Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node

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abstract

PURPOSE We have previously reported on the 3-year results of the phase III German Dermatologic Cooperative Oncology Group trial (DeCOG; ClinicalTrials.gov identifier: NCT02434107) comparing distant metastasis-free survival (DMFS), recurrence-free survival (RFS), and overall survival (OS) in patients with positive sentinel lymph-node biopsy who were randomly assigned to complete lymph node dissection (CLND) or observation. Here, we report the final analysis with 72 months of median follow up.

PATIENTS AND METHODS The multicenter randomized phase III trial included patients with cutaneous melanoma of the trunk and extremities who were randomly assigned (1:1) to undergo CLND or observation. DMFS was analyzed as the primary end point, and RFS, OS, and recurrences in the regional lymph node basin were secondary end points. The analysis was by intention to treat. Disease and survival information were collected quarterly.

RESULTS From January 2006 to December 2014, 5,547 patients were screened to identify 1,256 with metastases in the sentinel lymph node (SLN). Of these, 483 (39%) were included: 241 in the observation arm and 242 in the CLND arm. In the final analysis, median follow up was 72 months (interquartile range, 67-77 months). No significant treatment-related difference was seen in the 5-year DMFS between the observation and CLND arms (67.6% v 64.9%, respectively; hazard ratio [HR], 1.08; $P = .87$). The 5-year RFS and OS also showed no difference (HR, 1.01 and 0.99, respectively). Grade 3 and 4 adverse effects occurred in 32 patients (13%) in the CLND arm; lymphedema (n = 20) and delayed wound healing (n = 5) were most common and no serious adverse events were reported.

CONCLUSION The final results of the German Dermatologic Cooperative Oncology Group trial with a median follow up of 72 months showed higher event rates, but similar HRs compared with those at the 3-year analysis. These results confirm that immediate CLND in SLN-positive patients is not superior to observation in terms of DMFS, RFS, or OS and support not recommending CLND in patients with SLN metastasis.

INTRODUCTION

There is an ongoing discussion of whether radical surgery in patients with cancer can improve prognosis. Lymph node surgery has been recommended for patients with melanoma since the beginning of the last century. Until the 1990s, elective lymphadenectomy was recommended for patients with high risk of recurrence on the basis of the assumption of stepwise metastasis, as it was observed that two thirds of patients primarily develop regional lymph node recurrences.[1] Nonetheless, the benefits of radical lymphadenectomy were always controversially discussed, as this was associated with clear morbidity (lymphedema, seroma, and lymph fistula).

Elective lymph node dissection was replaced in 1992 by the minimally invasive sentinel lymph node biopsy (SLNB).[2] In patients without clinical evidence of metastasis but with melanoma with a tumor thickness of 1.0 mm or more, primary draining lymph nodes were removed and examined for metastasis in the SLN. In the case of metastasis in the SLN, complete lymph node dissection (CLND) was recommended[3,4] as sentinel lymph node (SLN) –positive patients had worse prognosis, which was dependent on the tumor load in the SLN.[5-7] The Multicenter Selective Lymphadenectomy Trial I (MSLT-I; ClinicalTrials.gov identifier: NCT00275496) compared outcomes of patients who were randomly assigned to nodal observation and

lymphadenectomy if nodal relapse occurred with those assigned to SLNB followed by immediate CLND in the case of SLN positivity. RFS was significantly improved for patients who were randomly assigned to SLNB with immediate CLND, and melanoma-specific survival (MSS) was improved for patients undergoing immediate CLND compared with those undergoing delayed lymphadenectomy at the time of clinically evident nodal recurrence. No benefit from immediate lymphadenectomy was found in disease-free survival or MSS, but the role of CLND in SLN-positive patients remained contentious.[3,4]

In recent years, two prospective randomized multicenter phase III studies analyzing whether CLND improved survival in SLN-positive patients were published. The primary analysis of the German Dermatologic Cooperative Oncology Group (DeCOG-SLT) study (ClinicalTrials.gov identifier: NCT02434107), after a median follow up of 34 months, did not demonstrate a benefit in distant metastasis-free survival (DMFS), overall survival (OS), and recurrence-free survival (RFS) in the CLND arm.[8] The MSLT-II study (ClinicalTrials.gov identifier: NCT00297895) randomly assigned 931 patients to observation with lymph node sonography and 824 patients underwent CLND.[9] No survival benefit was found for patients undergoing CLND after a median follow up of 43 months.

The final analysis of the DeCOG-SLT study was performed 3 years after the inclusion of the last patient, as prespecified in the protocol, with a median follow-up period of 72 months, which is relevant as data from the literature suggest that a subgroup of patients with melanoma develop delayed metastasis[10,11]

PATIENTS AND METHODS

Study Design and Patients

The DeCOG-SLT study was conducted as a multicenter, prospective randomized phase III trial. Patients were recruited from 41 German skin cancer centers from 2006 to 2014 after they had provided written consent. The study, protocol, the patient's information and consent form were approved by the institutional review board under the lead management of the ethics committee of the University of Munster. Data were collected at the participating centers and transmitted to the data management center in Tübingen. All authors attest to the accuracy and completeness of the data presented.

The study concept included a recruitment period of 6 years. Patients who were age 18 to 75 years with primary cutaneous melanoma with a tumor thickness of 1.0 mm or greater and metastasis in the SLN were eligible. Patients with head and neck melanoma, satellite, in-transit or distant metastases, macrometastases (involvement of the entire lymph node with capsular perforation), previous/concurrent melanoma or other malignancies (except nonmelanoma skin cancer), or immunosuppressive treatment were excluded.

Study design details of random assignment and standard operating procedures for SLNB and CLND were previously described in detail.[8]

Outcomes

The primary end point was DMFS, which was calculated from date of random assignment to date of first distant metastases, latest follow-up visit, or death from any cause. Secondary end points included RFS, OS, regional lymph node recurrences, and adverse effects in patients who underwent CLND. RFS was calculated from date of random assignment to first recurrence, last follow-up visit, or death from any cause. OS was determined from the date of random assignment to latest follow-up visit or death from any cause. For patients who were allocated to the CLND arm, adverse events and surgical complications were collected immediately postoperatively and 3 and 6 months after CLND. Grade 3 and 4 adverse effects, including delayed wound healing, infection, seroma, lymph fistula, lymphedema, and persistent staining after patent blue injection were recorded in the CLND arm to assess the adverse effects of CLND as previously described.[8] The present analysis was performed 156 months after recruitment initiation.

Statistical Analysis

As originally designed, the recruitment target was to randomly assign 556 patients. Results could be analyzed after 192 events had occurred on the basis of the assumption that DMFS follows an exponential distribution with a 3-year rate of 60% for patients in the observation arm. Three-year DMFS rate in the CLND arm was expected to be more than 10% higher than in the observation arm, resulting in a hazard ratio (HR) of 0.70. These targets were based on having 80% power to detect the superiority of CLND with a one-sided α error of 5%, corresponding to a two-sided α error of 10%.

The final analysis was performed after all patients had a minimum follow up of 3 years, accomplished with the intention-to-treat collective defined as all eligible randomly assigned patients. To check comparability, we evaluated clinical and demographic patient characteristics. Numerical variables were described by median value and interquartile range (IQR), and collectives were compared using Wilcoxon rank-sum test and two-sided χ^2 tests, as appropriate.

Five-year survival probabilities with 90% CIs were calculated using Kaplan-Meier analysis, and differences between groups were evaluated using log-rank tests. Subgroup analyses for DMFS were performed according to tumor load in the SLNB (size of metastases). The effect of the treatment group was analyzed by multivariable Cox proportional hazard regression models for DMFS, OS, and RFS, adjusted for tumor thickness (≤ 2 mm $v > 2$ mm), size of metastases (single cells ≤ 1 mm $v > 1$ mm), number of positive SLNs (one $v \geq 2$), ulceration (absent v present v unknown), and

interferon (IFN) therapy (no v yes). The model was settled using backward and forward stepwise procedures. HR and 90% CI were delineated in the Cox proportional hazards regression model. According to the study protocol, one-sided survival analyses at a .05 level would be performed, which is equivalent to two-sided analyses at a .10 level. Two-sided *P* values were reported throughout all analyses presented in this work and were considered statistically significant if less than .10. Statistical analyses were performed using SPSS21 software (SPSS, Chicago, IL).
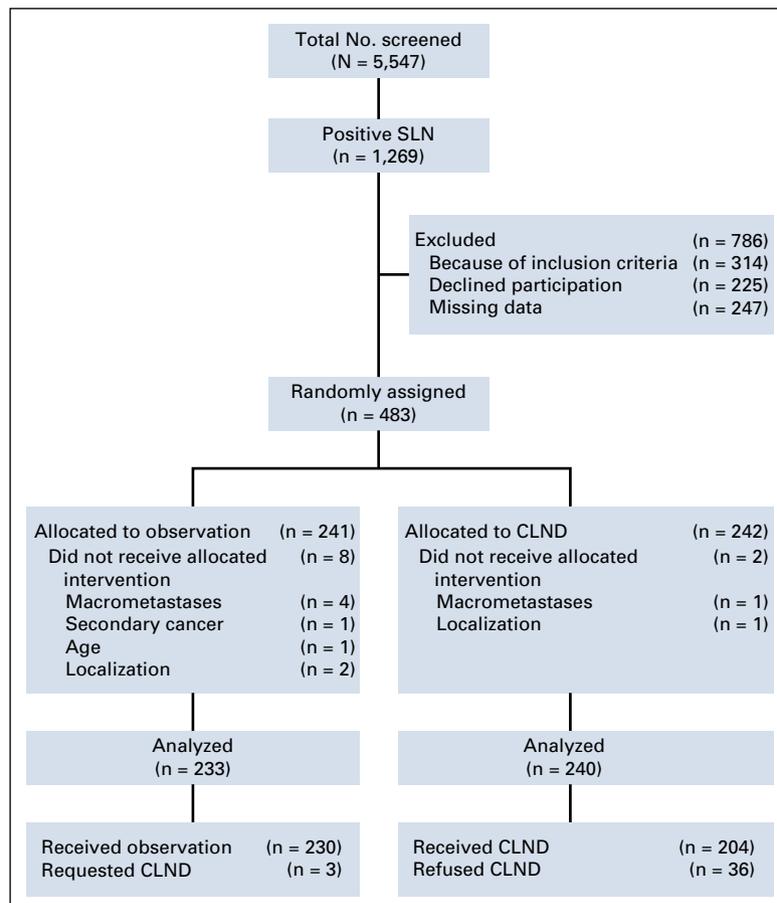
RESULTS

Patient Characteristics

Between January 1, 2006, and December 1, 2014, 5,547 patients were screened to identify 1,269 with positive SLN (Fig 1). Of these, a total of 483 patients were randomly assigned. Accrual was terminated early as a result of a much longer accrual time and lower event rate than expected. Ten patients had to be excluded from further analysis (Fig 1).

The intention-to-treat population consisted of 473 patients: 240 randomly assigned to the CLND arm and 233 to the observation arm. Follow-up compliance was similar. Per-protocol analysis excluded 39 patients as 36 in the CLND

arm did not undergo CLND and three patients in the observation arm underwent CLND.

Patient and tumor characteristics were well balanced (Data Supplement). Median patient age was 54 years (IQR, 45-66.5 years) and median tumor thickness was 2.4 mm (IQR, 1.6-4.0 mm) in both groups, and 286 (60.5%) of 473 patients had a tumor thickness of greater than 2.0 mm. Ulceration was absent in 288 (60.9%) of 473 patients. In 92 (31.9%) of 288 patients, ulceration status was unknown. Median number of excised SLNs was 2.0, and 435 (92.0%) of 473 patients had one positive SLN. One hundred forty-four (30.4%) of 473 patients had single cells or metastases of less than 0.5 mm, 167 (35.3%) of 473 had metastases of 0.5 to 1.00 mm, 91 (19.2%) of 473 had metastases of 1.01 to 2.0 mm, and 30 of (6.3%) 473 had metastases greater than 2.00 mm. Adjuvant IFN-α was administered in 288 (60.9%) of 473 patients. Patients were classified according to the 8th American Joint Committee on Cancer (AJCC) staging system[12]; 150 (31.7%) of 473 patients were classified into stage IIIA, 122 (25.8%) of 473 into stage IIIB, and 201 (42.5%) of 473 into stage IIIC. Imaging techniques in follow up were well balanced: 97 (41.6%) of 233 of patients in the observation arm received a computed tomography scan of the thorax versus 95 (39.6%) of 240 in the CLND arm, and 98 (42.1%) of 233 of

FIG 1. Trial profile (flowchart) shows the design and enrollment in the trial. Ten randomly assigned patients had to be excluded from the intention-to-treat population as a result of age (> 75 years, n = 1), localization at the neck (n = 3), macrometastases in the sentinel lymph node (SLN) biopsy (n = 5) with involvement of the entire lymph node with extracapsular extension, and secondary cancer (breast cancer; n = 1). CLND, complete lymph node dissection.

patients in the observation arm received a computed tomography scan of the abdomen versus 100 (41.8%) of 240 in the CLND arm.

In 59 (24.5%) of 240 patients who underwent CLND, no additional information on positive non-SLN (NSN) status was available. Of the 181 patients with additional details, 33 (18.2%) had one positive NSN, 10 (5.5%) had two or more positive NSNs, and 138 (76.2%) had no positive NSNs. Median number of NSNs in the CLND arm was 11.0, and more than 10 lymph nodes were excised in 91 (37.6%) of 242 patients. As NSN status is required for the current AJCC classification, we assessed the number of many patients in the CLND arm whose disease was upstaged on the basis of on NSN status. According to the 8th AJCC classification, three (1.7%) of 181 patients were upstaged by CLND: one patient from stage IIIA to stage IIIC and two patients from stage IIIB to stage IIIC.

Outcome Analyses

Melanoma-related death occurred in 116 (24.5%) of 473 patients: 57 (24.5%) of 233 in the observation arm and 59 (24.6%) of 240 in the CLND arm. One patient (0.2%) died of a different cancer and 16 (3.4%) of 473 of other diseases. We noted recurrences in 166 (35.1%) of 473 patients: 80 (34.3%) of 233 in the observation arm and 86 (35.8%) of 240 in the CLND arm (Table 1). Of these patients, 64 (13.6%) of 473 developed regional lymph node recurrences: 38 (16.3%) of 233 in the observation arm and 26 (10.8%) of 240 in the CLND arm. Distant metastasis occurred in 114 (24.1%) of 473 patients: 52 (22.3%) of 233 in the observation arm and 62 (25.8%) of 240 in the

CLND arm. Of 64 patients with regional lymph node recurrence, 41 (64.1%) of 64 developed distant metastases in the additional course: 22 (57.9%) of 38 in the observation arm and 19 (73.1%) of 26 in CLND arm.

Five-year DMFS rate was 64.9% (90% CI, 59.3% to 70.5%) in the CLND arm and 67.6% (90% CI, 62.1% to 73.1%) in the observation arm (HR, 1.08; 90% CI, 0.83 to 1.39; $P = .65$; Fig 2). Compared with the primary analysis, the number of events increased from 109 to 164 events, but the HR for DMFS was comparable (3-year DMFS: HR, 1.03; 90% CI, 0.71 to 1.50; $P = .87$). As a result of the increasing event rate, we also performed a two-sided statistical analysis (95% CI, 0.79 to 1.46). Results for the per-protocol population (N = 434) and for the as-treated population were similar (HR, 1.14; 90% CI, 0.88 to 1.49; $P = .42$; and HR, 1.19; 90% CI, 0.92 to 1.54; $P = .27$) for DMFS.

The five-year OS rate was 72.3% (90% CI, 67.0% to 77.6%) in the CLND arm and 71.4% (90% CI, 66.1% to 76.7%) in the observation arm (HR, 0.99; 90% CI, 0.74 to 1.31; $P = .94$; Fig 2). The five-year RFS rate was 59.9% (90% CI, 54.3% to 65.6%) in the CLND arm and 60.9% (90% CI, 55.3% to 66.5%; HR 1.01, 90% CI, 55.3% to 66.5%, P = .94) in the observation arm (Fig 2).

Subgroup analysis according to the tumor load in the SLN was performed for DMFS comparing both treatment arms. HRs (1.12 in patients with micrometastases ≤ 1.0 mm and 0.98 in patients with micrometastases > 1.0 mm) were similar (Fig 3).

Table 2 lists the multivariable proportional hazards regression analysis for DMFS, OS, and RFS. All variables in

TABLE 1. Follow-Up Time, Recurrences, and Cause of Death in the Intention-to-Treat Population

Variable	Observation (n = 233)	CLND (n = 240)	Total (N = 473)
Median follow-up time, months (IQR)	74.0 (55-96)	66.0 (50-97)	72.0 (67-77)
Recurrences, No. (%)			
Total	80 (34.3)	86 (35.8)	166 (35.1)
Regional LN without distant recurrence	16 (6.9)	7 (2.9)	23 (4.9)
Regional LN and distant recurrence	22 (9.4)	19 (7.9)	41 (8.7)
Distant without regional recurrence	30 (12.9)	43 (17.9)	73 (15.4)
Other	12 (5.2)	17 (7.1)	29 (6.1)
Cause of death, No. (%)			
MM	57 (24.5)	59 (24.6)	116 (24.5)
Other malignancy	1 (0.42)	0 (0.00)	1 (0.2)
Other disease	9 (3.9)	7 (2.0)	16 (3.4)

NOTE. For recurrences, more than one type of recurrence could occur in one patient. The distribution of recurrences and cause of death is given as purely descriptive. The total number of patients with LN recurrences is 34 (14.6%) in the observation arm and 20 (8.3%) in the complete lymph node dissection (CLND) arm. The total number of patients with distant recurrences is 43 (18.6%) in the observation arm and 42 (17.5%) the CLND arm. In patients who died of melanoma, no date of recurrence was documented before death in six of 38 in the observation arm and in eight of 36 in the CLND arm. In one of 36 patients in the CLND arm, the kind of recurrence could not be specified; therefore, this patient was excluded from the distant metastasis-free survival analysis.

Abbreviations: CLND, complete lymph node dissection; IQR, interquartile range; LN, lymph node; MM, melanoma.
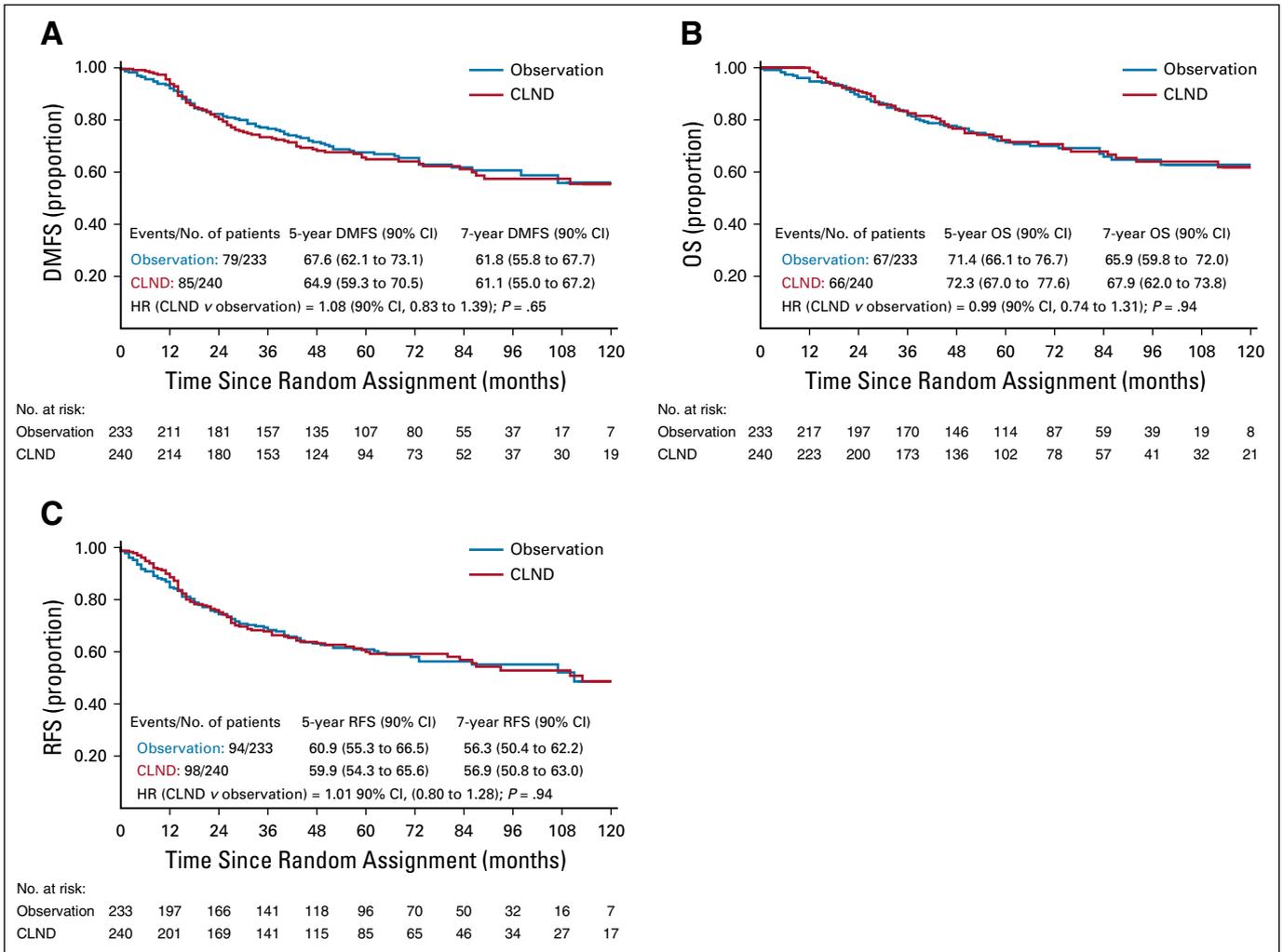
FIG 2. Analysis of (A) distant metastasis-free survival (DMFS), (B) overall survival (OS), and (C) recurrence-free survival (RFS) in the intention-to-treat population consisting of 473 patients. The observation arm is shown as a blue line and the complete lymph node dissection (CLND) arm is shown as a red line. HR, hazard ratio.

the Data Supplement were assessed for prognostic value, but only factors significant in univariable analysis with a one-sided P value of less than .1 (data not shown) were included in the multivariable model. HR estimates are listed in Table 2 on the basis of 473 patients. Tumor load in the SLN and tumor thickness were significant prognostic factors for DMFS, OS, and RFS, whereas CLND, the number of positive SLNs, nodal characteristics, and adjuvant IFN therapy were not. Ulceration, including unknown values, was a significant prognostic factor for DMFS ($P = .021$) and borderline for OS ($P = .063$) and RFS ($P = .054$; Table 2). A model including age and gender is shown in the Data Supplement. No significant interactions were noted between treatment group and any of the other factors. In addition, N status (N1a to N3a) according to the 8th AJCC staging criteria on the basis of the number of positive SLNs was not a prognostic factor (data not shown). We detected no evidence of heterogeneity of HRs across subgroups defined by prognostic factors. HR for DMFS for CLND versus observation in the multivariable

proportion hazards regression analysis was 1.19 (90% CI, 0.83 to 1.69; $P = .43$) and thus the originally expected HR of 0.70 for CLND, which was the assumption for the sample size calculation, was rejected.

As the NSN status was reported to be a significant prognostic factor in the CLND arm in the MSLT-II study, we included this variable in a multivariable model on the basis of 170 of 207 patients treated with CLND with nonmissing data (Data Supplement). NSN status failed to be a prognostic factor for DMFS ($P = .41$), OS ($P = .50$), and RFS ($P = .51$) in our analysis. In addition, we calculated a Cox proportional hazards regression model for the prognostic factors indicated in the MSLT-II study. Here, the studies showed overlapping confidence intervals (Data Supplement).

DISCUSSION

The final analysis of the randomized prospective German multicenter phase III study comparing CLND with observation
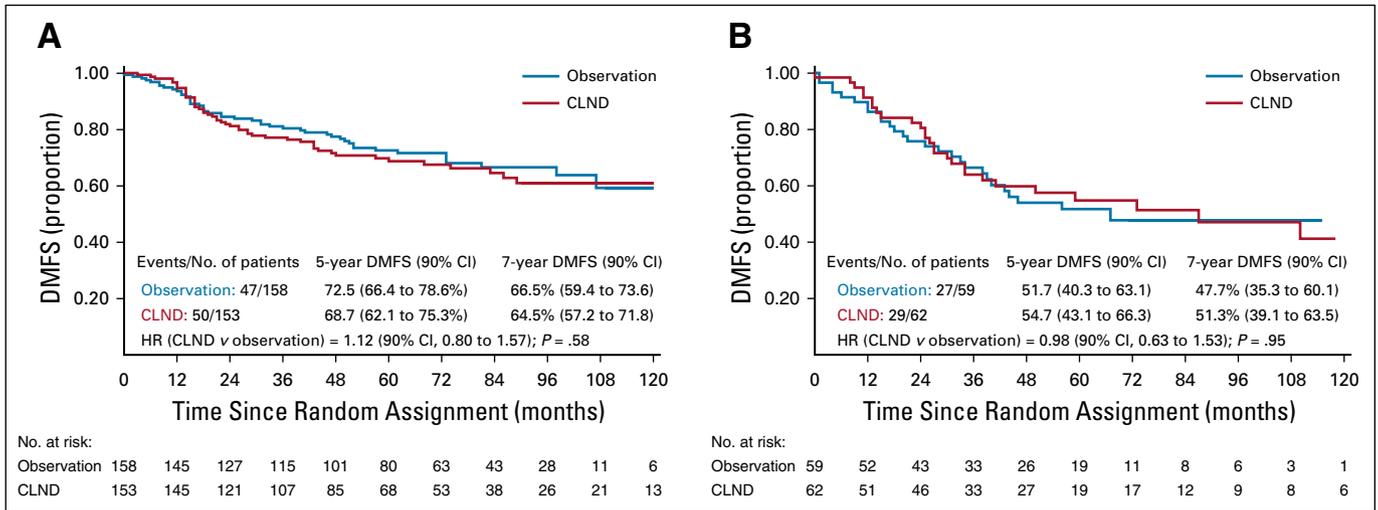
FIG 3. Subgroup analysis of distant metastasis-free survival (DMFS) according to tumor load in the sentinel lymph node, observation arm (blue line), and complete lymph node dissection arm (red line). (A) Tumor load of 1.0 mm or less and (B) tumor load of more than 1.0 mm in the intention-to-treat population of 473 patients. HR, hazard ratio.

in SLN-positive patients provides additional evidence that CLND is not associated with any survival benefit in terms of the primary end point DMFS and likewise in RFS and OS after a median follow up of 72 months. In multivariable analysis, the type of treatment (CLND v observation) was not an independent significant prognostic factor for DMFS, OS, and RFS. We observed a slight improvement in the disease control rate in the regional lymph node basin of 10.8% in the CLND arm compared with 16.3% in observation arm, though not significantly different.

Our final analysis confirmed that CLND was not superior to observation in patients with metastasis in the SLN. Our initial results of the 3-year analysis were supported by the large prospective randomized phase III trial, MSLT II.[9] The MSLT-II per-protocol analysis included 1,755 patients with metastases in the SLN, 824 in the dissection arm, and 931 in the observation arm. Mean 3-year MSS rate was similar in the dissection and observation arms (86% and 86%, respectively; P = .42) at a median follow up of 43 months. The 3-year RFS rate was slightly higher in the dissection arm than in the observation arm (68.7% and 63%, respectively; P = .05).[9]

In multivariable analyses, tumor load in the SLN, tumor thickness, and ulceration were associated with a higher risk of distant metastases, recurrences, and death (Table 2). Ulceration was not reported in 92 patients. It is known that some pathologists in the participating centers do not report on ulceration status when ulceration is absent, not because it is unknown. As an unknown ulceration had better outcomes than absent ulceration in DMFS, OS, and RFS, it seems obvious that most patients with unknown ulceration indeed have absent ulceration. As a result of the number of unknown ulceration status, ulceration is borderline significant in the Cox proportional hazards regression model for OS and RFS.

TABLE 2. Multivariable Proportional Hazards Regression Analysis of DMFS, OS, and RFS

Variable	DMFS		OS		RFS	
	HR (90% CI)	P	HR (90% CI)	P	HR (90% CI)	P
Treatment group (observation v CLND)	1.09 (0.79 to 1.50)	.622	0.95 (0.70 to 1.36)	.795	1.01 (0.75 to 1.36)	.941
Tumor load in the SLN, mm (single cells and micrometastases ≤ 1 v 1)	1.72 (1.23 to 2.40)	.001	2.21 (1.55 to 3.17)	< .001	1.60 (1.18 to 2.19)	.003
Tumor thickness, mm (≤ 2 v > 2)	2.15 (1.44 to 3.21)	< .001	2.26 (1.45 to 3.52)	< .001	2.28 (1.57 to 3.31)	< .001
Ulceration (no v yes, no v unknown)		.021		.063		.054
Yes	1.38 (0.95 to 1.99)	.089	1.27 (0.85 to 1.90)	.246	1.40 (0.99 to 1.98)	.055
Unknown	0.72 (0.43 to 1.21)	.212	0.67 (0.38 to 1.19)	.170	0.91 (0.57 to 1.44)	.679
No. of positive SLNs (1 v ≥ 2)	0.85 (0.44 to 1.62)	.616	1.00 (0.51 to 2.00)	.991	0.84 (0.47 to 1.53)	.572
Interferon therapy (no v yes)	0.93 (0.70 to 1.30)	.682	0.79 (0.55 to 1.40)	.209	0.94 (0.69 to 1.27)	.669

Abbreviations: CLND, complete lymph node dissection; DMFS, distant metastasis-free survival; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival; SLN, sentinel lymph node.

The question arises as to whether patients with a higher tumor burden in the SLN will potentially benefit from CLND. In the DeCOG-SLT study, 311 (65.8%) of 473 patients had metastases of 1 mm or less and 162 (34.2%) of 473 patients had metastases of more than 1 mm. Subgroup evaluation showed no effect of CLND on survival in both groups. In the MSLT-II trial, the proportion of patients with a tumor load in the SLN of 1 mm and less was 66%.[9] Similarly, forest plots showed no influence of CLND on survival in patients with low and high tumor burden in the SLN. For this reason, neither of the two studies can conclude that CLND is indicated for patients with a higher tumor burden in the SLN (Data Supplement).

As expected, fewer regional lymph node recurrences occurred in the CLND arm compared with the observation arm (26 [10.8%] of 240 v 38 [16.3%] of 233; Data Supplement). However, the occurrence of distant metastases in the additional course was not influenced by this. Patients with regional lymph node recurrences developed distant metastases in 22 (58%) of 38 patients in the observation arm and in 19 (73%) of 26 patients in the CLND arm. This is also reflected by the MSLT-II study in which CLND after a positive SLN improved local disease control, but did not increase MSS.[9]

CLND is associated with a higher morbidity than SLNB.[13-16] In the current study, only adverse effects in the CLND arm were recorded. Of 240 patients, 58 (24%) developed adverse effects after CLND, of these 32 (13%) of 240 patients developed grade 3 and 4 toxicity. Lymph edema was the most frequent grade 3 and 4 toxicity reported in 20 (8.3%) of 240 patients. Previously reported rates range from 23% to 61%.[17] In addition, it was reported that patients undergoing CLND in the axilla after axillary SLNB had more problems than those who underwent SLNB alone in the axilla or groin.[18]

In the CLND arm, information about NSN status was available in 181 (75.4%) of 240 patients. NSNs were involved with tumor in 24% of patients with available data. In addition, regional LN metastases were found in the additional course of 10.8% so that 35% of patients in the CLND arm seem to have NSN metastasis. In contrast, regional lymph node recurrences occurred in 14.6% in the observation arm; however, there are no data on how often NSN micrometastases can develop to macrometastases in the additional course. Nodal recurrences could have been underrecognized as only 65.7% had 10 or more nodes resected in the CLND arm. In the study protocol, a minimum of six lymph nodes had to be excised in a CLND performed in the inguinal region and at least 10 in the axillar region. Of 181 patients from whom information on the number of resected nodes in the CLND was available, 59.8% had a CLND in the axillar region and 39.2% in the inguinal region. In the axillar region, 10 or more nodes were resected in 75% of patients and in the inguinal region six or more nodes were resected in 84.5% of patients. In addition,

many patients underwent treatment with adjuvant IFN, and in some patients distant metastases could occur before regional recurrences were evident. The follow up of a median of 72.5 months could have been too short for the manifestation of all macrometastases in the NSN, as they may have a longer latency period.[11] Therefore, an approach of the two arms regarding the lymph node metastases could take place only in the additional course. Of 240 patients, information on NSN status was unavailable for 59 (24.5%) and of these, 36 refused CLND (classified as protocol violators) and 23 patients had missing values. NSN status was not a planned end point of the current study. Information on NSN was reported subsequently and is therefore incomplete. The rate of positive NSN is similar to other studies (12% to 20% NSN positivity).[19]

In the MSLT-II study, NSN metastasis was identified in 11.5% in the CLND arm and was a strong prognostic factor for relapse (HR, 1.78; $P = .005$).[9] To evaluate this observation in the current data set, we analyzed the prognostic value of NSN status (positive v negative) in a multivariable model where it failed to be an independent significant prognostic factor.

This final analysis demonstrates that CLND is not associated with a survival benefit and should therefore not be routinely performed considering the potential morbidity. In contrast, it could be argued that CLND should not be omitted as it might be valuable for prognosis and adjuvant therapy treatment decisions.[9] In the DeCOG study, NSN positivity was observed in 25% of patients, resulting in upstaging according to the AJCC 8th edition in approximately 2% of patients. These results disempower the arguments not to omit CLND. In addition, it was reported previously that tumor load in the SLN— a factor retrieved from solely performing an SLNB—is a predictor for NSN positivity[20]; therefore, tumor load in the SLN can be used as an alternative factor for classifying SLN-positive patients. Stratifying patients according to ulceration and tumor load results in four different groups with similar discrimination for MSS compared with stratifying by AJCC subgroups.[12] We therefore stratified patients into these four groups, which resulted in similar curves for DMFS and thus supports this classification (Data Supplement).

There are some limitations in this study. We overestimated the number of events in our sample size calculation as data on the survival of patients with SLN metastases were not available. We aimed to improve 3-year DMFS from 60% to 70%, but the 3-year DMFS rates were 77.0% for the observation arm and 74.9% for the CLND arm. Thus, the prognosis of patients with SLN metastases was clearly better than expected. We estimated 192 distant metastatic events after 3 years of follow up; however, we observed 164 events after 5 years. Compared with the original protocol, we still lack events but the current power is 74% (instead of the desired 80%).

Accrual was terminated early when 483 of the originally planned 556 patients were randomly assigned, as accrual was much lower than expected. Only every third patient with a positive SLN met the inclusion criteria or agreed to random assignment instead of the 66% as anticipated. Other studies had similar problems; the MSLT-II study extended the accrual period for an additional 3 years.[9]

In summary, CLND does not prolong survival in terms of DMFS, RFS, or OS in SLN-positive patients. As a therapeutic benefit for CLND could not be demonstrated, there is a question of whether CLND has prognostic significance. Therefore, the recommendation of CLND has to be discussed with caution, especially as new, promising adjuvant treatment modalities are available.

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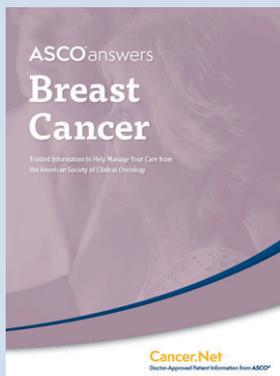**Manuscript writing:** All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node

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