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Complete lymph node dissection in cutaneous melanoma patients with positive sentinel lymph node: Outcome and predictors in a retrospective cohort study over 16 years

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Abstract *Background:* In melanoma treatment, complete lymph node dissection (CLND) has been considered the therapeutic gold standard in patients with positive sentinel lymph node biopsy (SLNB). This long-held approach was revised in 2017, with recent evidence questioning the therapeutic benefit of CLND in malignant melanoma (MM) therapy. In this study, we aimed to fill this knowledge gap by retrospectively analyzing the impact of CLND on MM patients' survival. Methods: We retrospectively analyzed the multi-center population-based Clinical Cancer Registry at the Tumor Center Regensburg (TUDOK) database (2004–2020) to identify

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Recurrence-free survival

patients who had been diagnosed with SLN-positive MM and underwent (non)invasive management thereof. Patient cohorts were subdivided according to the treatment received (CLND and waiving CLND). Primary outcomes included overall survival (OS), recurrence-free survival (RFS), and cumulative recurrence rate. Results: We identified 1143 MM patients, of whom 126 (11.0%) had positive SLN status. CLND was waived in the majority of SLN-positive MM cases (n = 71; 56.3%), with 55 (43.7%) patients undergoing CLND. Univariable and multivariable Cox regression revealed no significant advantage for CLND patients compared to non-CLND patients in OS (HR=0.970, p = 0.915 and HR=1.295, p = 0.479, respectively), RFS (HR=1.050, p = 0.849 and HR=1.220, p = 0.544, respectively), and cumulative recurrence rate (HR=1.234, p = 0.441 and HR=1.220, p = 0.544), respectively). Conclusion: We found that CLND had no significant impact on patient survival and MM recurrence rate, thus corroborating the validity of current clinical guidelines.

Malignant melanoma (MM) constitutes a leading cancer diagnosis in the developed world, creating a persisting public health burden. Over the past four decades, the global incidence of MM has increased substantially, affecting more than one million patients (5-year prevalence).[1] Especially in developed and fair-skinned countries, such as Germany, the number of diagnosed MM cases is steadily growing.[2] Albeit the 5-year survival of MM patients has risen to over 90%, stage IV diseases are still associated with a dismal prognosis.[3] It is, therefore, imperative to investigate risk factors and optimize MM treatment outcomes.

Previously, the status of regional lymph nodes in MM patients has been identified as reliable predictor of tumor control and patient survival, with the presence of nodal disease (at initial diagnosis) being the most significant risk indicator for increased mortality in MM patients.[4,5] In 1992, Morton and colleagues introduced a groundbreaking method, aiming to detect occult regional metastases.[6] This so-called sentinel lymph node biopsy (SLNB) is commonly performed in MM with a Breslow thickness of more than 1.0 mm. In case of ulceration, high mitosis index, and patient age under 40 years SLNB is also recommended for MM with a Breslow thickness from 0.8 mm.[7,8] Over the last three decades, SLNB has established as an efficient alternative to the preventive removal of unsuspicious regional lymph nodes (i.e., elective lymph node dissection), particularly in early-stage MM. In this context, it is important to note that elective lymph node dissection is associated with a plethora of adverse events and essentially no therapeutic benefit.[9,10] By contrast, SLNB is an evidence-based diagnostic procedure to determine the prognosis in MM. These findings were underscored by the Multicenter Selective Lymphadenectomy Trial (MSLT-I).[11-14]

Originally, SLNB served as a procedure to assess patients' eligibility for subsequent CLND. However, long-term clinical experience and a robust body of evidence revealed that most patients with metastases in sentinel lymph nodes (SLN) had no metastases in non-SLN, thus rendering CLND redundant for this specific use case. Recent data from the MSLT-II and the German Dermatologic Cooperative Oncology Group Trial (DeCOG-SLT), as well as the comprehensive, retrospective study by Bilimoria et al. validated these observations and led to an adjustment of the clinical practice guidelines.[15-17] The reworked guidelines suggest continuous observation of the regional lymph nodes.[14,16]

Our aim was to investigate the clinical-therapeutic value of CLND in a long-term multi-center study. Ultimately, this line of research may provide further insight into prognostic parameters of survival and tumor recurrence.

Methods

Data source and patient selection

In this population-based multicenter cohort analysis, data of primarily resected MM patients were extracted from the Clinical Cancer Registry at the Tumor Center Regensburg (TUDOK), Bavaria, Germany. All included cases have been newly diagnosed with MM and received initial therapy with curative intent within a 17-year period between January 1st, 2004, and December 31st, 2020. The TUDOK database is a regional, multi-institutional, and high-quality catalog of tumor patients, covering a population of around 2.3 million inhabitants of the regions from Lower Bavaria to Upper Palatinate. Patient data were collected from the University Hospital Regensburg, more than 50 regional hospitals, and approximately 1500 private practices.

Variable extraction

Clinical and histopathological variables were extracted from electronic and written medical records. Patient characteristics included (i) patient demographics, such as age and gender, and (ii) other diagnostic factors, including the year of diagnosis, family history, and previous tumor diseases. Tumor characteristics were defined as tumor localization (i.e., International Statistical Classification of Diseases and Related Health Problems [ICD]-10 diagnosis), histological subtype, TNM classification, Union for international cancer control (UICC) stage, and tumor thickness

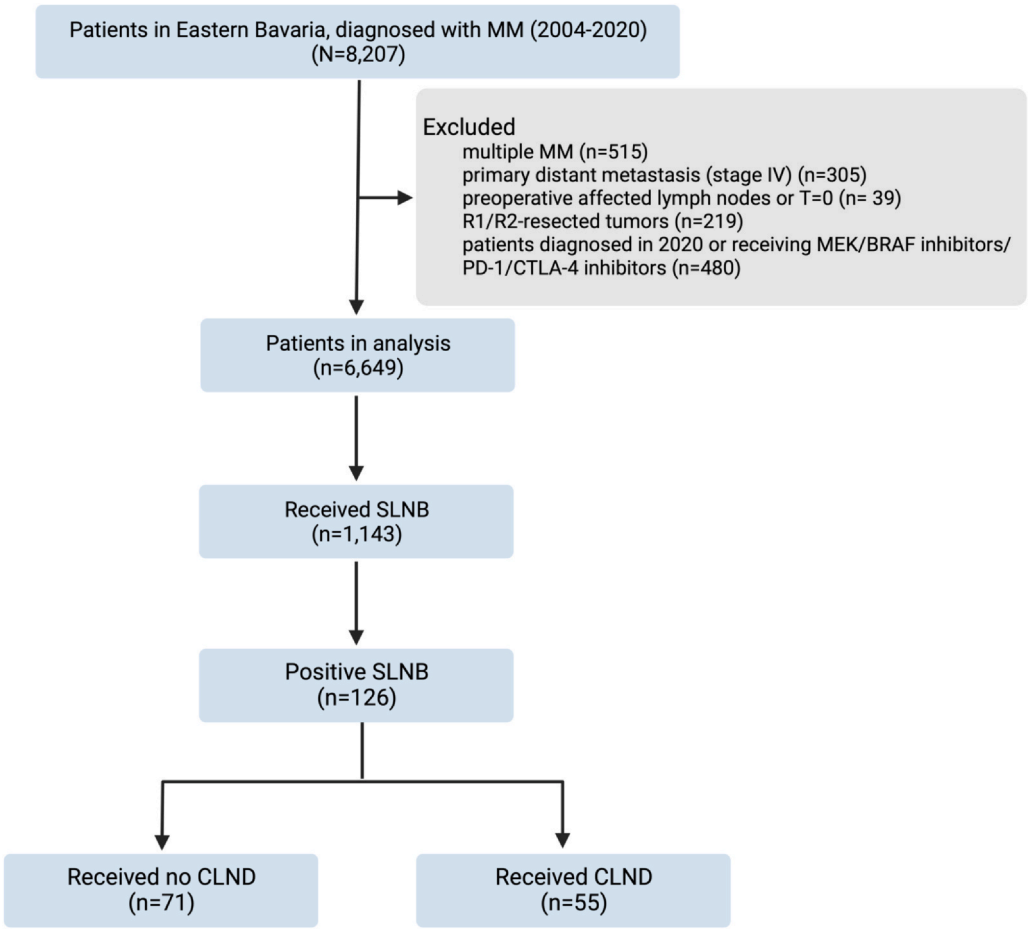


Figure 1 Study profile (flow chart). 1180 patients were excluded from the initial study population because of the occurrence of multiple MM, distant metastasis at primary diagnosis, preoperative affected lymph nodes, missing identification of primary melanoma (i.e., T = 0), R1/R2-resected tumors, diagnosis in 2020, and receiving MEK/BRAF inhibitors, or PD-1/CTLA-4 inhibitors.

in mm. Moreover, details on (additional) treatment and surgical variables (e.g., resection margin) were collected. In terms of outcomes, follow-up data, such as actual life status and death certificates, were retrieved directly from the regional registration offices to complement the databank of the Quality Management and Health Services Research of the University Hospital of Regensburg. Disease relapse was defined by local tumor recurrence or distant metastasis, which were diagnosed via radiological imaging with clinical correlation or histologic confirmation. Based on these follow-up variables, overall survival (OS), cumulative recurrence rate (i.e., overall recurrence rate including local, regional, and distant recurrence), and recurrence-free survival (RFS) were estimated.

Cases with secondary MM, UICC stage IV, preoperatively affected lymph nodes, and R1/R2-resected tumors were excluded. Patients diagnosed in 2020 were excluded from the study cohort because of biases caused by surgery curtailment during the COVID-19 pandemic. To overcome treatment bias, patients receiving adjuvant checkpoint-inhibitor therapy and targeted therapy were also excluded. Figure 1 illustrates the flow diagram of the screening and selection process. Tumor staging was performed manually and according to the eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging.[18] While adjuvant therapy in the form of adjuvant radiation, immunotherapy, and/or interferon therapy was administered based on the recommendation of a multidisciplinary tumor board, only adjuvant interferon therapy was included in multivariable analysis. Patient data were encoded via pseudonymized numbers, justifying this analysis as non-human subject research.

Statistical analysis

Data were analyzed with IBM SPSS Statistics Version 28.0 (IBM Corp., Armonk, N.Y., USA). Continuous variables are reported as means with standard deviations and were analyzed with Student's t-tests in case of log-normal distribution. Otherwise, Mann-Whitney U-test was used. Categorical variables were

Table 1 Patient characteristics according to CLND (n = 126).

		CLND						
		Yes		No		Total		X^2
		Count	(%)	Count	(%)	Count	(%)	p
Sex	Male	39	70.9%	43	60.6%	82	65.1%	0.227
	Female	16	29.1%	28	39.4%	44	34.9%	
Age at diagnosis	Median	52.397 + 14.537		57.177 + 15.656		56.252 + 15.651		
	< 50	22	40.0%	23	32.4%	45	35.7%	0.748
	50–59	13	23.6%	17	23.9%	30	23.8%	
	60–69	8	14.5%	10	14.1%	18	14.3%	
	70+	12	21.8%	21	29.6%	33	26.2%	
Year of diagnosis	2004–09	18	48.7%	19	51.3%	37	100%	0.027
	2010–14	26	54.2%	22	45.8%	48	100%	
	2015–19	11	26.8%	30	73.2%	41	100%	
Family history	Yes	14	25.5%	16	22.5%	30	23.8%	0.703
	No/unknown	41	74.5%	55	77.5%	96	76.2%	
Previous tumor diseases	Yes	4	7.3%	12	16.9%	16	12.7%	0.107
	No/unknown	51	92.7%	59	83.1%	110	87.3%	
	Total	55	100.0%	71	100.0%	126	100.0%	

analyzed for their independence with Pearson's Chi-square. Statistical significance was set at p values < 0.05. OS, RFS, and cumulative recurrence rates were calculated from the date of primary tumor resection to the date of first recurrence, the date of death from any cause, or the date of last survival until the cut-off date of December 31st, 2021. Patients, who were alive after the cut-off date or had missing follow-ups, are reported as censored cases. Kaplan-Meier and Cox-regression methods were used for survival analysis. The log-rank test was calculated to assess differences in outcome estimates. To investigate the impact of CLND and other risk factors on OS and RFS, univariable and multivariable Cox regression were performed for the entire study cohort and subgroups. Results were reported as hazard ratios (HR) and 95% confidence intervals (CI).

Results

Patient and tumor characteristics

The study population included 1143 MM patients who underwent SLNB over a 16-year review period between 2004 and 2019. Of these, 126 (11.0%) had positive SLN status. CLND following a positive SLNB was performed in 55 patients, and CLND was not performed in 71 patients. More than one-third of MM was located at the trunk (n = 49, 38.2%), while 51 cases were histopathologically classified as nodular melanoma (40.5%). The resection margin at excision of the primary tumor exceeded 1 cm in the majority of cases (n = 65, 51.6%). Adjuvant interferon therapy was given to 33 patients (26.2%). Table 1 and Table 2 present patient demographics and tumor characteristics of the total study population.

In terms of prognostic factors (such as age, sex, family history), we found no significant differences between patients with versus without CLND following positive SLNB. CLND was performed significantly more frequently between 2004 and 2014 than at later time stamps (p = 0.027) (Figure 2).

Survival analysis

While a total of 49 patients died during the study period, tumor recurrence was recorded in 54 cases. The mean follow-up was 5.6 years (median: 5.2 years). The 5-year OS was 67.1% for the CLND group and 65.2% for the non-CLND group (Figure 3). Multivariable Cox regression (HR = 1.295, 95% CI: 0.632–2.653, p = 0.479) revealed that CLND had no significant impact on patient survival. In addition, poorer OS among patients with CLND was also seen in the subgroup of patients diagnosed between 2010 and 2014 (HR = 7.531, 95% CI: 1.317–43.064, p = 0.023). Table 4 and Table 5 present multivariable survival analyses of OS for MM patients according to accomplished CLND.

No significant correlation between CLND performed and recurrence rate was found in the multivariable Cox regression (HR = 1.773, 95% CI: 0.858–3.666, p = 0.122). Analyzing recurrence rates in subgroups, patients

Table 2 Tumor characteristics according to CLND (n = 126).

		CLND						x^2
		Yes		No		Total		p
		Count	(%)	Count	(%)	Count	(%)	
Localization (ICD-10)	Trunk (C43.5)	21	38.2%	28	39.4%	49	38.2%	0.097
	Face/Neck (C43.0-4)	2	3.6%	6	8.5%	8	6.3%	
	Upper extremities (C43.6)	15	27.3%	8	11.3%	23	18.3%	
	Lower extremities (C43.7)	17	30.9%	29	40.8%	46	36.5%	
Side	Left	21	38.2%	38	53.5%	59	46.8%	0.103
	Right	29	52.7%	24	33.8%	53	42.1%	
	Middle/unknown	5	9.1%	9	12.7%	14	11.1%	
Histological subtype	Superficial spreading	11	20.0%	19	26.8%	30	23.8%	0.815
	Nodular	26	47.3%	25	35.2%	51	40.5%	
	Lentigo maligna	1	1.8%	1	1.4%	2	1.6%	
	Acral-lentiginous	2	3.6%	3	4.2%	5	4.0%	
	Amelanotic	3	5.5%	3	4.2%	6	4.8%	
	Malignant (NOS)	12	21.8%	20	28.2%	32	25.4%	
T	T1	1	1.8%	3	4.2%	4	3.2%	0.666
	T2	13	23.6%	21	29.6%	34	27.0%	
	T3	25	45.5%	26	36.6%	51	40.5%	
	T4	16	29.1%	21	29.6%	37	29.4%	
	TX	0	0.0%	0	0.0%	0	0.0%	
N	N1	38	69.1%	56	78.9%	94	74.6%	0.229
	N2	13	23.6%	11	15.5%	24	19.0%	
	N3	4	7.3%	2	2.8%	6	4.8%	
	NX	0	0.0%	2	2.8%	2	1.6%	
Tumor thickness (mm)	< 1	1	1.8%	2	2.8%	3	2.4%	0.498
	1-2	10	18.2%	19	26.8%	29	23.0%	
	2-4	25	45.5%	24	33.8%	49	38.9%	
	> 4	18	32.7%	22	31.0%	40	31.7%	
	Unknown	1	1.8%	4	5.6%	5	4.0%	
Resection margin (mm)	< 5	0	0.0%	0	0.0%	0	0.0%	0.116
	5-9	0	0.0%	0	0.0%	0	0.0%	
	> 10	24	43.6%	41	57.7%	65	51.6%	
	Unknown	31	56.4%	30	42.3%	61	48.4%	
Number of positive SLN	1	45	81.8%	61	85.9%	106	84.1%	0.532
	2	10	18.2%	10	14.1%	20	15.9%	
Adjuvant Interferon therapy	Yes	18	32.7%	15	21.1%	33	26.2%	0.142
	No	37	67.3%	56	78.9%	93	73.8%	
	Total	55	100.0%	71	100.0%	126	100.0%	

receiving no interferon-alpha therapy (HR = 3.317, 95% CI:1.187-8.289, p = 0.021) and patients diagnosed between 2010 and 2014 (HR = 3.317, 95% CI:1.187-8.289, p = 0.021) showed significantly higher tumor recurrence in multivariate analysis when they were treated with CLND. Furthermore, prognostic factors, such as tumor localization (HR=18.953, 95% CI: 3.427-104.826, p < 0.001) and age (HR = 3.319, 95% CI: 1.267-8.692, p = 0.015) had a significant impact on disease recurrence. Detailed multivariable survival analyses of the recurrence rate for MM patients (stratified by CLND performed) are listed in Table 4 and Table 5.

Regarding RFS, there were no significant differences between patients with versus without CLND (HR = 1.220, 95% CI: 0.641-2.322, p = 0.544). Subgroup analysis revealed significantly improved RFS of patients undergoing CLND among patients with MM classified as histological subtypes other than superficial spreading and nodular (HR = 0.006, 95% CI: 0.000-0.208, p = 0.005). Again, tumor localization (HR=16.409, 95% CI: 3.630-74.170,

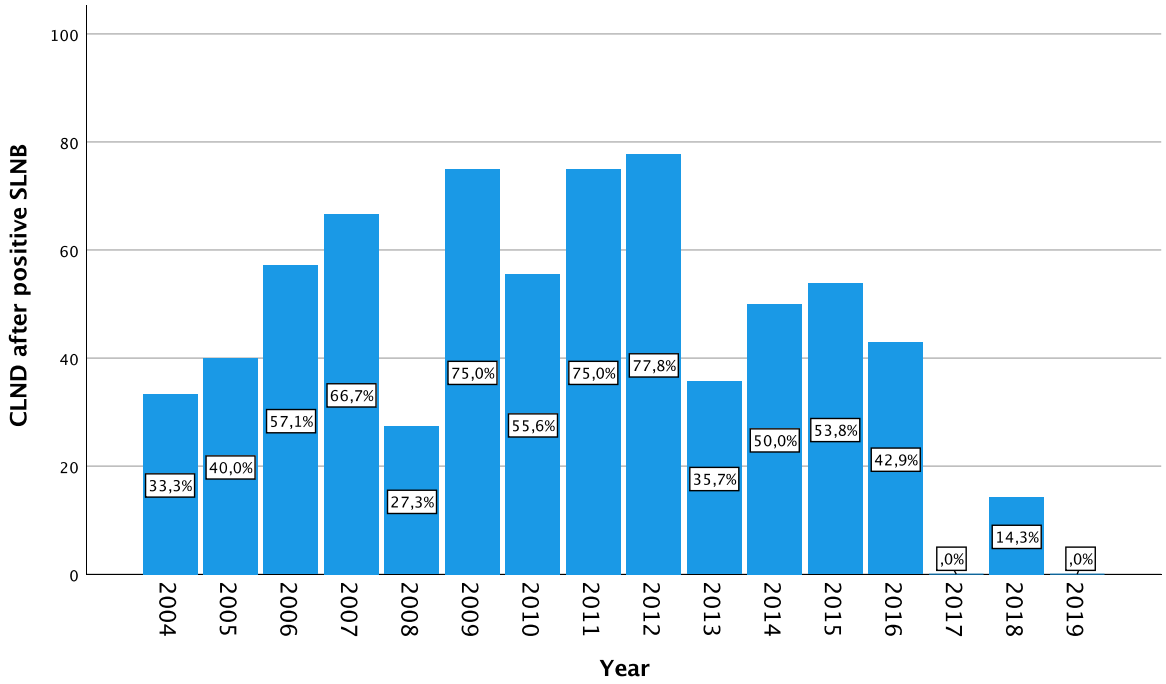
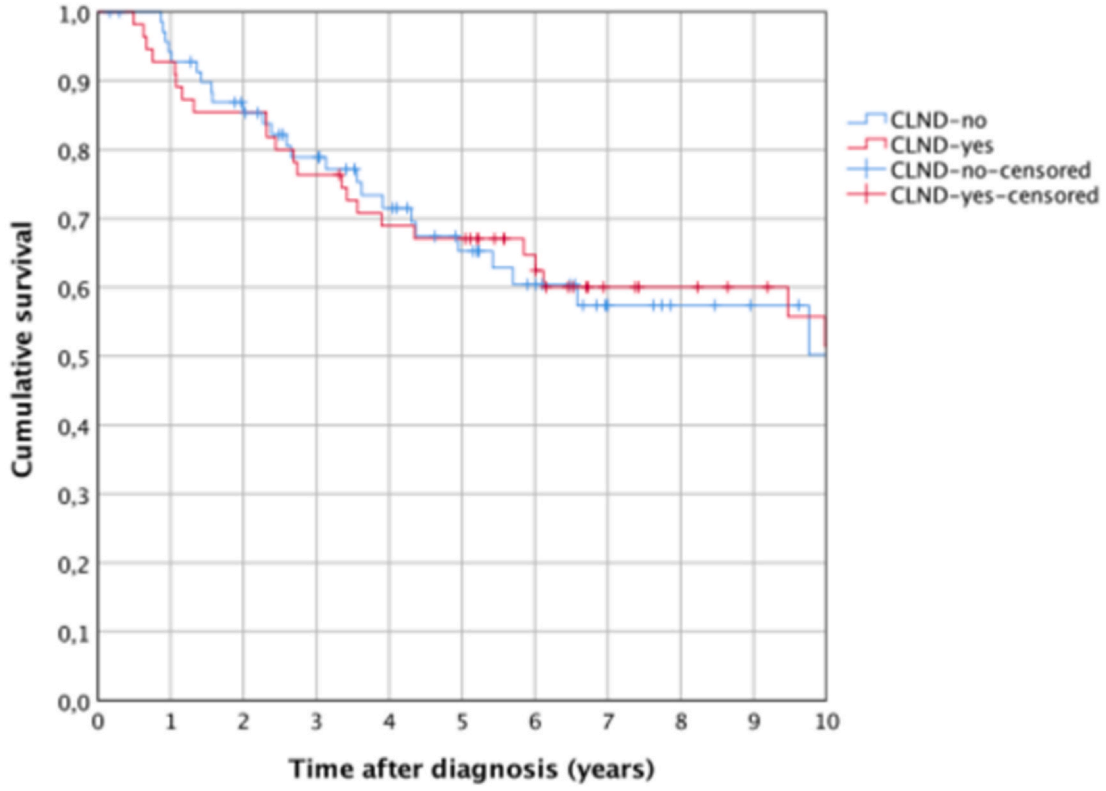


Figure 2 Proportion of cutaneous melanoma patients receiving CLND per year.



	Number of Patients	Events	5-year OS	10-year OS
CLND-no	71	25	65.2%	50.2%
CLND-yes	55	24	67.1%	51.5%

Figure 3 Survival in melanoma patients: Kaplan Meier estimates of OS in patients with and without CLND ($p = 0.915$).

Table 4 Survival analysis of OS, cumulative recurrence rate, and RFS for cutaneous melanoma patients according to accomplished CLND.

		OS				Recurrence rate				RFS			
		p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI
CLND	No		1.000				1.000				1.000		
	Yes	0.479	1.295	0.632	2.653	0.122	1.773	0.858	3.666	0.544	1.220	0.641	2.322
Sex	Male		1.000				1.000				1.000		
	Female	0.033	0.387	0.162	1.926	0.378	0.723	0.352	1.487	0.247	0.663	0.330	1.331
Age at Diagnosis	< 50		1.000				1.000				1.000		
	50-59	0.622	1.267	0.495	3.245	0.037	2.415	1.054	5.532	0.056	2.125	0.982	4.601
	60-69	0.477	0.665	0.216	2.045	0.303	0.546	0.172	1.727	0.773	0.869	0.335	2.255
	70+	0.286	1.712	0.637	4.600	0.015	3.319	1.267	8.692	0.052	2.395	0.993	5.775
Year of Diagnosis	2004-2009		1.000				1.000				1.000		
	2010-2014	0.414	0.637	0.216	1.881	0.081	0.399	0.142	1.121	0.342	0.645	0.262	1.591
	2015-2019	0.052	0.230	0.052	1.013	0.014	0.197	0.053	0.724	0.059	0.327	0.102	1.045
Family History	No/unknown		1.000				1.000				1.000		
	Yes	0.844	0.918	0.390	2.162	0.112	1.839	0.868	3.893	0.100	1.774	0.896	3.509
Previous tumor dieseases	No/unknown		1.000				1.000				1.000		
	Yes	0.036	3.318	1.082	10.174	0.720	1.237	0.387	3.950	0.416	1.512	0.559	4.088
Localization (ICD-10)	Trunk (C43.5)		1.000				1000				1.000		
	Head and Neck (C43.0-4)	0.010	9.095	1.699	48.699	< 0.001	18.953	3.427	104.826	< 0.001	16.409	3.630	74.170
	Upper extremities (C43.6)	0.623	0.754	0.244	2.325	0.826	0.877	0.271	2.841	0.786	0.867	0.310	2.424
	Lower extremities (C43.7)	0.227	1.750	0.706	4.336	0.338	1.547	0.634	3.775	0.379	1.440	0.639	3.243
Side	Left		1.000				1.000				1.000		
	Right	0.082	0.460	0.192	1.105	0.367	0.697	0.318	1.528	0.625	0.836	0.408	1.713
	Middle/Unknown	0.251	0.458	0.121	1.737	0.620	0.637	0.219	2.471	0.821	0.880	0.291	2.658
Histological subtype	Superficial spreading		1.000				1.000				1.000		
	Nodular	0.776	1.171	0.394	3.480	0.343	0.626	0.238	1.649	0.872	0.928	0.373	2.307
	Other (Lentigo maligna, Acral-lentigious, Amelanotic, Melanoma NOS)	0.728	0.822	0.271	2.489	0.057	0.359	0.125	1.033	0.294	0.595	0.225	1.571
Tumor size	T1/2		1000				1.000				1000		
	T3	0.370	2.175	0.397	11.909	0.287	3.258	0.371	28.621	0.937	0.059	0.258	4.351
	T4	0.193	4.148	0.487	35.351	0.201	5.140	0.418	63.239	0.595	1.635	0.267	10.028
Nodal status	N1		1.000				1.000				1000		
	N2	0.141	1.764	0.828	3.756	0.450	1.329	0.636	2.779	0.375	1.363	0.687	2.706
	N3	0.343	1.851	0.518	6.610	0.108	2.563	0.813	8.082	0.078	2.755	0.894	8.485
	NX	0.969	-	-	-	0.971	-	-	-	0.969	-	-	-

(*continued on next page*)

Table 4 (*continued*)

		OS				Recurrence rate				RFS			
		p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI
Tumor thickness (mm)	< 1		1.000				1.000				1.000		
	1-2	0.298	0.354	0.050	2.504	0.799	1.371	0.121	15.590	0.207	0.338	0.063	1.825
	2-4	0.456	0.412	0.040	4.246	0.825	0.710	0.034	14.865	0.519	0.523	0.073	3.747
	> 4	0.483	0.364	0.022	6.144	0.833	1.438	0.049	42.135	0.900	0.858	0.078	9.396
	Unknown	0.759	0.590	0.020	17.205	0.860	1.403	0.032	60.984	0.688	0.550	0.030	10.214
Resection margin (mm)	> 10		1.000				1.000				1.000		
	Unknown	0.624	0.788	0.305	2.039	0.158	0.513	0.203	1.296	0.383	0.691	0.302	1.583
Adjuvant Interferon therapy	No/unknown		1.000				1.000				1.000		
	Yes	0.102	0.450	0.173	1.172	0.360	1.461	0.649	3.293	0.866	1.067	0.499	2.282

"-": small number of cases.
OS, cumulative recurrence rate, and RFS were analyzed by using multivariable Cox regression (n = 126).

$p < 0.001$) was identified to be an important predictor for RFS. In a ten-year analysis, Kaplan-Meier estimates indicated that there was neither lower OS and lower RFS nor higher risk of recurrence for MM patients who did not receive CLND after positive SLNB (Figure 3 and Figure 4, and Figure 5).

Discussion

Real-world implementation of clinical guidelines with regard to CLND

The management of nodal metastases in MM patients has changed fundamentally over the past two decades. At the time of this study's completion, four years have passed since the DeCOG study was published, introducing revised guidelines on CLND, which were reaffirmed by the MSLT-II one year later. Interestingly, findings of the aforementioned trials about the efficacy of CLND following a positive SLNB were immediately implemented into the clinical workflow. In our study, one year before the DeCOG, CLND accounted for 53.8% (7/13). In the following year, however, the proportion of CLND decreased to 42.9% (3/7), and one year after publication of the MSLT II, the number of CLND eventually dropped to 14.3% (1/6). This trend of declining CLND rates was also noted internationally, as evidenced by studies from the United States, Canada, Poland, and Germany.[19-21]

While numerous population-based studies investigated the benefits of CLND in the decade prior to the dogmatic shift in clinical guidelines, there is a scarcity of research work analyzing the impact of the guideline changes through a clinical lens.[5,22] This study is the first multicenter effort to address this knowledge gap by comparing both treatment eras. Ultimately, the herein presented insights may help clinicians better understand the clinical impact and relevance of the current guidelines.

Insufficient therapeutic effects of CLND on survival and recurrence

Consistent with the landmark trials DCOG and MSLT II, we found no survival benefit of SLNB-positive patients undergoing CLND – both in OS and melanoma-specific survival (MSS) (HR=1.295, 95% CI: 0.632–2.653, $p = 0.479$).[14,16] Moreover, in the DeCOG trial, no significant differences in RFS were observed between patients with versus without CLND. In the MSLT II trial, no benefit was noted in terms of distant metastasis-free survival in the CLND arm.[14,16] Our study confirmed these findings in a population-based setting (HR=1.220, 95% CI: 0.641–2.322, $p = 0.544$).

The assumption of lacking therapeutic value of CLND following positive SLNB, which was initially revealed in the two pivotal trials, was confirmed by recent population-based studies. While the analysis of clinical data is crucial in this context, studies are often limited by their single-center design or short study periods[19,21,23-27] (Table 6). Compared to previous retrospective trials, our analysis of multicenter

Table 5 Subgroup analysis of OS, cumulative recurrence rate, and RFS for cutaneous melanoma patients receiving CLND versus waiving CLND.

		OS				Recurrence rate				RFS			
		p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI
Sex	Male	0.605	0.785	0.314	1.963	0.084	2.481	0.886	6.949	0.662	1.224	0.495	3.031
	Female	-	-	0.170	5.875	-	-	0.214	4.678	-	-	0.214	4.678
Age at Diagnosis	< 50	0.689	1.736	1.116	25.893	0.421	0.493	0.088	2.758	0.422	0.493	0.088	2.764
	50-59	-	-	0.180	5.561	-	-	0.228	4.383	-	-	0.239	4.177
	60-69	-	-	0.001	879.954	-	-	-	-	0.966	0.450	-	-
	70+	-	-	-	-	-	-	0.058	17.201	-	-	0.064	15.685
Year of Diagnosis	2004-2009	0.922	6.030	-	-		0.462	53.405	0.001	0.334	17.413	0.053	5747.058
	2010-2014	0.023	7.531	1.317	43.064	0.025	9.373	1.332	65.961	0.067	4.336	0.901	20.873
	2015-2019	0.836	0.025	-	-	0.814	105.327	-	-	0.961	4.693	-	-
Family History	No/unknown	0.138	1.930	0.809	4.606	0.152	1.997	0.776	5.139	0.273	1.591	0.694	3.646
	Yes	-	-	0.015	65.287	0.112	1.839	0.868	3.893	-	-	0.038	26.296
Previous tumor dieseases	No/unknown	0.646	1.195	0.558	2.562	0.242	1.563	0.740	3.301	0.759	1.111	0.566	2.181
	Yes	0.515	27.310	0.001	-	0.581	496.334	-	-	0.513	151.424	-	-
Localization (ICD-10)	Trunk (C43.5)	0.148	4.196	0.600	29.325	0.112	4.710	0.695	31.904	0.933	0.938	0.211	4.168
	Head and Neck (C43.0-4)	0.777	1563.414	-	-	0.633	34.377	-	-	0.803	6.490	-	-
	Upper extremities (C43.6)	-	-	0.003	371.883	0.186	43.547	0.162	-	-	-	0.012	85.869
	Lower extremities (C43.7)	0.396	0.424	0.059	3.071	0.872	1.189	0.144	9.817	0.934	0.928	0.157	5.495
Side	Left	-	-	0.373	2.680	-	-	0.360	2.779	-	-	0.380	2.633
	Right	0.697	1.346	0.301	6.009	0.015	10.964	1.579	76.144	0.020	7.727	1.377	43.374
	Middle/Unknown	-	-	-	-	0.607	-	-	-	0.371	-	-	-
Histological subtype	Superficial spreading	0.883	133.469	-	-	0.321	-	-	-	0.471	-	-	-
	Nodular	0.580	1.550	0.328	7.327	0.696	1.460	0.219	9.756	0.893	1.082	0.343	3.412
	Other (Lentigo maligna, Acral-lentigious, Amelanotic, NOS)	-	-	-	-	0.029	0.011	0.000	0.637	0.005	0.006	0.000	0.208
Tumor size	T1/2	0.710	-	-	-	0.867	0.036	-	-	0.064	0.028	0.001	1.239
	T3	0.677	1.451	0.252	8.356	0.146	4.122	0.610	27.840	0.093	4.061	0.793	20.780
	T4	0.094	0.172	0.022	1.346	0.205	2.832	0.567	14.152	0.826	1.174	0.279	4.944
Nodal status	N1	0.075	2.522	0.911	6.985	0.147	2.018	0.781	5.211	0.236	1.670	0.715	3.901
	N2	-	-	0.005	219.844	-	-	0.003	354.077	-	-	0.003	328.705
	N3	0.304	-	-	-	0.240	0.016	0.000	15.479	0.240	0.016	0.000	15.479
	NX	-	-	-	-	-	-	-	-	-	-	-	-
Tumor thickness (mm)	< 1	0.681	0.026	-	-	0.681	0.026	-	-	0.509	0.019	-	-
	1-2	0.981	0.123	-	-	0.930	0.245	-	-	0.864	0.001	-	-
	2-4	0.417	2.116	0.346	12.956	0.120	3.897	0.701	21.675	0.156	3.396	0.627	18.402
	> 4	0.273	0.390	0.072	0.444	1.796	0.400	8.064	42.135	0.717	1.316	0.298	5.808
	Unknown	0.616	434.450	-	-	0.616	434.450	-	-	0.616	434.450	-	-

(*continued on next page*)

Table 5 (*continued*)

		OS				Recurrence rate				RFS			
		p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI	p	HR*	Lower 95%-CI	Upper 95%-CI
Resection margin (mm)	> 10	-	-	0.309	3.240	-	-	0.335	2.981	-	-	0.357	2.801
	Unknown	0.682	0.729	0.161	3.308	0.765	0.799	0.183	3.486	0.219	0.496	0.162	1.517
Adjuvant Interferon therapy	No/unknown	0.541	1.306	0.555	3.072	0.021	3.137	1.187	8.289	0.377	1.421	0.652	3.097
	Yes	0.986	0.522	-	-	0.885	-	-	-	0.885	-	-	-

"-": small number of cases.
OS, cumulative recurrence rate, and RFS were analyzed by using multivariable Cox regression (n = 126).

data over 16 years corroborated previously established prognostic factors, including age, number of positive SLN, and primary site.[5,24,28]

However, this study is the first to find an increased risk of recurrence in patients receiving no interferon-alpha therapy (HR=3.317, 95% CI:1.187–8.289, p = 0.021) and patients diagnosed between 2010 and 2014 (HR=3.317, 95% CI:1.187–8.289, p = 0.021) undergoing CLND. The DeCOG-SLT suggested similar findings reporting a slight trend of higher distant metastasis-free survival (DFS) in the observation group compared to the CLND group. In contrast, studies by Faries et al. and Lee et al. show trends of improved disease-free survival in the CLND group.[29] These outcomes remain to be confirmed in larger-scale studies. Theoretically, the presented findings could be due to the fact that distant metastases were present at the time of CLND surgery, not yet identified by imaging, or the long follow-up of 67.2 months.

In addition, we found that patients suffering from MM in the face and neck region and patients older than 70 years showed an increased risk of cancer recurrence. This finding is notable in that previous evidence has shown that MM in the head and neck area is associated with reduced survival and higher tumor recurrence.[30,31]

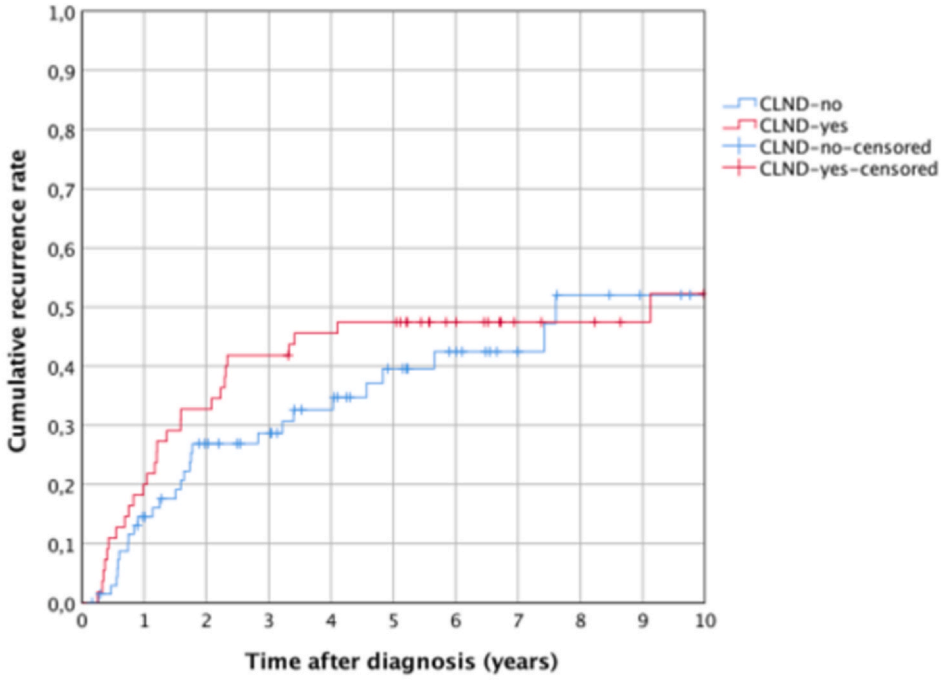
Particularly, MM of the scalp are more likely to exhibit aggressive clinicopathological features, such as increased tumor thickness due to delayed diagnosis and a higher proportion of melanomas with rapid vertical growth (i.e., nodular MM, desmoplastic MM).[32]

Further, head and neck MM underlie complex lymph drainage patterns and compact arborization in the nodal drainage. This fact and the higher density of sentinel lymph nodes in the head and neck complicate tumor control compared to other anatomical areas.[33]

In addition, this study is the first to find survival benefit of CLND in MM classified as histological subtypes other than superficial spreading and nodular MM (HR = 0.006, 95% CI: 0.000–0.208, p = 0.005). Besides Lentigo maligna (LMM), Acral-lentigious (ALM), and Amelanotic melanoma (AMM), a relatively large proportion of this subgroup is represented by Melanoma NOS.

Recent studies on the association of patient survival and histological subtype of melanoma revealed that ALM and Amelanotic Melanomas have a generally dismal prognosis with a high metastasis rate.[34] One may hypothesize that the unique histologic characteristic of the acral skin as well as the molecular signature of ALM underlie this increased ALM-related risk. Survival differences of Amelanotic melanomas can be explained by advanced stages at diagnosis. While the high rate of metastasis for these subtypes may render CLND an advisable diagnostic approach, there has been sparse research effort to investigate metastasis patterns of LLM, ALM, and AMM.

Our findings of a high percentage of melanoma NOS in our study correspond with previous research derived from population-based studies. Interestingly, one research group suggested that NOS might be a distinct genetic subtype requiring further research considering the significant association with clinical outcome.[35]



	Number of Patients	Events	5-year recurrence rate	10-year recurrence rate
CLND-no	71	27	39.6%	52.0%
CLND-yes	55	27	47.4%	52.2%

Figure 4 Survival in melanoma patients: Kaplan-Meier estimates of the cumulative recurrence in patients with and without CLND ($p = 0.440$).

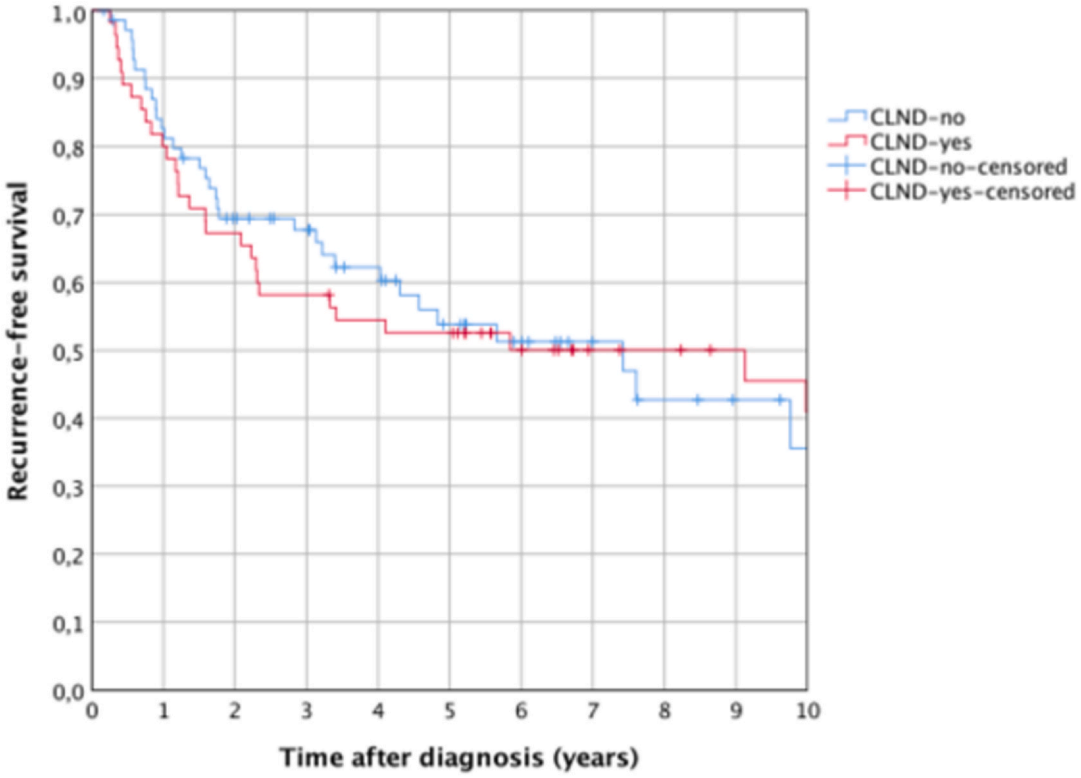
Although CLND after positive SLNB is not recommended in the current guidelines, case-by-case decisions with individual indications for CLND remain part of the routine clinical practice. In MM cases with a greater tumor burden detected in the SLN, particularly increased size of the metastasis, the procedure of CLND is still indicated.[7] In this context, the present study help identify patient subgroups that can benefit particularly from CLND.

Systemic adjuvant therapy in the post- MSLT-II /DeCOG-SLT era

Nowadays, the surgical procedure of CLND is gradually replaced by the administration of systemic adjuvant therapies, such as interferon alpha, MEK/BRAF inhibitors, or PD-1/CTLA-4 inhibitors. More specifically, MEK/BRAF inhibitors and PD-1/CTLA-4 inhibitors have shown promising therapeutic potential even in advanced MM.[36-38]

Our patient cohort represents a unique pool encompassing different possible combinations of MM therapies, thereby documenting the clinical impact of guideline updates in the last 20 years. We further excluded potential confounders such as adjuvant PD-1/CTLA-4 inhibitors and MEK/BRAF inhibitors to ensure objective assessment of CLND effects.

Adjuvant therapies were implemented into the clinical guidelines in 2017. As a consequence, there is a paucity of studies that specifically investigate the therapeutic effects of such novel treatments on OS. For example, Susok et al. found no significant difference in 10-year melanoma-specific survival between the non-CLND and CLND groups. Novel systemic therapy approaches were not listed as exclusion criteria, nor were they implemented into the survival analysis.[24] Another study reported comparable RFS rates between the non-CLND group and the CLND group without positive non-sentinel lymph nodes. While 61.6% of patients underwent PD-1-inhibitor therapy and 12.1% underwent targeted therapy,



	Number of Patients	Events	5-year RFS	10-year RFS
CLND-no	71	33	53.8%	35.6%
CLND-yes	55	29	52.6%	40.9%

Figure 5 Survival in melanoma patients: Kaplan-Meier estimates of RFS in patients with and without CLND ($p = 0.849$).

again, novel therapy options were not considered in multivariable analysis.[26] However, different studies highlighted that novel systemic treatments can significantly prolong patient survival.[36–38] Therefore, patients treated with those medications may show improved survival rates even if they do not undergo CLND. Checkpoint inhibitors and targeted therapy improve the survival of patients treated with both, novel systemic therapies and CLND. Overall, different combinations of these novel therapy approaches remain to be investigated in future randomized trials.

Limitations

The results of the study should be interpreted in light of its inherent limitations. Due to the retrospective study design, selection and indication biases in patient recruitment for CLND and adjuvant therapy represent possible confounding factors, which we accounted for by using multivariable regression methods. In particular, we performed multivariable Cox regression analyses to account for the skewed distribution of nodal disease and tumor thickness in our patient population. Although there were no significant differences in the patient cohorts in terms of clinically relevant prognostic variables, there may be unbalanced factors influencing survival, that the study did not capture. A lack of data on specific histopathological findings, such as capsular infiltration of the SLN or SLN invasion level, might have led to possible computational gaps when statistically adjusting prognostic factors for survival analysis. In addition, despite the relatively large sample size, future large-scale prospective studies are warranted to substantiate our findings.

Table 6 Overview of works analyzing survival benefits of CLND.

First author/year	Number of patients included in the analysis	Study design	Study period		CLND arm	Observation arm (OBS)	Findings
MSLT-II Faries et al. 2017	1755	randomized	2004–2014	Cohort size	824 of 1755 (47.0%)	931 of 1755 (53.0%)	
				3-year MSS	86 ± 1.3%,	86 ± 1.2%	HR 1.08, 95% CI 0.88–1.34, p = 0.42
				3-year DFS	68 ± 1.7%	63 ± 1.7%	HR 1.10, 95% CI, 0.92–1.31, p = 0.31
DeCOG-SLT Leiter et al. 2016	473	randomized	2006–2014	Cohort size	240 of 473 (50.7%)	233 of 473 (49.3%)	
				3-year OS	81.2% (76.1–86.3; 40 events)	81.7% (90% CI 76.8–86.6; 44 events)	HR 0.96, 90% CI 0.67–1.38, p = 0.87
				3-year DFS	74.9% (69.5–80.3; 54 events)	77% (90% CI 71.9–82.1; 55 events)	HR 1.03, 90% CI 0.71–1.50, p = 0.87
Van der Ploeg et al. 2012	1174	retrospective, multicenter	1993–2008	Cohort size	1113 of 1174 (95%)	61 of 1174 (5.2%)	
				3-year DSS	76·9%	74.0%	HR 0.89, 95% CI 0.58 — 1.37, p = 0.60
Susok et al. 2021	258	retrospective, single center	1999–2020	Cohort size	209 of 258 (81.0%)	49 of 258 (19.0%)	
				10-year MSS			HR 1.1, 95% CI 0.67–1.9
				20-year MSS			HR 1.3, 95% CI 0.8–2.3
Zietek et al. 2023	557	retrospective, multicenter	2017–2021	Cohort size	248 of 557 (45%)	309 of 557 (55.5%)	
				3-year OS	77.5%	81.2%	
				3-year RFS	68.5%	69.0%	
Zhong et al. 2023	130	retrospective, single center	2017–2021		99 of 130 (76.2%)	31 of 130 (23.8%)	
				2-year RFS	55.9%	78.2%	
Baecher et al.2024	126	retrospective, multicenter	2004–2019		55 of 126 (43.7%)	71 of 126 (56.3%)	
				5-year OS	67.1%	65.2%	HR 1.30, 95% CI 0.63–2.65, p = 0.48
				5-year RFS	52.6%	53.8%	HR 1.22, 95% CI 0.64–2.32, p = 0.54

Conclusion

Our multicenter 16-year analysis confirmed that waiving CLND after positive SLNB was not associated with worse outcomes in OS, RFS, or cumulative recurrence rate. Subgroup analysis revealed that patients receiving no interferon-alpha therapy and patients diagnosed between 2010 and 2014 showed higher rates of MM recurrence when undergoing CLND. Overall, we could verify the validity of current clinical guidelines on CLND using population-based clinical data.

Financial disclosure statement

Nothing to declare.

Standardized reporting guidelines

The authors adhered to the STROBE guidelines to ensure a standardized report of this cohort study.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the University of Regensburg Ethics Committee (GeschZ 23-3426-104).

Informed Consent Statement

Based on a retrospective analysis, a fully anonymized set of clinical data and in agreement with the decision of the Ethics Committee, signing an informed consent was not required.

Data Available Statement

Derived data supporting the findings of this study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Conceptualization, S.H., K.D. and H.B.; methodology, H.B., M.G. and S.H.; software, H.B., M.G., L.K. and S.K.; validation, M.K.-S., M.B. and S.H.; formal analysis, H.B., M.G. and S.H.; investigation, H.B., M.B., K.D. and S.H.; resources, M.G., M.K.-S., M.B and S.H.; data curation, M.G., M.K.-S., M.B. and S.H.; writing—original draft preparation, H.B., L.K. and S.K. writing—review and editing, M.G., M.A., M.K.-S., M.B., K.D. and S.H.; visualization, H.B., M.G., K.D. and M.A.; supervision, H.B., M.G. and S.H.; project administration, H.B., K.D. and S.H. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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