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Completion of nodal dissection in cutaneous melanoma with metastatic sentinel nodes: Prognostic impact in a population-based cohort study

Alessandra Buja[1], Massimo Rugge[2], Chiara Trevisiol[3*], Anna Zanovello[1], Marcodomenico Mazza[3], Luigi Dall'Olmo[3,4], Manuel Zorzi[5], Antonella Vecchiato[3], Paolo Del Fiore[3], Carlo Riccardo Rossi[4] and Simone Mocellin[3,4]

Abstract

Background In primary cutaneous melanoma (CM) with metastatic sentinel lymph node(s) (SLNB), treatment strategies may include completing a regional lymph node dissection (CLND). The prognostic benefit of this therapeutic approach remains a topic of debate. This retrospective, population-based cohort study explores the prognostic impact of CLND in a real-world clinical setting.

Methods This study analysed 280 incident cases of AJCC stage III CM with metastatic SLNB, as recorded by the Veneto population-based Regional Cancer Registry in 2015, 2017, and 2019. The overall survival and CM-specific survival rates were compared between patients who underwent CLND and those who did not. Kaplan-Meier analysis, Cox regression, and Fine-Gray models for competing risks tested the relationship between lymphadenectomy and overall and CM-specific survival.

Results Among CM patients with metastatic SLNB, 199/280 (71.1%) proceeded with CLND. When compared to those who did not receive treatment, CLND did not demonstrate significant advantages in terms of overall survival and CM-specific survival rates. The cost analysis found no significant differences in treatment choice (estimated costs: €23,695.71 for the treated group and €25,003.55 for the untreated group [$p = 0.69$]).

Conclusions The present real-world data support omitting CLND in stage III CM with histologically documented sentinel nodal metastasis.

Keywords Cutaneous melanoma, Melanoma surgery, Lymphadenectomy, Survival, Direct costs, Cohort study, Real-world data

*Correspondence:
Chiara Trevisiol
chiara.trevisiol@iov.veneto.it
Full list of author information is available at the end of the article

Introduction

Cutaneous melanoma (CM) is a melanocytic aggressive skin malignancy accounting for up to 75% of skin cancer deaths, and its incidence has steadily increased in recent decades [1–4]. Surgical-wide excision of the primary malignancy, combined with regional ("sentinel") nodal biopsy, is the elective treatment in locoregional disease [2].

The clinical management of primary CM with regional (lymph nodal, *i.e.* nodal) metastasis has changed drastically over the past decade. Effective targeted and immuno-therapies have been shown to improve CM prognosis, providing additional treatment options for surgically-resected CM patients at high risk of recurrence and death [3, 4].

Two key clinical trials conducted in highly specialised settings - the German Cooperative Dermatologic Oncology Group study (DeCOG-SLT) and the Second Multicenter Selective Lymphadenectomy Trial (MSLT-II) - found no significant difference in CM-specific survival between patients who underwent complete lymph node dissection (CLND) and those who were monitored closely through clinical and instrumental follow-up [5, 6]. Furthermore, patients treated with complete nodal removal often experience lymphedema, which can lead to severe functional limitations. In this controversial context, the CLND option has steadily declined, while alternative observational strategies, used either alone or in combination with adjuvant systemic therapies, have become increasingly applied [7].

No trials have compared the prognosis of patients with and without CLND or those receiving alternative non-surgical treatments. More information is needed to understand better the clinicopathological characteristics of patients who might benefit from CLND. Additionally, the DeCOG and MSLT-II trial results may have limited applicability outside of highly specialised centres, where the trial participants received regular, well-scheduled follow-ups and high-quality nodal ultrasounds.

In real-world clinical practice, the present retrospective population-based cohort study investigated the survival and direct costs of CLND patients compared to those who didn't undergo any further surgical treatment after sentinel metastatic nodal detection.

Methods

Study setting and clinical-pathological methods

This retrospective cohort study includes all incident cases of AJCC stage III CM with metastatic deposits in the sentinel lymph node biopsy (SLNB) as recorded in the population-based high-resolution Italian Regional Veneto Cancer Registry (RTV) for the years 2015, 2017, and 2019. The RTV is a certified, population-based cancer registry covering the entire regional population, accounting for about 5,000.00, residents [8]. The procedures for recording cancer rely on various informative sources, such as pathology reports, clinical charts, death certificates, and health-system administrative records.

The variables considered in this study included socio-demographics, such as age and sex T; CM histotype (superficial spreading, nodular, lentigo maligna, acral-lentiginous, desmoplastic, Spitzoid CM or malignant melanoma not otherwise specified); CM anatomical site (lower limbs, upper limbs, head, hands/feet and trunk); CM growth phase (radial *versus* vertical); ulceration (present *versus* absent); tumour-infiltrating lymphocytes ([TIL]; present *versus* absent); mitotic count (number of mitoses per mm^2); pathological nodal status (pN stages) at diagnosis (AJCC 8^{th} edition) [9]; treatment which the patients underwent (chemotherapy, radiotherapy, target therapy or immune checkpoint inhibitor therapy); lymphadenectomy (Yes or No); adequacy in the number of nodes obtained from CLND (Yes: adequate number when no less than 12 and 6 nodes were obtained from axillary and inguinal lymphadenectomy, respectively; No: inadequate) [10]; vital status and the cause of death. The assessment of nodal metastasis included either extensive or micro-metastatic deposits, as microscopically detected through serial histological sections of sentinel nodes. Due to the inconsistent availability of immunohistochemical assessments for isolated tumour cells (ITC), varying approaches to histological reporting and the debated prognostic significance of isolated metastatic cells in regional nodes, ITCs were not included in the analysis [11]. Patients with metastatic nodes in sites other than the regional area were excluded.

Cost assessment

Data on hospital admission(s) and examinations in outpatient clinics, the emergency department drug prescriptions, and the use of medical devices were obtained from the following administrative databases:

> The hospital admissions database defines the DRG (Diagnosis-Related Group) for each admission, valued at the rate reported in the NTPO (*Nomenclature Tariffario delle Prestazioni Ospedaliere*), the range of fees for inpatient services covering all hospital treatments for longer stay or day hospital admissions.
>
> The emergency department admissions database includes the costs of each admission, derived from the rates for all medical services and procedures performed during admissions.
>
> The outpatient database collects information on medical services and procedures that can be delivered at outpatient facilities under the National

Healthcare System funding, valued at the rate reported in the NTPA (*Nomenclature Tariffario delle Prestazioni Ambulatoriali*).

The regional databases of outpatient drug prescriptions and in-hospital drug consumption record the costs of all medical therapies, including high-cost drugs administered in/out hospital.

The medical devices database reports the device-associated costs sustained by the regional authorities.

The costs were determined based on rates set by the Regional Authority for all the CM-related medical procedures incurred within two years of diagnosis. Each patient was linked to the administrative data using an anonymous identification code.

Statistics

The categorical and quantitative variables were described by absolute frequencies and percentages or by mean/median and standard deviation (SD)/interquartile range (Q1-Q3), respectively.

The Chi-squared test or the Fisher test evaluated clinicopathological differences between the two study groups (SLNB alone *versus* SLNB + CLND). The latter was used only when the absolute frequencies were fewer than five in the contingency tables. The Mann-Whitney test was used to check the hypothesis of equality in age distribution between the two study groups. When three groups of lymphadenectomies were considered (No CLND, CLND with an inadequate number of lymph nodes, CLND with an adequate number of lymph nodes), the Wilcoxon test was performed. To compute the test statistics, subjects with missing values in the variables considered were excluded.

The overall survival was computed as the time from incidence to death for any cause. The melanoma-specific survival was computed as the time from incidence to death due to melanoma. Both types of survival times were censored at the latest date available. Overall survival curves and percentages and the respective 95% confidence interval were estimated using the Kaplan-Meier method, and the differences between different subgroups of the population were verified using the Peto & Peto modification of the Gehan-Wilcoxon test. Melanoma-specific survival curves and percentages were estimated in a competing risk setting by computing 1 minus the cumulative incidence mortality estimates and considering deaths from causes different from melanoma as competing risks. Melanoma-specific survival estimates for groups were compared with Gray's test. For computational details of survival analysis in competing risk settings see https://CRAN.R-project.org/package=tidycmprsk. When different cohorts were compared, survival times were truncated to have the same observational period and to balance the censoring of the different cohorts. The association between the type of surgery (SLNB alone *versus* SLNB + CLND) and overall survival or melanoma-specific survival was estimated by fitting Cox and Fine-Gray multivariate models, respectively. The effect size measures we estimated were the Cox model's hazard ratio (HR) and the Fine-Gray model's subdistribution hazard ratio (sHR). First, univariate Cox models were fitted for all the clinicopathological characteristics to exclude variables with p-value cut-off =<0.005. Then, a multivariate Cox model was estimated using the selected independent variables. The model was stratified for cohort and pT stage, chemotherapy and radiotherapy to meet the proportional hazard assumption. The structure of the final model was used to fit the multivariate Fine-Gray model for melanoma-specific survival. The same procedure was used for the CLND group with an adequate number of lymph nodes removed. The resulting model included cohort and pT stage as stratification factors.

Results were deemed statistically significant when p<0.005 according to Bonferroni correction for multiple comparisons. All the statistical analyses were conducted using numerical computing environment R 4.3.1.

Results

Patients' outcomes according to the surgical treatment

This study included 280 p-stage III CM incident cases with histologically assessed (H&E stain on serial microtomic sections) metastatic SLNB (M:F=186:94). Eighty-two (29.3%) cases were diagnosed in 2015, 96 (34.3%) in 2017 and 102 (36.4%) in 2019. The mean age of the sample was 59.8 (standard deviation: 14.9, Q1-Q3: 48–72). CLND was performed on 199/280 (71.1%) patients. The 81 patients who did not undergo CLND were candidates for clinical follow-up. These patients were older (mean age: 62.9 *versus* 58.6 years) and had lower pN stages (pN-stage 1: 64% *versus* 59.3%, pN-stage 2: 32.1% *versus* 27.6%, pN-stage 3: 2.5% *versus* 13.1%) (Table 1).

Three years from diagnosis, in the overall population, the deaths for any cause were 53, and the estimated survival was 81.1% (95% CI 76.6–85.8); CM-specific deaths and survival probability were 40 and 85.7% (95% CI 81.3–89.5), respectively. Overall and CM-specific survival did not differ in the two groups: 3-year overall survival in the CLND group was 82.9% (95% CI 77.9–88.3) and 76.5% (95% CI 67.9–86.4) in the non-CLND group; CM-specific survival was 85.9% (95% CI 80.6–90.3) *versus* 85.2% (95% CI 76.5–91.9), respectively (Fig. 1).

A sensitive analysis stratifying by pN-stage associated with the pN1 subgroup showed a better 3-year overall survival for the patients who undergo lymphadenectomy (93.2% *versus* 82.7%, p-value 0.04) (data not shown).

Table 1 Stage III CM patients with positive SLNB. Descriptive statistics of the clinicopathological profile by type of lymph node surgery

	n (%)	n (%)		*P* value
		CLND		
	Overall	No	Yes	
	N=280	*N*=81 (28.9%)	*N*=199 (71.1%)	
Age (at diagnosis)				
mean (SD)	59.8 (15.8)	62.9 (17.3)	58.6 (15.0)	0.017 (0.049*)
median (IQR)	61 (48–72)	66 (50–79)	60 (46–71)	
Sex				
Male	186 (66.4%)	51 (63.0%)	135 (67.8%)	0.520
Female	94 (33.6%)	30 (37.0%)	64 (32.2%)	
pN-value				
1	170 (60.7%)	52 (64.2%)	118 (59.3%)	0.029
2	81 (28.9%)	26 (32.1%)	55 (27.6%)	
3	28 (10.0%)	2 (2.5%)	26 (13.1%)	
Missing	1 (0.4%)	(1.2%)	0 (0.0%)	
Breslow-thickness				
≤ 1	26 (9.3%)	7 (8.6%)	19 (9.6%)	0.757
> 1–2	73 (26.1%)	24 (29.6%)	49 (24.6%)	
> 2–4	94 (33.6%)	24 (29.6%)	70 (35.2%)	
> 4.00	73 (26.1%)	22 (27.2%)	51 (25.6%)	
Missing	14 (5.0%)	4 (4.9%)	10 (5.0%)	
Ulceration				
Present	125 (44.6%)	35 (43.2%)	90 (45.2%)	0.869
Absent	145 (51.8%)	43 (53.1%)	102 (51.3%)	
Missing	10 (3.6%)	3 (3.7%)	7 (3.5%)	
Mitotic count				
0	10 (3.6%)	4 (4.9%)	6 (3.0%)	0.675
1–6	161 (57.5%)	45 (55.6%)	116 (58.3%)	
> 6	86 (30.7%)	25 (30.9%)	61 (30.7%)	
Missing	23 (8.2%)	7 (8.6%)	16 (8.0%)	
Median (Q1-Q3)	5 (2–9)	4 (2.25–8.75)	5 (2.00–8.50)	0.936
TILs				
Present	179 (63.9%)	49 (60.5%)	130 (65.3%)	0.994
Absent	74 (26.4%)	21 (25.9%)	53 (26.6%)	
Missing	27 (9.6%)	11 (13.6%)	16 (8.0%)	
Growth pattern				
Vertical	221 (78.9%)	62 (76.6%)	159 (79.9%)	1
Radial	3 (1.1%)	1 (1.2%)	2 (1.0%)	
Missing	56 (20.0%)	18 (22.2)	38 (19.1%)	
Anatomical site				
Upper limbs	28 (10.0%)	5 (6.2%)	23 (11.6%)	0.355
Lower limbs	45 (16.1%)	15 (18.5%)	30 (15.1%)	
Hands/feet	25 (8.9%)	6 (7.4%)	19 (9.6%)	
Head	21 (7.5%)	9 (11.1%)	12 (6.0%)	
Trunk	155 (55.4%)	43 (53.1%)	112 (56.3%)	
Missing	6 (2.1%)	3 (3.7%)	3 (1.5%)	

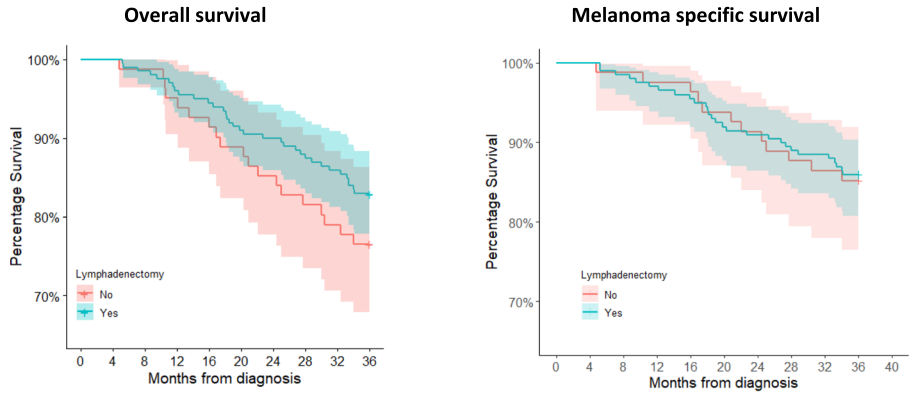
Table 1 (continued)

	n (%)	n (%)		*P* value
		CLND		
	Overall	No	Yes	
	N=280	*N*=81 (28.9%)	*N*=199 (71.1%)	
Histotype				
Superficial spreading	135 (48.2%)	32 (39.5%)	103 (51.8%)	0.028 (ssp vs nod: 1.000)
Nodular melanoma	95 (33.9%)	26 (32.1%)	69 (34.7%)	
Other	12 (4.3%)	5 (6.2%)	7 (3.5%)	
Not specified	38 (13.6%)	18 (22.2%)	20 (10.0%)	
Therapy				
Chemotherapy	111 (39.6%)	24 (29.6%)	87 (43.7%)	0.040
Checkpoint inhibitors	75 (26.8%)	17 (21.0%)	58 (29.1%)	0.212
Target therapy	62 (22.1%)	21 (25.9%)	41 (20.6%)	0.416
Radiotherapy	32 (11.4%)	4 (4.9%)	28 (14.1%)	0.037

n frequencies, *%* percentages, *SD* standard deviation, *IQR* interquartile range, *TIL* tumor-infiltrating lymphocytes

Bold: statistically significant value (p< 0.005)

* with t-test



CLND	N	Overall			Melanoma specific		
		Deaths	3-year survival (95% CI)	P value	Deaths	3-year survival (95% CI)	P value
No	81	19	76.5% (67.9-86.4)	0.20	12	85.2% (76.5-91.9)	0.88
Yes	199	34	82.9% (77.9-88.3)		28	85.9% (80.6-90.3)	

Fig. 1 Overall and melanoma-specific survival curves and rates by type of lymph node surgery for stage III CM patients with positive SLNB

Higher pN-stage and age at diagnosis were associated with poorer overall and CM-specific survival. Completing nodal dissection did not significantly affect survival (Table 2).

The adequacy of nodal dissection was analysed in 185 CM patients undergone CLND: 77 patients (29.0%) were diagnosed in 2015, 93 (35.0%) in 2017, and 96 (36.1%) in 2019. This analysis excluded 14 patients with lymph node metastasis outside the axillary or inguinal sites. The patients' mean age was 59.9 (standard deviation/Q1-Q3: 15.8/47.3–72), and the sample included 125 males (67.5%) and 60 females (32.4%). Fourteen (5.3%) subjects had an inadequate number of removed lymph nodes; the remaining 171 (64.3%) had an adequate number of removed nodes. The patients who did not undergo CLND were the oldest, followed by those with an adequate number of removed nodes, while the remaining group was the youngest (*p*-value 0.023) (Table 3).

Within three years of diagnosis, 91/266 patients died (non-CM-specific deaths= 52: CM-specific: 39). The

Table 2 Multivariate regressions of overall and melanoma-specific survival for stage III CM patients with positive SLNB

	Overall survival			Melanoma-specific survival		
	HR	95% CI	*P* value	sHR	95% CI	*P* value
Age	1.04	1.02–1.06	**<0.001**	1.03	1.01–1.05	**0.002**
pN-value						
N3 vs. N1-2	4.38	2.04–9.41	**<0.001**	3.88	1.91–7.86	**<0.001**
CLND						
T1 Yes vs. No	0.54	0.21–1.40	0.206	1.30	0.31–1.88	0.564
T2 Yes vs. No	0.87	0.34–2.23	0.768	0.88	0.35–3.65	0.835
Histotype						
Nodular vs. Superficial Spreading	0.61	0.33–1.12	0.109	0.63	0.34–1.16	0.139
Other vs. Superficial Spreading	0.70	0.23–2.12	0.524	1.21	0.47–3.13	0.690
Not specified vs. Superficial Spreading	0.52	0.16–1.64	0.265	0.42	0.09–1.90	0.258

HR hazard ratio, *sHR* subdistribution hazard ratio, *CI* confidence interval, *t1* from 0 to 770 days from diagnosis, *t2* more than 770 days from diagnosis

Bold: statistically significant value ($p<0.005$)

3-year overall survival was 80.5% (95% CI 75.8–85.4), while CM-specific survival was 85.3% (95% CI 80.8–89.3). The 3-year overall survival in the three groups was 76.4% (95% CI 67.9–86.4), 64.3% (95% CI 43.5–95.0) and 83.6% (95% CI 78.3–89.4) respectively; CM-specific survival was 85.2% (95% CI 76.5–91.9), 71.4% (95% CI 46.6–91.8) and 86.5% (95% CI 81.0–91.2). Figure 2 shows the overall and CM-specific survival curves by lymphadenectomy group for the whole sample, no significant differences between lymphadenectomy groups was detected.

Multivariate analysis revealed that overall and CM-specific survival rates did not differ based on the type of surgical treatment (CLND *versus* non-CLND) (Table 4). Patients with pN3 disease exhibited a higher mortality hazard ratio compared to pN1 and pN2 patients.

Costs of the treatments

The average overall cost for the two years following diagnosis was € 25,003.55 for patients who did not undergo CLND compared to € 23,695.71 for those who did. The difference in average treatment costs between the two groups was not statistically significant (*p* value 0.69) (Table 5).

Discussion

This population-based cohort study focused on p-stage III CM patients with metastatic sentinel nodes at their initial surgical treatment. The study compared the clinical outcomes and treatment costs of patients who underwent complete nodal dissection (CLND) with those without additional surgical interventions.

Treatment options

In the present cohort of CM patients, the number of individuals undergoing CLND steadily decreased from 2015 to 2019. This trend aligns with the findings from reference trials such as DeCOG and MSLT-II, the international guidelines and the results obtained by studies featuring the percentage of CLND procedures significantly dropping from 88% to 42% in 2016 and further declining from 41% to 14.3% in 2018 [8, 9, 13–20]. A web-based survey involving 65 surgeons belonging to the Melanoma and Skin Cancer Trials Group (MASC) found that only 5% of respondents routinely recommended CLND. In contrast, most (55%) surgeons limited CLND to selected cases. The key factors in determining the "completion option" included the size of the sentinel nodal deposits, the number of metastatic sentinel nodes, and the patient's likelihood of adhering to the surveillance regimen [21].

Consistent with previous studies, the present findings did not reveal a significant association between the primary CM site and CLND treatment [12, 18].

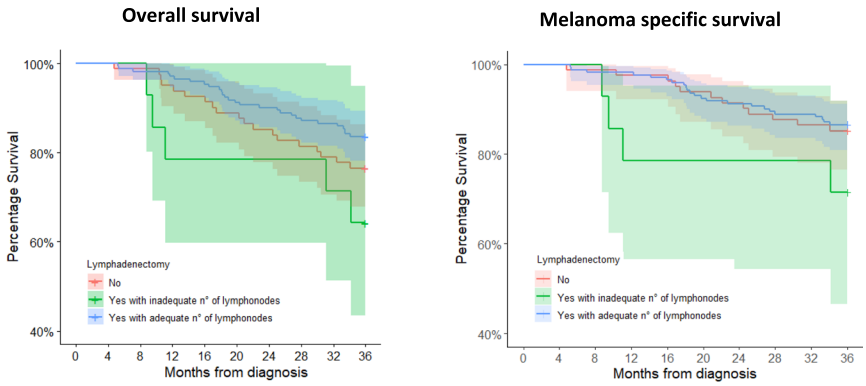
In line with a large body of literature, including DeCOG and MLST-II trials and more recent retrospective studies, the present report did not associate overall and CM-specific survival advantages to CLND patients, supporting the strategy of close clinical/ultrasound follow-up [8, 9, 14, 16, 17, 19–21]. Such a choice is potentially reinforced by the recent availability of systemic therapies, including immune checkpoint inhibitors and targeted treatments. Implementing these therapies in the neoadjuvant or adjuvant setting may reduce the need for extensive surgical nodal dissections. A more aggressive (CLND) therapeutic option is recommended

Table 3 Stage III CM patients with metastatic (axillary or inguinal) SLNB. Clinicopathological profile by performance of lymphadenectomy

	n (%)	CLND n (%)			*P* value
	Total	No	Yes, with inadequate no of lymph nodes	Yes, with adequate no of lymph nodes	
	N=266	*N*=81 (30.5%)	*N*=14 (5.3%)	*N* = 171 (64.3%)	
Age (at diagnosis)					
mean (SD)	59.9 (15.8)	62.9 (17.3)	53.8 (14.7)	58.5 (15.0)	0.023
median (IQR)	61 (47.3–72)	66 (50–79)	52.5 (43–66.8)	60 (46–70)	
Sex					
Male	176 (66.2%)	51 (63.0%)	9 (64.3%)	116 (67.8%)	0.753
Female	90 (33.8%)	30 (37.0%)	5 (35.7%)	55 (32.2%)	
pN-value					
1	163 (61.3%)	52 (64.2%)	8 (57.1%)	103 (60.2%)	**0.003**
2	76 (28.6%)	26 (32.1%)	1 (7.1%)	49 (28.7%)	
3	26 (9.8%)	2 (2.5%)	5 (35.7%)	19 (11.1%)	
Missing	1 (0.3%)				
Breslow-thickness					
≤ 1	26 (9.8%)	7 (8.6%)	0 (0.0%)	19 (11.1%)	0.686
> 1–2	68 (25.6%)	24 (29.6%)	5 (35.7%)	39 (22.8%)	
> 2–4	88 (33.1%)	24 (29.6%)	4 (28.6%)	60 (35.1%)	
> 4	71 (26.7%)	22 (27.2%)	5 (35.7%)	44 (25.7%)	
Missing	13 (4.9%)	4 (4.9%)	0 (0.0%)	9 (5.3%)	
Ulceration					
Present	120 (45.1%)	35 (43.2%)	6 (42.9%)	79 (46.2%)	0.867
Absent	137 (51.5%)	43 (53.1%)	8 (57.1%)	86 (50.3%)	
Missing	9 (3.4%)	3 (3.7%)	0 (0.0%)	6 (3.5%)	
Mitotic count					
0	10 (3.8%)	4 (4.9%)	0 (0.0%)	6 (3.5%)	0.603
1–6	154 (57.9%)	45 (55.6%)	11 (78.6%)	98 (7.1%)	
> 6	80 (30.1%)	25 (30.9%)	2 (14.3%)	53 (31.0%)	
Missing	22 (8.3%)	7 (8.6%)	1 (7.1%)	14 (8.2%)	
Median (Q1-Q3)	5 (2–8)	4 (2.25–8.75)	3 (2–5)	5 (2–8)	0.615
TILs					
Present	169 (63.5%)	49 (60.5%)	9 (64.3%)	111 (64.9%)	1
Absent	71 (26.7%)	21 (25.9%)	4 (28.6%)	46 (26.9%)	
Missing	26 (9.8%)	11 (13.6%)	1 (7.1%)	14 (8.2%)	
Anatomical site					
Upper limbs	26 (10.0%)	5 (6.2%)	0 (0.0%)	21 (12.3%)	**0.003**
Lower limbs	44 (17.0%)	15 (18.5%)	2 (14.3%)	27 (15.8%)	
Hands/feet	24 (9.0%)	6 (7.4%)	3 (21.4%)	15 (8.8%)	
Head	11 (4.0%)	9 (11.1%)	1 (7.1%)	1 (0.6%)	
Trunk	155 (58.0%)	43 (53.1%)	7 (50.0%)	105 (61.4%)	
Missing	6 (2.0%)	3 (3.7%)	1 (7.1%)	2 (1.2%)	
Histotype					
Superficial spreading	127 (47.7%)	32 (39.5%)	5 (35.7%)	90 (52.6%)	0.030 (ssp vs nod: 1.000)
Nodular melanoma	91 (34.2%)	26 (32.1%)	8 (57.1%)	57 (33.3%)	
Other	11 (4.1%)	5 (6.2%)	1 (7.1%)	5 (2.9%)	
Not specified	37 (13.9%)	18 (22.2%)	0 (0.0%)	19 (11.1%)	
Therapy					
Chemotherapy	104 (39.1%)	24 (29.6%)	8 (57.1%)	72 (42.1%)	0.060
Checkpoint inhibitors	70 (26.3%)	17 (21.0%)	5 (35.7%)	48 (28.1%)	0.351
Target therapy	59 (22.2%)	21 (25.9%)	4 (28.6%)	34 (19.9%)	0.449
Radiotherapy	30 (11.3%)	4 (4.9%)	2 (14.3%)	24 (14.0%)	0.068

n frequencies, *%* percentages, *SD* standard deviation, *IQR* interquartile range, *TIL* tumour-infiltrating lymphocytes

Bold: statistically significant value ($p < 0.005$)



CLND	N	Overall			Melanoma specific		
		Deaths	3-year survival (95% CI)	P value	Deaths	3-year survival (95% CI)	P value
No	81	19	76.5% (67.9-86.4)		12	85.2% (76.5-91.9)	
Yes, with inadequate n° of lymph nodes	14	5	64.3% (43.5-95.0)	0.09	4	71.4% (46.6-91.8)	0.28
Yes, with adequate n° of lymph nodes	171	28	83.6% (78.3-89.4)		23	86.5% (81.0-91.2)	

Fig. 2 Overall and melanoma-specific survival curves and rates by performance of lymphadenectomy for stage III CM patients with metastatic (axillary or inguinal) SLNB

Table 4 Multivariate regressions of overall and melanoma-specific survival for stage III CM patients with metastatic (axillary or inguinal) SLNB

	Overall survival			Melanoma-specific survival		
	HR	95% CI	*P* value	sHR	95% CI	*P* value
Age	1.04	1.02–1.06	**<0.001**	1.04	1.01–1.06	**0.001**
pN-value						
N3 vs. N1-2	4.95	2.47–9.92	**<0.001**	6.33	2.92-1.37	**<0.001**
CLND						
T1 Yes, inadequate vs. No	1.18	0.24–5.79	0.840	2.80	0.48–16.41	0.255
T1 Yes, adequate vs. No	0.42	0.70–1.02	0.055	0.51	0.18–1.44	0.202
T2 Yes, inadequate vs. No	1.18	0.28–5.07	0.819	1.77	0.34–9.20	0.496
T2 Yes, adequate vs. No	1.52	0.64–3.59	0.344	2.12	0.68–6.68	0.198
Anatomical site						
Upper limbs vs. Hands/Feet	0.83	0.29–2.41	0.734	1.21	0.41–3.55	0.724
Lower limbs vs. Hands/Feet	0.85	0.36–2.05	0.722	0.96	0.37–2.54	0.941
Head vs. Hands/Feet	0.38	0.08–1.85	0.228	0.37	0.05–2.91	0.345
Trunk vs. Hands/Feet	1.02	0.47–2.22	0.954	0.98	0.45–2.12	0.951
Missing vs. Hands/Feet	0.52	0.05–6.09	0.606	<0.01	9*10^(−10)–6*10^(−8)	**<0.001**
Histotype						
Nodular vs. Superficial Spreading	0.70	0.41–1.20	0.190	0.61	0.34–1.12	0.111
Other vs. Superficial Spreading	0.79	0.23–2.60	0.697	1.32	0.49–3.60	0.583
Not specified vs. Superficial Spreading	0.58	0.22–1.57	0.287	0.50	0.15–1.65	0.255

HR hazard ratio, *sHR* sub-distribution hazard ratio, *CI* confidence interval, *t1* from 0 to 770 days from diagnosis, *t2* more than 770 days from diagnosis

Bold: statistically significant value ($p < 0.005$)

Table 5 Stage III CM patients with positive SLNB. Mean costs of treatments (€ in the 2 years after diagnosis by type of lymph node surgery)

	CLND	
	No (*N*= 81)	**Yes (*N*= 199)**
Hospitalization	2,377.96	3,610.12
Emergency room	192.69	51.33
Outpatient visits	5,469.65	5,511.98
Pharmacy costs	16,962.13	14,514.93
High-cost drugs	484.54	523.45
Medical devices	728.82	1343.82
Psychiatric care	1.12	7.35
Total	**25,003.55**	**23,695.71**

for patients with clinical/instrumental suspects of metastatic nodes (Therapeutic Lymph Node Dissection) [16, 17, 19–21].

Stage III CM encompasses a diverse range of neoplastic diseases, with an expected 5-year overall survival rate varying widely from 30% to 60%.

Costs of therapy

When considering adjuvant systemic therapies, toxicity and costs must be addressed [20]. The initial adjuvant systemic therapy trial reported that 43% of patients treated with ipilimumab experienced grade 3 or 4 side effects. Recently, this percentage has significantly decreased to around 14% [21, 22]. In radically treated stage III patients, the drop in toxicity rate has been associated with a 1-year disease-free survival of 70.5% and 75.4% among patients treated with anti-PD-1 agent nivolumab and adjuvant pembrolizumab, respectively [23].

When considering therapy's high dropout rates and in a cost-effectiveness perspective, many clinicians are currently concerned about making the combination of adjuvant systemic treatment(s) with appropriate follow-up of the regional nodal basin accessible to all patients. In such a perspective, the CLND would be clinically preferred and potentially cost-saving [24].

In this study, hospitalisation was the main cost factor for patients who underwent CLND. In contrast, pharmacy costs were the most significant for patients who did not undergo CLND. Although the total direct costs were lower for the CLND group, there were no significant differences in the average costs between the two groups.

This study acknowledges limitations. The study relies on data from the Regional Cancer Registry (RTV) and regional health administration records. Due to the nature of the available data set, the study design focused solely on the CM patients' survival without including punctual information on CM relapses or recurrences. However, this report offers important insights into real-world CM management through its population-based design. This perspective, which differs from that of specialized medical institutions, potentially may reveal key areas for clinical improvement. In such a real-world context, the study did not include the potential prognostic impact of a set of variables (i.e. ITC of circulating cancer cells) considered only in highly specialized clinical centres [11, 25, 26].

Conclusion

In p-stage III CM patients with metastatic sentinel nodes, the results indicate that completing the nodal dissection (CLND) and the number of nodes removed by CLND do not affect CM-specific survival significantly. These real-world results support the current international recommendation of omitting CLND for these patients. However, due to the "low strength" of the current guidelines, any therapeutic decisions should include a clinical assessment of the patient's condition, accounting for comorbidities, the availability of new adjuvant therapies, the patient's ability to adhere to follow-up appointments and the patient's personal choice.

Abbreviations

CLND Completion of lymph-node dissection
CM Cutaneous melanoma
ITC Isolated tumor cells
RTV Veneto Cancer Registry
SLNB Sentinel lymph node biopsy

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Not applicable.

Authors' contributions

AB and SM were involved in the conceptualization of the study AB, MR, CT, and PDF contributed to the design of the work; AZ and MZ participated in data acquisition and analysis; AB, CT, MM, LDO, AV, and CR interpreted the data; AB, CT and AZ drafted the work AB, CT, MM and SM substantively revised it All authors read and approved the final manuscript.

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Data availability

The data supporting this study's findings are held by the Veneto Cancer Registry (RTV) and were used under license for this work. The anonymized minimal data set necessary to replicate our findings have been made publicly available at the following link: https://doi.org/10.6084/m9.figshare.28061159.

Declarations

Ethics approval and consent to participate

This retrospective study involving human participants was in accordance with the ethical standards of the institutional research committee and with the

1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Italian legislation identifies cancer registries as collectors of personal data for surveillance purposes, with no need to obtain individuals' explicit informed consent [REF: https://www.gazzettaufficiale.it/eli/id/2017/05/12/17A03142/sg].
This study project was formally approved by the Ethics Committee of the Veneto Oncological Institute (protocol number 52/2016).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiological, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy. [2]Department of Medicine-DIMED, Pathology and Cytopathology Unit, University of Padua, Padua, Italy. [3]Soft-Tissue, Peritoneum, and Melanoma Surgical Oncology Unit, Veneto Institute of Oncology IOV – IRCCS, Via Gattamelata, 64, 35128 Padua, Italy. [4]Department of Surgery, Oncology, and Gastroenterology - DISCOG, University of Padua, Padua, Italy. [5]Veneto Tumour Registry, Azienda Zero, Padua, Italy.

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