0.70	0.49 - 0.99	0.047*	0.70	0.47 - 1.02	0.062
Breslow	cont.	783	1.13	1.08 - 1.19	<0.0001*	1.11	1.05 - 1.17	<0.0001*
Ulceration	Absent	370	ref.			ref.		
	Present	379	1.52	1.05 - 2.20	0.025*	1.05	0.70 -1.59	0.805
	Unknown	35	0.68	0.23 - 1.99	0.483	0.79	0.24 - 2.57	0.696
SN tumour burden	<0.1mm	73	ref.			ref.		
	0.1-1.0mm	334	2.06	0.85 - 4.99	0.110	2.07	0.82 - 5.23	0.124
	>1mm	377	3.50	1.47 - 8.34	0.005*	3.11	1.22 - 7.90	0.017*
Pos SN ratio	cont.	784	2.10	1.11 - 3.98	0.022*	2.53	1.27 - 5.01	0.008*
CLND interval	cont.	784	0.99	0.99 - 0.99	0.003*	0.99	0.98 - 1.00	0.133

Univariable and multivariable binominal logistic regression model for presence of positive non-sentinel nodes. Positive SN ratio was calculated as the number of positive SNs divided by the number of retrieved SNs. Abbreviations: SN, sentinel node; OR, odds ratio; 95% CI, 95% confidence interval; ref, reference value; cont., continuous; Pos, positive; CLND, completion lymph node dissection.

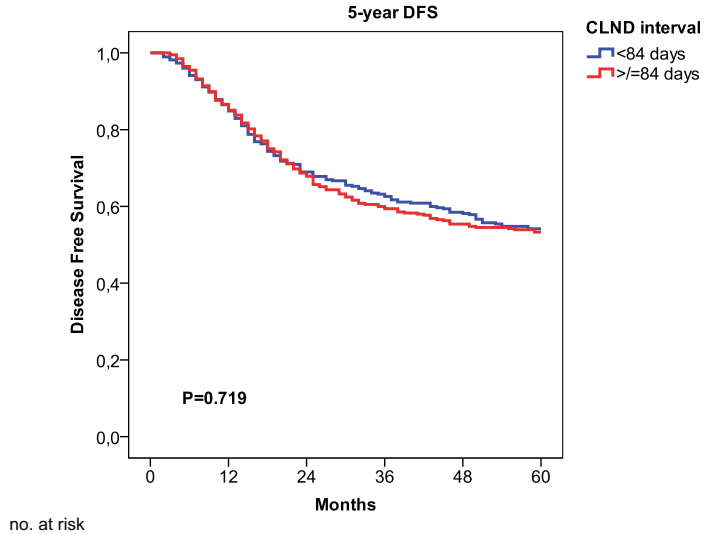
Discussion

The current study investigated whether timing of CLND after a positive SNB is associated with non-SN positivity, DFS and/or MSS differences in a large European cohort of melanoma patients.

No association between CLND interval and DFS or MSS was found in this study.

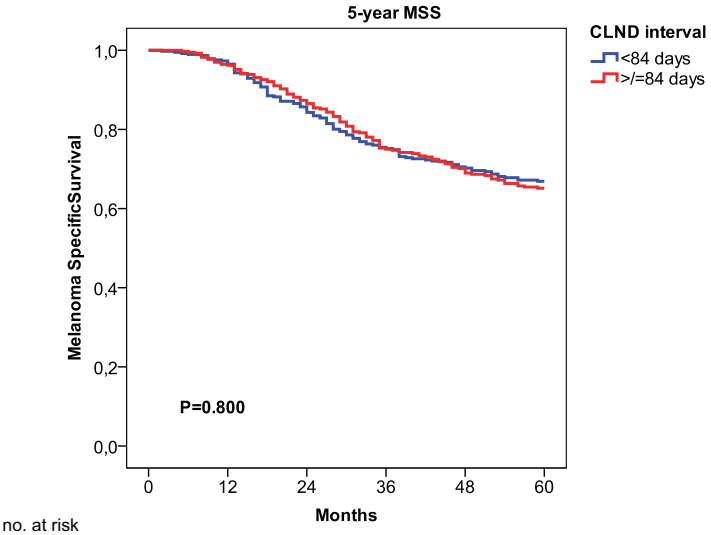
Nineteen percent of all patients had positive non-SNs, which is in line with other studies[22].

The prognostic indicators found in the multivariable Cox model (Breslow thickness, ulceration status, SN tumour burden, and number of positive non-SNs) are also in line with previous reports[13, 22], indicating the fact that the current cohort consists of a common, representative SN positive melanoma population.



no. at risk						
<84 days	384	315	241	216	195	169
>=84 days	400	339	255	217	187	172

Figure 1. Five-year Disease Free Survival per CLND Interval Category. Kaplan-Meier curve displaying 5-year disease free survival for completion lymphadenectomy (CLND) within 84 days (blue line) vs. CLND after more than 84 days (red line) post diagnosis. Difference in survival calculated with the log-rank test.



no. at risk						
<84 days	384	356	305	261	239	213
>=84 days	400	377	324	272	239	214

Figure 2. Five-year Melanoma Specific Survival per CLND Interval Category. Kaplan-Meier curve displaying 5-year melanoma specific survival for completion lymphadenectomy (CLND) within 84 days (blue line) vs. CLND after more than 84 days (red line) post diagnosis. Difference in survival calculated with the log-rank test.

The number of positive non-SNs is one of the most potent prognostic indicators (HR 1.24 per 1 node increase) (**table 3**). The fact that CLND interval was not associated with an increased number of positive non-SNs implies that at least for the time frame in which all CLNDs were performed in this study (0 – 178 days after diagnosis, IQR 65 – 105 days), the risk of metastatic spread to adjacent lymph nodes was not significantly increased for patients with a longer interval to undergo their CLND. This is reflected in the similar survival outcomes for patients with early CLND vs. late CLND in the current study.

Additionally, this study investigated whether the time interval between SNB and CLND was associated with survival; this was not the case. Previously Oude Ophuis et al. have reported on the timing of SNB after diagnosis of a new melanoma in SN positive patients; no significant effects on DFS or MSS were found in a cohort of over 1,000 SN positive patients[7]. Recently 2 series have been published reporting on SNB timing for both SN negative patients and a smaller number of SN positive patients, with strikingly conflicting results[5, 6]. Tejera-Vaquerizo et al. concluded that SN negative patients would profit from a longer time interval, while Fortes et al. stated that SN positive patients would benefit from a short time interval. Oude Ophuis et al. performed a larger study concerning SNB timing for over 3,500 SN positive and SN negative patients in which SNB timing was also not associated with survival or SN positivity. The fact that both studies from Tejera-Vaquerizo and Fortes show contradicting results, based on post-hoc analyses, and that Oude Ophuis et al. have investigated the largest SN series to date[8], affirm that can be assumed with a high degree of certainty that the effect of SNB timing is negligible.

As the therapeutic value of CLND itself continues to be questioned, it can be argued that CLND may no longer need to be performed at all, considering the invasive nature of the procedure, and association with considerable morbidity in a relevant proportion of patients[11]. Recently the results of the DeCOG have been reported, which showed no survival benefit of CLND vs. nodal observation for patients with a tumour positive SN at 3 years follow-up in 483 patients[10]. As they have mentioned, the study was underpowered due to a lower accrual rate than anticipated, moreover the majority of patients had a low SN tumour burden (≤1 mm) contributing to a low event rate, and reported results cover only the first three years of follow-up. The final results of DeCOG have to be awaited, as well as and more importantly the final results of the MSLT2 in order to be able to fully assess the value of CLND. Meantime, the presented data show that a limited delay in CLND (max 178 days after diagnosis) can be considered safe, as it did not affect survival or CLND tumour burden.

Due to the retrospective nature, this study is inevitably associated with limitations due to selection bias and missing data. Thus, the findings of this study should be interpreted with caution. From the initial study cohort consisting of 9 centres, only data from 8 centres could be included. Data from these centres were checked meticulously

Table 3. Uni- and Multivariable Cox Regression Analysis Melanoma Specific Survival

			Univariable			Multivariable		
Covariate		n	HR	95% CI	p	HR	95% CI	p
Centre	1	102	ref			ref		
	2	55	0.83	0.45 - 1.53	0.554	0.71	0.37 - 1.39	0.319
	3	228	1.62	1.10 - 2.39	0.016*	1.14	0.75 - 1.72	0.537
	4	114	0.61	0.36 - 1.03	0.066	0.50	0.28 - 0.89	0.019*
	5	110	0.84	0.51 - 1.36	0.469	0.71	0.43 - 1.19	0.193
	6	63	0.85	0.48 -1.50	0.576	0.74	0.41 -1.36	0.331
	7	55	0.50	0.25 - 1.01	0.055	0.68	0.33 - 1.40	0.294
	8	57	0.98	0.54 - 1.81	0.958	0.93	0.47 - 1.82	0.824
Gender	female	366	ref			ref		
	male	418	1.31	1.02 - 1.69	0.036*	1.29	0.98 - 1.69	0.070
Age	cont.	784	1.01	1.00 - 1.02	0.026*	1.01	0.99 - 1.02	0.188
Location	Extremity	380	ref			ref		
	Trunk	376	1.40	1.08 - 1.81	0.011*	1.29	0.97 - 1.72	0.079
	Head/neck	28	1.26	0.66 - 2.41	0.487	1.41	0.66 - 3.03	0.372
Histology	SSM	330	ref			ref		
	NM	300	1.54	1.16 - 2.06	0.003*	0.99	0.73 - 1.36	0.981
	Other	46	1.60	0.95 - 2.69	0.08	1.47	0.84 - 2.55	0.174
	Unknown	108	1.70	1.16 - 2.50	0.006*	1.32	0.87 - 2.03	0.196
Breslow	cont.	783	1.08	1.06 - 1.10	<0.0001*	1.06	1.04 - 1.08	<0.0001*
Ulceration	Absent	370	ref			ref		
	Present	379	2.22	1.69 - 2.90	<0.0001*	1.54	1.16 - 2.05	0.003*
	Unknown	35	2.01	1.12 - 3.60	0.020*	2.09	1.05 - 4.15	0.036*
SN tumour burden	<0.1mm	73	ref			ref		
	0.1-1.0mm	334	2.95	1.29 - 6.77	0.011*	2.59	1.11 - 6.07	0.028*
	>1mm	377	7.13	3.16 - 16.1	<0.0001*	5.55	2.05 - 11.1	<0.0001*
# nodes CLND	cont.	775	1.01	0.99 - 1.03	0.083	1.00	0.98 - 1.02	0.962
# positive non SNs	cont.	784	1.21	1.15 - 1.29	<0.0001*	1.24	1.15 - 1.33	<0.0001*
CLND interval	cont.	784	0.99	0.99 - 1.00	0.490	1.00	0.99 - 1.01	0.846

Univariable and multivariable Cox regression model for 5-year melanoma specific survival. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; ref, reference value; cont., continuous; SSM, superficial spreading melanoma; NM, nodular melanoma; SN, sentinel node; CLND, completion lymph node dissection.

for any missing data on CLND (i.e. date of CLND, number of removed nodes and number of positive nodes) which was added when available; and additionally all follow-up was updated, creating a mature cohort of SN positive patients from 8 tertiary referral mela-

noma group centres. There was a significant difference between centres for the median time interval until CLND and for the proportion of patients with positive non-SNs, which is illustrated by the high odds ratios of some of the centres at logistic regression (**table 2**), and by the significantly lower HR for centre 4 at multivariable analysis. These findings can be explained partially by the variety of case-mix between centres; some centres had more patients with a high or low Breslow thickness or performed all surgeries within 60 days. To correct for these potentially confounding differences, adjustment for centre was performed in all multivariable analyses.

The time frame in which CLNDs were performed ranged from 0 – 178 days (IQR 65 – 105 days), making it impossible to draw any conclusions on the effects of CLNDs performed after this time frame. It could be that the turning point for potential therapeutic benefit lies outside the time interval reported in this study, but before the point of development of clinically evident lymph node involvement as used in the MSLTI and DeCOG[10, 22]. Unfortunately, extracapsular extension (ECE), known to be a prognostic indicator[23], was not available for the majority of the patients in this study. However, ECE is rarely seen in SN and CLND cases (2.2%)[12]. SN tumour burden was available for all patients, which also could clearly identify high risk patients at multivariable Cox regression survival analysis. As CLND timing was not significant at univariable nor at multivariable analysis after adjustment for confounding and prognostic indicators, the current study provides valuable information for daily clinical practice in which surgery is often still prioritized based on patient anxiety and potential reduction of doctor's delay due to long referral times. Ultimately MSLT 2 will provide a definitive answer on the question whether CLND is therapeutic (10 year follow up results anticipated in 2022)[9]. Until then, this study provides a valuable insight that there is no rush to perform a CLND, if chosen to be performed.

Conclusions

The current study shows that in this retrospective cohort of 784 SN positive melanoma patients, non-SN positivity and survival were not associated with CLND timing; indicating that it is safe to wait for at least 3 months (105 days, third quartile) after diagnosis, as there is no need to perform CLND as soon as possible. This information can be used to counsel patients and referring physicians and can potentially relieve pressure on the wait list.

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Part III – (Extent of) Groin Dissections