ACTAS
Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org

ORIGINAL ARTICLE

[Translated article] Multicenter Analysis of the Surgical Management and Adjuvant Therapy of Patients With Melanoma and a Positive Sentinel Lymph Node Biopsy

E. Samaniego-González[a,*], S. Podlipnik[b], S. Ribero[c], E. Nagore[d], A. Boada[e], J. Cañueto[f], S. Paradela[g], B. de Unamuno[h], P. Rodríguez-Jiménez[i], S. Puig[b], J. Malvehy[b], C. Carrera[b], G. Roccuzzo[c], C. Requena[d], E. Manrique-Silva[d], N. Richarz[e], A. Ruiz-Villanueva[j], V. Traves[k], S. España-Fernández[l], R. Botella-Estrada[h], M.A. González-Morán[m], A. Tejera-Vaquerizo[n,o]

[a] *Servicio de Dermatología, Complejo Asistencial Universitario de León, Instituto de Biomedicina (IBIOMED), Universidad de León, León, Spain*
[b] *Servicio de Dermatología, IDIBAPS, Hospital Clínic de Barcelona, Universitat de Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Raras, Barcelona, Spain*
[c] *Dermatologic Clinic, Department of Medical Sciences, University of Turin, Turin, Italy*
[d] *Servicio de Dermatología, Instituto Valenciano de Oncología, Valencia, Spain*
[e] *Servicio de Dermatología, Hospital Germans Trias i Pujol de Badalona, Badalona, Spain*
[f] *Servicio de Dermatología, Complejo Asistencial Universitario de Salamanca, Instituto de Investigación Biomedica (IBSAL) (CANC-30), Salamanca, Spain*
[g] *Servicio de Dermatología, Complejo Hospitalario A Coruña, A Coruña, Spain*
[h] *Servicio de Dermatología, Hospital la Fe de Valencia, Valencia, Spain*
[i] *Servicio de Dermatología, Hospital La Princesa de Madrid, Madrid, Spain*
[j] *Servicio de Dermatología, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain*
[k] *Servicio de Anatomía Patológica, Instituto Valenciano de Oncología, Valencia, Spain*
[l] *Servicio de Oncología Médica, Instituto Catalán de Oncología, Hospital Germans Trias i Pujol de Badalona, Badalona, Spain*
[m] *Servicio de Anatomía Patológica, Complejo Asistencial Universitario de León, León, Spain*
[n] *Unidad de Oncología Cutánea, Hospital San Juan de Dios de Córdoba, Córdoba, Spain*
[o] *Servicio de Dermatología, Instituto Dermatológico GlobalDerm, Palma del Río, Córdoba, Spain*

Received 5 April 2024; accepted 21 July 2024
Available online 24 December 2024

KEYWORDS
Melanoma;
Surveillance;

Abstract
Introduction: Complete lymph node dissection (CLND) was the standard practice for patients with melanoma and a positive sentinel lymph node biopsy (SLNB) until the results of two clinical trials published in 2016 and 2017 demonstrated that it did not improve melanoma-specific

DOI of original article: https://doi.org/10.1016/j.ad.2024.07.017
* Corresponding author.
E-mail address: esamaniego@saludcastillayleon.es (E. Samaniego-González).

https://doi.org/10.1016/j.ad.2024.12.005

Lymph node dissection;
Sentinel lymph node biopsy;
Adjuvant therapy;
Pathology

survival (MSS). However, it continues to be performed in some scenarios. No studies have ever been published on lymph node management after a positive SLNB in the routine clinical practice in our setting.
Objectives: To determine the evolution of the indication for CLND in patients with a positive SLNB, as well as the characteristics associated with its performance.
Material and methods: We conducted a multicenter retrospective observational study with patients with skin melanoma and positive sentinel lymph nodes diagnosed from 2017 through 2022 at 8 Spanish centers and 1 Italian center.
Results: A total of 430 patients were included, 54% men, with 323 (75.1%) aged between 45 and 80 years. A total of 133 cases (31%) exhibited Breslow thickness >4 mm, 206 cases (49%) were ulcerated, and in 213 cases (55.7%), lymph node metastasis was >1 mm. Isolated lymphadenectomy or followed by adjuvant therapy was performed in 146 patients (34.1%). After multivariate logistic regression, the factors associated with the performance of CLND were the acral lentiginous melanoma histological subtype, lymph node metastasis size >1 mm, extracapsular spread, and the participant hospital. Age >80 years was inversely associated.
Conclusion: While the frequency of CLND in patients with melanoma and positive SLNB has decreased, the indication for systemic adjuvant therapy in these patients has increased. However, CLND is still indicated in patients with high-risk characteristics.

PALABRAS CLAVE
Melanoma;
Seguimiento;
Disección ganglionar;
Biopsia de ganglio centinela;
Terapia adyuvante;
Patología

Análisis multicéntrico del manejo quirúrgico y tratamiento adyuvante de los pacientes con melanoma y positividad en la biopsia selectiva del ganglio centinela

Resumen
Introducción: La disección ganglionar completa (DGC) era la práctica estándar en pacientes con melanoma y biopsia selectiva del ganglio centinela (BSGC) positiva hasta que en 2016 y 2017 se publicaron los resultados de dos ensayos clínicos que no demostraron que mejorase la supervivencia específica por melanoma. Sin embargo, continúa realizándose en algunos escenarios. No existen estudios que recojan el manejo ganglionar tras BSGC positivo en la práctica clínica en nuestro medio.
Objetivos: Determinar la evolución de la indicación de la DGC en pacientes con BSGC positiva, así como las características que se asocian a su realización.
Material y métodos: Estudio observacional retrospectivo multicéntrico que incluye pacientes con melanoma cutáneo y ganglio centinela positivo diagnosticados entre los años 2017 y 2022 en ocho centros españoles y uno italiano.
Resultados: Se incluyeron 430 pacientes, 54% hombres; 323 (75,1%) tenían entre 45-80 años, y de ellos, 133 casos (31%) presentaban un Breslow >4 mm, 206 casos (49%) estaban ulcerados, y en 213 casos (55,7%) la metástasis ganglionar era >1 mm. Se realizó la linfadenectomía aislada o seguida de adyuvancia en 146 pacientes (34,1%). Tras una regresión logística multivariante, los factores asociados a la realización de DGC fueron el subtipo histológico melanoma lentiginoso acral (MLA), un tamaño de metástasis ganglionar >1 mm, la extensión extracapsular y el hospital participante. La edad >80 años se asoció inversamente.
Conclusión: Mientras que ha disminuido la frecuencia de realización de la DGC en pacientes con melanoma y BSGC positiva, ha aumentado la indicación del tratamiento sistémico adyuvante en estos pacientes. Sin embargo, se sigue indicando la DGC en pacientes con características de alto riesgo.

Introduction

The treatment of patients with melanoma and positive sentinel lymph node biopsy (SLNB) has drastically changed after the publication of two clinical trials that advised against performing complete lymph node dissection (CLND) due to the lack of benefit in melanoma-specific survival (MSS).[1,2] Clinical practice guidelines on the management of melanoma have incorporated this change in their recommendations, though not uniformly.[3–6] Thus, while the performance of CLND in these patients has significantly decreased in clinical practice,[7–12] it is still recommended and performed in some clinical contexts considered high risk, such as the presence of lymphovascular invasion or immunosuppression. CLND has also been maintained in cases with clinical characteristics for which there is less evidence, as these were underrep-

resented in the above-mentioned clinical trials, such as extracapsular extension of lymph node metastasis, involvement of three or more nodes, metastasis >1 mm in size, melanoma located in the head and neck, or involvement of two or more lymphatic regions.[13–15]

Change in the surgical treatment of patients with regional metastasis has coincided with an increase in survival, both relapse-free and melanoma-specific, achieved in the last decade thanks to new adjuvant therapies.[16–19] Among the recommended options in the guidelines for stage III patients are dabrafenib plus trametinib for patients with BRAF (serine/threonine protein kinase B-raf) V600 mutation (not funded in Spain) and nivolumab or pembrolizumab regardless of BRAF status (only funded in Spain for stages IIIC and IIID during the study period).[6,20]

In our region, there are no studies analyzing the surgical treatment of patients with melanoma with a positive SLNB in recent years. Understanding clinical practice could contribute to better optimization of health care resources. The primary endpoint of this study was to evaluate the progression and current status of CLND indication in patients with melanoma and positive SLNB. Secondary endpoints included analyzing clinical and pathological characteristics associated with CLND, and determining whether CLND impacts survival in these patients.

Materials and methods

Participants and study design

We conducted a retrospective multicenter observational study, including patients from 9 reference hospitals participating in sentinel lymph node studies in these patients, known as SENTIMEL.[21] The participant hospitals are Hospital Clínic, Barcelona (Spain); University Hospital Città della Salute e della Scienza di Torino, Turin (Italy); Instituto Valenciano de Oncología, Valencia (Spain); Hospital Germans Trias i Pujol, Badalona (Spain); Hospital Universitario de Salamanca, Salamanca (Spain); Hospital Universitario de A Coruña, A Coruña (Spain); Complejo Asistencial Universitario de León, León (Spain); Hospital de La Fe, Valencia (Spain); and Hospital de la Princesa, Madrid (Spain).

Patients treated after the publication of the MSLT-II clinical trial results,[1] from January 1st, 2017 through January 31st, 2022, were included. All patients with cutaneous melanoma and positive sentinel lymph node biopsy (SLNB) were included. The protocol prior to performing SLNB is similar across all participant hospitals and includes screening for lymph node involvement via locoregional ultrasound and melanomas >T3b, also metastasis screening using imaging modalities (CT/PET-CT/MRI).

The study was approved by Hospital Universitario de León Ethics Committee for Clinical Research with Medicines (CEIM) (Code No. 23112, date 28/7/2023). The STROBE guidelines were used for reporting observational studies.[22]

Regarding the variables, for the main objective of the study, whether CLND was performed was considered. For survival studies, the time until local recurrence was analyzed, defined as melanoma recurrence at the primary site and within 2 cm of it, regional nodal recurrence, or death. Patients without the event at the last available follow-up were considered censored.

Other variables included were the year of diagnosis of the primary tumor, the hospital of origin, age (categorized as <45, 45–60, >60–80, and >80 years), sex at birth, functional status according to the Eastern Cooperative Oncology Group (ECOG) scale, location (head and neck, trunk, upper extremities, lower extremities, hands-feet, other), immunosuppression, tumor thickness ($\leq$1, 1.1–2, 2.1–4, >4 mm), ulceration, mitotic index[23] (0–1, 2–5, >6 mitoses/mm^2), lymphovascular invasion, microsatellitosis, histological type (lentigo maligna melanoma [LMM], superficial spreading melanoma [SSM], nodular melanoma [NM], acral lentiginus melanoma [ALM], desmoplastic, other), number of sentinel lymph nodes excised (1–2, 3–4, >4), number of positive sentinel lymph nodes (1, $\geq$2), size of lymph node metastasis according to Rotterdam criteria[24] (<0.1, 0.1–1, >1 mm), extracapsular extension, and number of affected lymph node regions (1 vs >1). For logistic regression analysis, the desmoplastic and LMM histological types were grouped within the ''other'' category due to a small sample size. Similarly, hospitals with <50 included patients were grouped together (variable called combined group).

Statistical analysis

In the descriptive study, the chi-square or Fisher's test was used to assess the association of categorical variables. The Student's *t*-test, however, was used for quantitative variables. Logistic regression was employed to analyze the variables associated with CLND. First, each variable association with the outcome variable was evaluated using univariate logistic regression. All variables that were statistically significant ($p < 0.1$) were included in a stepwise backward logistic regression model (xi: stepwise command in STATA). A Hosmer–Lemeshow test was performed to assess goodness of fit. A significance level of $p < 0.05$ was considered in the model. Finally, the effect of performing CLND, treatment types, and patient stage on relapse-free survival (RFS), nodal or lymphatic relapse-free survival (NRFS), melanoma-specific survival (MSS), and overall survival (OS) was analyzed. Kaplan–Meier curves were generated, and differences in survival were analyzed using the log-rank test. All analyses were performed using Stata v.14.2 (Stata Corp. 2015. Stata Statistical Software: Release 14, College Station, Texas, United States: StataCorp LP).

Results

A total of 449 patients who underwent a positive SLNB were included, 19 of whom were excluded due to incomplete data regarding dates, inclusion errors, lack of follow-up, or localization in mucosa (Fig. 1). A total of 430 patients were analyzed, and their descriptive data are shown in Table 1. Regarding gender, cases were more common in men ($n = 233$ [54.2%]) vs women. The most common age group was between 60 and 80 years ($n = 169$ [39.3%]), followed by the 45–60 years group ($n = 154$ [35.8%]). The least common group was elderly patients >80 years ($n = 35$ [8.1%]), and this age group also had the lowest rate of CLNDs (only 4 [11.4%]; $p = 0.02$). The trunk was the most

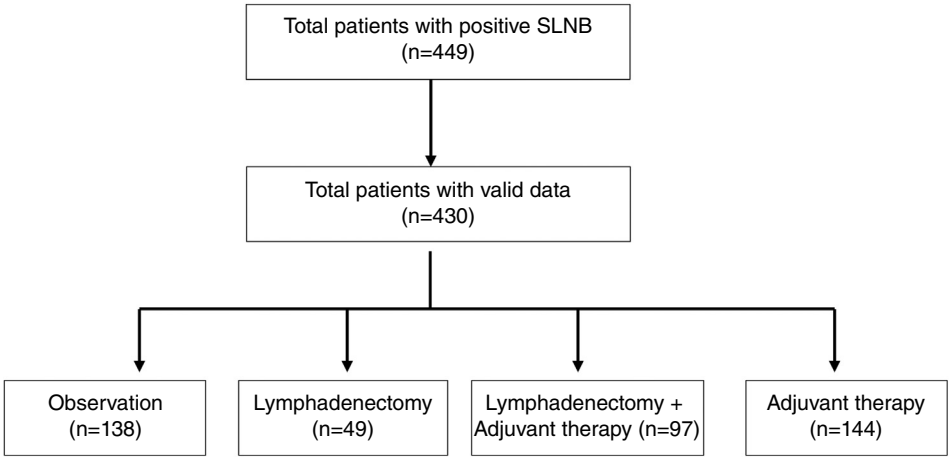

Figure 1 Flow diagram of patients with cutaneous melanoma and a positive sentinel lymph node biopsy from 2017 through 2022.

common tumor location ($n = 179$ [41.7%]), followed by the lower limbs ($n = 81$ [18.9%]), and the head and neck ($n = 75$ [17.5%]). Regarding tumor thickness, 37.3% ($n = 157$) had a Breslow thickness of 2.1 mm up to 4 mm, while thin tumors ≤1 mm accounted for 6.89% of the sample ($n = 29$). There was a trend towards increased CLND proportional to tumor thickness and pathological T stage. The most common histological subtype was SSM ($n = 214$ [53.6%]), followed by MN ($n = 115$ [28.8%]). For SLNB metastases, most cases had a single metastatic lymph node ($n = 305$ [70.9%]), and metastasis size was >1 mm in 55.8% ($n = 213$). CLNDs increased both in cases with ≥2 positive nodes and those with metastasis sizes ≥0.1 mm.

Over the study period, the largest group consisted of 144 patients (33.7%) who received only adjuvant therapy. CLND was performed alone in 49 patients (11.4%), and the combination of CLND plus adjuvant therapy occurred in 97 cases (22.7%). Observation was chosen for 138 patients (32.2%) (Table 1). Stage distribution is shown in Fig. 1 (supplementary data). Importantly, these proportions changed over the years of the study. In fact, CLND in these patients with positive SLNs was predominantly performed early in the study period (2017), becoming marginal in the most recent year, 2022 (Fig. 2). Similarly, treatment strategies shifted significantly, with CLND decreasing and adjuvant therapy becoming more prominent during the study period (Fig. 3).

In univariate analysis, variables associated with CLND were tumor thickness >4 mm (OR, 2.7 [95% CI, 1.1–7.1]; $p = 0.04$), nodular melanoma histological subtype (OR, 1.7 [95% CI, 1.1–2.8]; $p = 0.03$), ≥2 positive nodes (OR, 1.7 [95% CI, 1.1–2.6]; $p = 0.013$), lymph node metastasis size >1 mm (OR, 11.4 [95% CI, 2.6–49]; $p = 0.001$), Turin hospital (OR, 4 [95% CI, 2.2–7.2]; $p = 0.001$), the combined group (OR, 3.1 [95% CI, 1.7–5.7]; $p = 0.001$), and extracapsular extension (OR, 5.2 [95% CI, 2.1–13.1]; $p < 0.001$). Age >80 years was inversely associated with CLND (OR, 0.3 [95% CI, 0.1–0.9]; $p = 0.02$). Multivariate logistic regression analysis found independent variables associated with CLND were age >80 years (OR, 0.3 [95% CI, 0.1–1]; $p = 0.05$), MLA histological subtype (OR, 2.94 [95% CI, 1.95–6.92]; $p = 0.01$), metastasis size >1 mm (OR, 7.91 [95% CI, 1.71–36.47]; $p = 0.008$), extracapsular extension of metastasis in SLNs (OR, 4.81 [95% CI, 1.51–15.28]; $p = 0.008$), Turin hospital (OR, 4.4 [95% CI, 2.11–9.32]; $p < 0.001$), and the combined group (OR, 3.34 [95% CI, 1.58–7.08]; $p < 0.001$) (Table 2).

Univariate analysis showed no differences in various survival measures (LRFS, RRFS, DSS, and OS) between patients undergoing CLND vs observation. However, when analyzed by treatment type (Fig. 4), worse survival was observed in patients undergoing CLND alone vs others ($p = 0.04$). Survival differences by stage are shown in Fig. 2 (supplementary data).

Discussion

This is the first study describing the treatment of patients with melanoma and positive SLNB in a selection of centers in Southern Europe (Spain and Italy). A notable decrease in the number of CLNDs performed has been observed, and conversely, there has been an increasingly frequent use of adjuvant therapy in these patients.

Based on the Multicenter Selective Lymphadenectomy Trial-II (MSLT-II) and the German Dermatologic Cooperative Oncology Group-Selective Lymphadenectomy Trial (DeCOG-SLT), there is clear evidence that performing CLND in patients with a positive SLNB does not benefit melanoma-specific survival vs routine ultrasound-based lymph node follow-up.[1,2] A recent meta-analysis even found that, paradoxically, the observation group had a slight survival advantage at 3 and 5 years. These results are consistent and can be explained by the way melanoma spreads. Its hematogenous spread is independent of lymphatic dissemination and is not progressive or orderly as previously hypothesized during the 1990s.[25–27]

The findings of this study have also been reported in previous observational studies conducted in other countries, including a major international multicenter study[7] and two large population-based studies from the U.S. National Cancer Database,[8,12] which reflect a significant decrease in the number of CLNDs in recent years.[28]

The landmark clinical trials on the topic of discussion are no stranger to criticism, particularly since most patients included (~70%) had a small tumor burden (<1 mm), meaning that high-risk recurrence patients, such as those with

Table 1 Characteristics of patients with cutaneous melanoma and positive sentinel lymph node biopsy categorized by complete lymph node dissection vs observation ($n = 430$).

Variable	CLND (%[a])	Observation (%[a])	Total (%[b])	*p*-Value
Sex				
Male	77 (33.1)	156 (66.9)	233 (54.2)	0.6
Female	69 (33.0)	128 (67.0)	197 (45.2)	
Age (years)				0.02
<45	24 (33.3)	48 (66.7)	72 (16.7)	
45–60	56 (38.4)	98 (63.4)	154 (35.8)	
>60–80	62 (36.7)	107 (63.3)	169 (39.3)	
>80	4 (11.4)	31 (88.6)	35 (8.1)	
ECOG				0.17
0	113 (38.2)	183 (61.8)	296 (84.6)	
1	11 (26.2)	31 (73.8)	42 (12.0)	
2	5 (55.6)	4 (44.4)	9 (2.6)	
3	2 (66.7)	1 (33.3)	3 (0.8)	
Location				0.5
Head and neck	24 (32.0)	51 (68.0)	75 (17.5)	
Trunk	61 (34.1)	118 (65.9)	179 (41.7)	
Upper limbs	11 (25.0)	33 (75.0)	44 (10.3)	
Lower limbs	29 (35.8)	52 (64.2)	81 (18.9)	
Hands/feet	20 (43.5)	26 (56.5)	46 (10.7)	
Others	1 (25.0)	3 (75.0)	4 (0.9)	
(Lost = 1)				
Immunosuppression				0.7
No	102 (42.5)	138 (57.5)	241 (97.6)	
Yes	3 (50.0)	3 (50.0)	6 (2.4)	
(Lost = 153)				
Tumor thickness (mm)				0.04
≤1	6 (20.7)	23 (79.3)	29 (6.9)	
1.01–2	28 (27.4)	74 (72.6)	102 (24.2)	
2.01–4	53 (33.8)	104 (66.2)	157 (37.3)	
>4	56 (42.1)	77 (57.9)	133 (31.6)	
(Lost = 9)				
T stage				0.03
T1a	1 (33.3)	2 (66.7)	3 (0.7)	
T1b	5 (19.2)	21 (80.8)	26 (6.2)	
T2a	18 (23.1)	60 (76.2)	78 (18.5)	
T2b	10 (41.7)	14 (58.3)	24 (5.7)	
T3a	29 (42.0)	40 (56.0)	69 (16.4)	
T3b	24 (27.3)	64 (72.7)	88 (20.9)	
T4a	18 (43.9)	23 (56.1)	41 (9.7)	
T4b	38 (41.3)	54 (58.7)	92 (21.8)	
Ulceration				0.5
No	67 (31.6)	146 (68.5)	213 (50.8)	
Yes	71 (34.5)	135 (65.5)	206 (49.2)	
(Lost = 11)				
Mitosis (mitoses/mm^2)				0.7
0–1	20 (28.6)	50 (71.4)	70 (17.2)	
2–5	56 (33.3)	112 (66.7)	168 (41.3)	
≥6	58 (34.3)	111 (65.7)	169 (41.5)	
(Lost = 23)				
Vascular invasion				0.9
No	92 (30.6)	209 (69.4)	301 (81.6)	
Yes	25 (36.8)	43 (63.2)	68 (18.4)	

Table 1 (*Continued*)

Variable	CLND (%[a])	Observation (%[a])	Total (%[b])	*p*-Value
(Lost = 61)				
Microsatellitosis				0.1
No	105 (29.8)	247 (70.2)	352 (91.0)	
Yes	15 (42.9)	20 (57.1)	35 (9.0)	
(Lost = 43)				
Histological subtype				0.1
SSM	62 (29.0)	152 (71.0)	214 (53.6)	
NM	46 (40.0)	69 (60.0)	115 (28.8)	
ALM	18 (43.9)	23 (56.1)	41 (10.3)	
Other	9 (31.0)	20 (69.0)	29 (7.3)	
(Lost = 31)				
Number of excised lymph nodes				0.6
1–2	46 (32.6)	95 (67.4)	141 (33.2)	
3–4	74 (35.2)	136 (64.8)	210 (49.5)	
≥4	21 (28.8)	52 (71.2)	73 (17.2)	
(Lost = 6)				
Number of positive lymph nodes				0.02
1	93 (30.5)	212 (69.5)	305 (70.9)	
≥2	53 (42.4)	72 (57.6)	125 (29.1)	
Metastasis size in SLN (mm)				<0.001
≤0.1	2 (6.3)	30 (93.7)	32 (8.4)	
>0.1–1	27 (19.7)	110 (80.3)	137 (35.9)	
>1	89 (41.8)	124 (58.2)	213 (55.8)	
(Lost = 44)				
Extracapsular extension				<0.001
No	115 (30.3)	265 (69.7)	380 (94.3)	
Yes	16 (69.6)	7 (30.4)	23 (5.7)	
(Lost = 27)				
Number of lymph node regions				0.6
1	135 (33.5)	268 (66.5)	403 (93.6)	
>1	10 (34.5)	16 (61.5)	26 (6.1)	
Treatment groups				
Observation only	–	–	138 (32.2)	
Lymphadenectomy	–	–	49 (11.4)	
Lymphadenectomy + adjuvants	–	–	97 (22.7)	
Adjuvants only	–	–	144 (33.7)	
(Lost = 2)				
Year				<0.001
2017	32 (56.1)	25 (43.9)	57 (13.3)	
2018	29 (33.3)	58 (66.7)	87 (20.2)	
2019	38 (41.3)	54 (58.7)	92 (21.4)	
2020	21 (24.4)	65 (75.6)	86 (20.0)	
2021	25 (27.8)	65 (72.2)	90 (21.0)	
2022	1 (5.6)	17 (94.4)	18 (4.2)	
Hospital center				<0.001
Hospital Barcelona	26 (20.5)	101 (79.5)	127 (29.0)	
Hospital Turin	51 (51.0)	49 (49.0)	100 (23.3)	
Hospital Valencia (IVO)	15 (26.3)	42 (73.7)	57 (3.3)	

Table 1 (*Continued*)

Variable	CLND (%[a])	Observation (%[a])	Total (%[b])	*p*-Value
Hospital Badalona	14 (25.0)	42 (75.0)	56 (13.0)	
Hospital Salamanca	17 (60.7)	11 (39.3)	28 (6.5)	
Hospital A Coruña	7 (30.4)	16 (69.6)	23 (5.3)	
Hospital León	5 (29.4)	12 (70.6)	17 (3.9)	
Hospital Valencia (La Fe)	4 (28.6)	10 (71.4)	14 (3.0)	
Hospital Madrid	7 (87.5)	1 (12.5)	8 (1.9)	

ECOG: Eastern Cooperative Oncology Group; CLND: complete lymph node dissection; SSM: superficial spreading melanoma; NM: nodular melanoma; ALM: acral lentiginous melanoma; SLN: sentinel lymph node; IVO: Instituto Valenciano de Oncología.
[a] Percentages are expressed in columns (CLND vs observation).
[b] Percentages are expressed across the different categories of the variable.

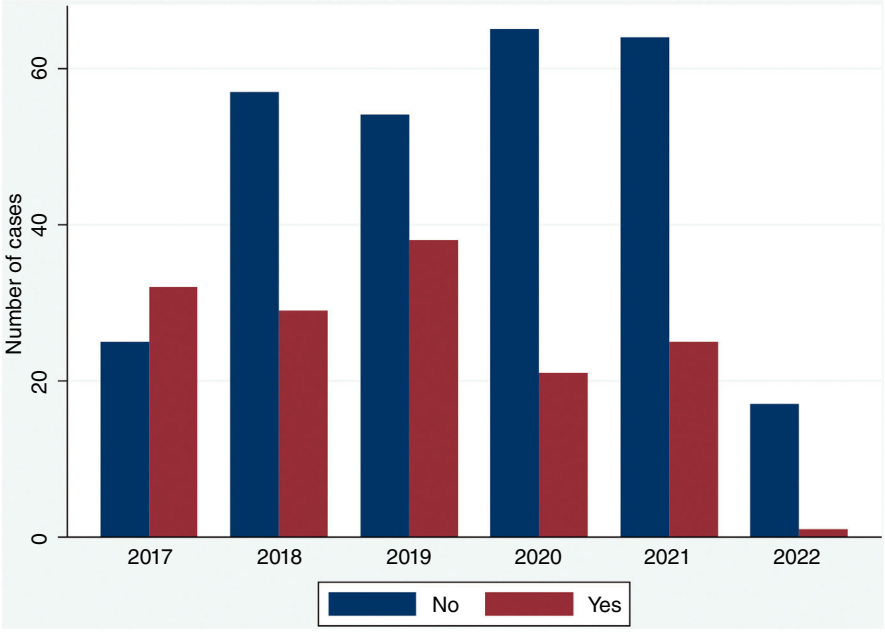

Figure 2 Distribution of patients with and without complete lymph node dissection from 2017 through 2022.

a large tumor burden in the sentinel node, extracapsular extension, >3 affected nodes, >2 affected regions, or even those with melanoma located in the head and neck region, were underrepresented. For example, the head and neck region are absent in the DeCOG-SLT and underrepresented in the MSLT-II, which observed a trend toward better survival in the CLND group, but without reaching statistical significance (HR, 1.60 [0.96–2.66]; $p = 0.07$) with 113 vs 128 patients in the dissection vs observation groups.

Since our study is based on the routine clinical practice, it more accurately reflects the characteristics most widely seen in patients with positive SLNB. For example, more than half of the patients had a tumor burden in the node >1 mm. This and other high-risk factors, such as extracapsular extension, were associated with the performance of CLND, as was having a melanoma thicker than 4 mm. Conversely, elderly patients (>80 years) underwent CLND less frequently. In literature, most published studies have also found an inverse relationship between CLND and age.[8,10–12] Other related factors include the number of affected nodes and tumor size.[7,11] Localization has been associated with a higher frequency of CLND, with melanoma in the head and neck region more likely to lead to lymphadenectomy, while localization in the lower limbs is inversely related.[7,12] Decision-making regarding melanoma in the head and neck region is especially controversial, not only because of the results of the MSLT-II but also due to the contradictory findings in observational studies in this localization.[29–31] Some argue in favor of CLND in this region for better regional control of the disease, as recurrence could lead to significant morbidity.[32] Furthermore, CLND of cervical nodes has lower morbidity vs other regions such as axillary and inguinal, which can experience up to 50% complications, including infection, seroma, and lymphedema. However, the higher complication rates following inguinal CLND likely explain the trend of avoiding CLND in melanoma located in the lower limbs, as reported by several studies.[33]

No differences in survival were found between patients undergoing CLND and those in the observation group in univariate analysis. However, it would be interesting to compare survival across patients who underwent CLND vs observation, particularly for those with high-risk melanoma

Table 2 Univariate and multivariate logistic regression of factors associated with performing complete lymph node dissection after a positive sentinel lymph node biopsy.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Sex				
Male	1			
Female	1.1 (0.7–1.6)	0.84		
Age (years)				
<45	1		1	
45–60	1.3 (0.7–2.3)	0.46	1.3 (0.6–2.8)	0.84
>60–80	1.3 (0.7–2.3)	0.44	1.3 (0.7–2.8)	0.44
>80	0	0.02	0.3 (0.1–1)	0.05
ECOG				
0	1			
1	0.5 (0.2–1.1)	0.13		
2	1.8 (0.5–7)	0.37		
3	2.9 (0.3–32.8)	0.38		
Location				
Head and neck	1			
Trunk	1.1 (0.6–2.2)	0.57		
Upper limbs	0.8 (0.3–1.9)	0.61		
Lower limbs	1.2 (0.6–2.4)	0.6		
Hands/feet	1.6 (0.7–3.6)	0.21		
Others	0.7 (0.1–7.3)	0.78		
Immunosuppression				
No	1			
Yes	1.3 (0.3–6.8)	0.72		
Tumor thickness (mm)				
≤1	1			
1.01–2	1.3 (0.5–3.6)	0.61	–	
2.01–4	1.9 (0.7–5.1)	0.18	–	
>4	2.7 (1.1–7.1)	0.04	–	
Ulceration				
No	1			
Yes	1.7 (0.8–1.8)	0.45		
Mitosis (mitoses/mm^2)				
0–1	1			
2–5	1.3 (0.7–2.4)	0.42		
≥6	1.4 (0.8–2.6)	0.25		
Vascular invasion				
No	1			
Yes	1.3 (0.7–2.3)	0.35		
Microsatellitosis				
No	1			
Yes	1.8 (0.8–3.7)	0.13		
Histological subtype				
SSM	1			
NM	1.7 (1.1–2.8)	0.03	0.6 (1.3–2.8)	0.49
ALM	2 (1–4.2)	0.051	2.9 (1.9–6.9)	0.01
Other	1.1 (0.5–2.5)	0.86	1.3 (0.8–10.1)	0.74
Number of excised lymph nodes				
1–2	1			
3–4	0.9 (0.6–1.6)	0.92		
≥4	0.7 (0.4–1.4)	0.34		

Table 2 (*Continued*)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Number of positive lymph nodes				
1	1			
≥2	1.7 (1.1–2.6)	0.013	–	
Metastasis size in SLN (mm)				
≤0.1	1			
>0.1–1	4 (0.9–18.1)	0.08	1.5 (0.3–8)	0.65
>1	11.4 (2.6–49)	0.001	7.9 (1.7–36.4)	0.008
Extracapsular extension				
No	1			
Yes	5.2 (2.1–13.1)	<0.001	4.8 (1.5–15.3)	0.008
Number of lymph node regions				
1	1			
>1	1.2 (0.5–2.8)	0.61		
Hospital				
Barcelona	1		1	
Turin	4 (2.2–7.2)	<0.001	4.4 (2.1–9.3)	<0.001
Badalona	1.3 (0.6–2.7)	0.51	1.6 (0.7–3.8)	0.27
IVO	1.4 (0.7–2.8)	0.39	1.1 (0.4–2.6)	0.85
Combined group*	3.1 (1.7–5.7)	<0.001	3.3 (1.6–7.1)	<0.001

ECOG: Eastern Cooperative Oncology Group; OR: odds ratio; CI: confidence interval; SSM: superficial spreading melanoma; NM: nodular melanoma; ALM: acral lentiginous melanoma; SLN: sentinel lymph node; IVO: Instituto Valenciano de Oncología.
* This group includes hospitals with <50 patients.

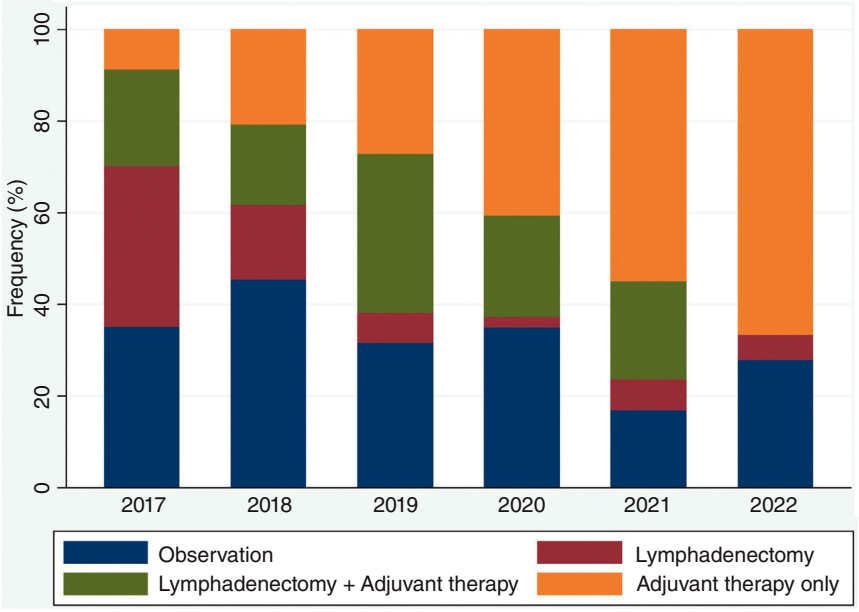

Figure 3 Distribution of patients based on the management received after positive results in the selective sentinel lymph node biopsy from 2017 through 2022.

and positive SLNB (extracapsular extension, high tumor burden, >3 affected nodes, >2 affected lymphatic regions, and head and neck localization).[13–15] Yes, the current trend assumes that the biological behavior and the rationale for observation vs CLND are independent of these characteristics.

Variability in hospital practices regarding the recommendation of CLND in these patients has been observed, reflecting differences in the temporal adaptation to the clinical practice guidelines across centers, and differences in the availability of clinical trials, appropriate radiological follow-up, or status of reference centers.[12]

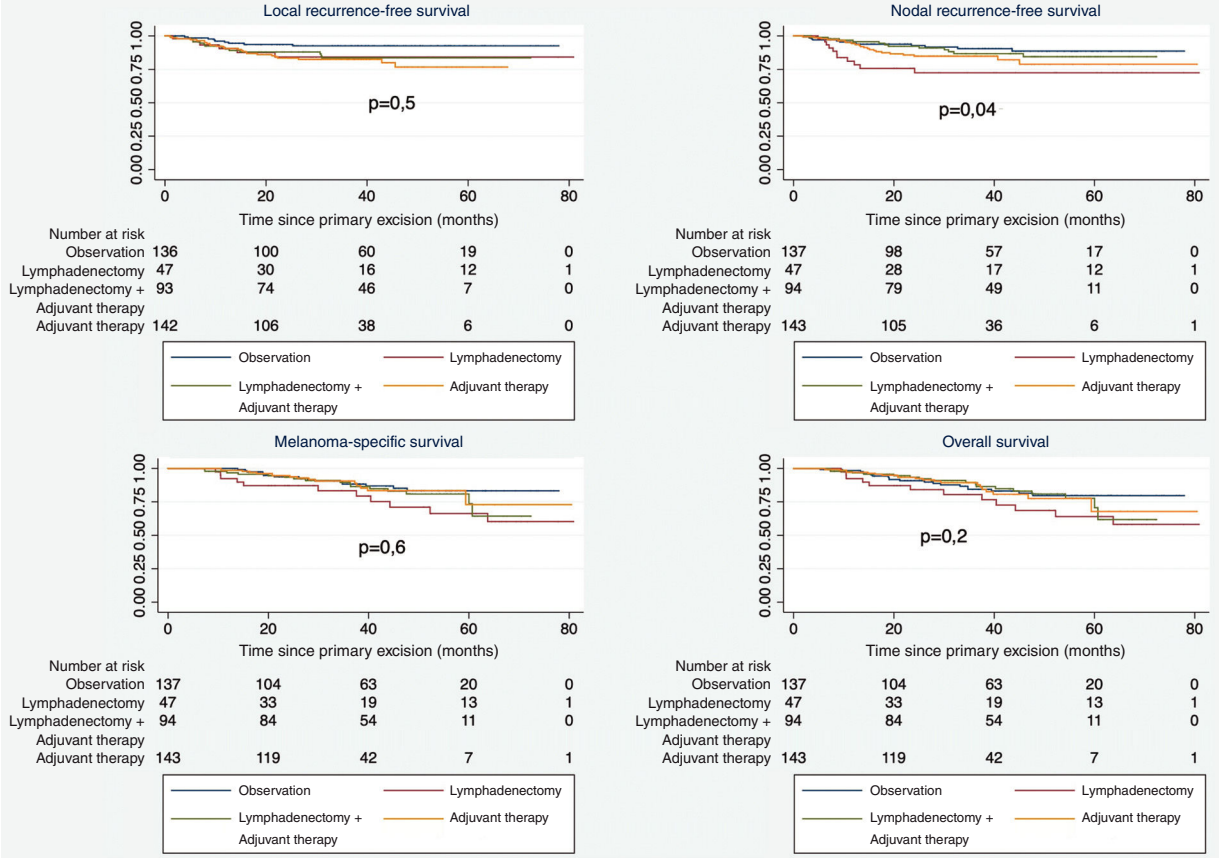

Figure 4 Local recurrence-free survival, regional lymphatic recurrence-free survival, disease-specific survival, and overall survival using the Kaplan–Meier method based on treatment received in patients with melanoma and positive sentinel lymph node biopsy ($n = 430$).

Our study shows the growing role of adjuvant therapy in recent years, with nearly 60% of patients receiving systemic adjuvant therapy. More than half of these patients did not undergo CLND, particularly in the later years of the study. These data are consistent with treatment patterns described in the literature.[7,8,11]

Even before the publication of the MSLT-II and DeCOG-SLT data, studies had shown improved relapse-free survival in melanoma with positive SLNB on adjuvant immunotherapy.[12,16,17] However, these studies only included patients who had undergone CLND, so the technique continued to be recommended initially. A new study on the efficacy of systemic adjuvant therapy in patients with melanoma and positive SLNB who did not undergo CLND showed a 67% improvement in relapse-free survival at 24 months in the adjuvant therapy group.[19]

As limitations, it should be noted that this is a retrospective study, the sample size is smaller vs other similar studies, and there are differences in the number of cases included across hospitals. However, the geographical distribution of the reference centers involved gives the study generalizability and current relevance. Furthermore, this is the only study of its kind conducted in centers in the Mediterranean area.

Based on the recent evidence included in current versions of clinical practice guidelines, there has been a significant decrease in the number of CLNDs performed in patients with melanoma and positive SLNB. This study demonstrates this same decrease in reference hospitals in our area. At the same time, there is an increased use of adjuvant therapy in this patient group, particularly since 2019. However, CLND continues to be performed in certain cases in clinical practice, as its recommendation has not been entirely eliminated from the guidelines, due to the presence of high-risk groups where the role of lymphatic dissection remains unclear. Further studies are needed to evaluate the effect of CLND in high-risk melanoma patients with positive SLNB.

Funding

This research has not received specific funding from public agencies, commercial sectors, or nonprofit organizations for the participating centers, except for research conducted by the Melanoma Working Group at Hospital Clínic in Barcelona, which is supported by the Center for Biomedical Research on Rare Diseases (CIBERER) from Instituto de Salud Carlos III (Madrid, Spain); AGAUR 2017_SGR_1134 and the CERCA Program from the Generalitat de Catalunya, Spain; a Research Grant from ''Fundación Científica de la Asociación Española Contra el Cáncer'' GCB15152978SOEN, Spain; the European Commission under the 6th Framework Program, Contract No. LSHC-CT-2006-018702 (GenoMEL), the 7th Framework Program, Diagnoptics; the European Commission under the

HORIZON2020 Framework Program, iTobos and Qualitop; and the European Commission under the Horizon Europe Program, HORIZON-MISS-2021-CANCER-02, MELCAYA (reference 101096667). This research was partly supported by grants from the Health Research Fund P.I. 18/00419 and 22/01467, Spain. Part of the work was conducted at the Esther Koplowitz Center in Barcelona, Spain.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.ad.2024.12.005.

References

1. Faries MB. Intralesional immunotherapy for metastatic melanoma: the oldest and newest treatment in oncology. Crit Rev Oncog. 2016;21:65–73, http://dx.doi.org/10.1615/CritRevOncog.2016017124.
2. Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016;17:757–67, http://dx.doi.org/10.1016/S1470-2045(16)00141-8.
3. Cutaneous M. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) NCCN.org NCCN guidelines for patients®; 2024. Available from: www.nccn.org/patients [accessed 01.06.24].
4. Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. Sydney: Cancer Council Australia; 2019.
5. Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald JE, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019;80:208–50, http://dx.doi.org/10.1016/j.jaad.2018.08.055.
6. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: update 2022. Eur J Cancer. 2022;170:236–55, http://dx.doi.org/10.1016/j.ejca.2022.03.008.
7. Broman KK, Hughes T, Dossett L, Sun J, Kirichenko D, Carr MJ, et al. Active surveillance of patients who have sentinel node positive melanoma: an international, multi-institution evaluation of adoption and early outcomes after the Multicenter Selective Lymphadenectomy Trial II (MSLT-2). Cancer. 2021;127:2251–61, http://dx.doi.org/10.1002/cncr.33483.
8. Sharon CE, Straker RJ, Li EH, Karakousis GC, Miura JT. National practice patterns in the management of the regional lymph node basin after positive sentinel lymph node biopsy for cutaneous melanoma. Ann Surg Oncol. 2022;29:8456–64, http://dx.doi.org/10.1245/s10434-022-12364-9.
9. Jones O, Murphy SH, Biosse-Duplan G, Patel AJK, Roshan A, Durrani AJ. Lymph node dissections in cutaneous malignancy: where are we now? A review of 10 years' experience at a tertiary centre. J Plast Reconstr Aesthet Surg. 2021;74:2993–8, http://dx.doi.org/10.1016/j.bjps.2021.03.115.
10. Bamboat ZM, Konstantinidis IT, Kuk D, Ariyan CE, Brady MS, Coit DG. Observation after a positive sentinel lymph node biopsy in patients with melanoma. Ann Surg Oncol. 2014;21:3117–23, http://dx.doi.org/10.1245/s10434-014-3758-7.
11. Parvez E, Khosrow-Khavar F, Dumitra T, Nessim C, Bernard-Bédard É, Rivard J, et al. Multicenter adoption and outcomes of nodal observation for patients with melanoma and sentinel lymph node metastases. Ann Surg Oncol. 2023;30:1195–205, http://dx.doi.org/10.1245/s10434-022-12695-7.
12. Leonard LD, Beaty L, Thomas M, Quinn C, Colborn KL, de Araujo TB, et al. Unmeasured factors are associated with the use of completion lymph node dissection (CLND) in melanoma. J Surg Oncol. 2023;127:716–26, http://dx.doi.org/10.1002/jso.27153.
13. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. Ann Surg Oncol. 2018;25:356–77, http://dx.doi.org/10.1245/s10434-017-6267-7.
14. Moreno-Ramírez D, Boada A, Ferrándiz L, Samaniego E, Carretero G, Nagore E, et al. Disección ganglionar en el paciente con melanoma y metástasis en el ganglio centinela: propuesta de decisión basada en la evidencia actual. Actas Dermosifiliogr. 2018;109:390–8, http://dx.doi.org/10.1016/j.ad.2018.02.008.
15. Botella-Estrada R, Boada-García A, Carrera-Álvarez C, Fernández-Figueras M, González-Cao M, Moreno-Ramírez D, et al. Clinical practice guideline on melanoma from the Spanish Academy of Dermatology and Venereology (AEDV). Actas Dermosifiliogr. 2021;112:142–52, http://dx.doi.org/10.1016/j.ad.2020.07.003.
16. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377:1824–35, http://dx.doi.org/10.1056/nejmoa1709030.
17. Eggermont AMM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015;16:522–30, http://dx.doi.org/10.1016/S1470-2045(15)70122-1.
18. Placzke J, Teterycz P, Quaglino P, Cybulska-Stopa B, Tucci M, Rubatto M, et al. The analysis of trends in survival for patients with melanoma brain metastases with introduction of novel therapeutic options before the era of combined immunotherapy – multicenter Italian–Polish report. Cancers (Basel). 2022;14:5763, http://dx.doi.org/10.3390/cancers14235763.
19. Eroglu Z, Broman KK, Thompson JF, Nijhuis A, Hieken TJ, Kottschade L, et al. Outcomes with adjuvant anti-PD-1 therapy in patients with sentinel lymph node-positive melanoma without completion lymph node dissection. J Immunother Cancer. 2022;10:e004417, http://dx.doi.org/10.1136/jitc-2021-004417.
20. Moreno-Ramírez D, Fernández-Orland A, Ferrándiz L. Inmunoterapia vs. terapia diana en el paciente con melanoma avanzado y mutación BRAF V600 ¿por cuál comenzar? Actas Dermosifiliogr. 2024;115:48–55, http://dx.doi.org/10.1016/j.ad.2023.05.023.
21. Tejera-Vaquerizo A, Ribero S, Puig S, Boada A, Paradela S, Moreno-Ramírez D, et al. Survival analysis and sentinel lymph node status in thin cutaneous melanoma: a multicenter observational study. Cancer Med. 2019;8:4235–44, http://dx.doi.org/10.1002/cam4.2358.
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of

observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Gac Sanit. 2008;22:144–50.
23. Tejera-Vaquerizo A, Pérez-Cabello G, Marínez-Leborans L, Gallego E, Oliver-Martínez V, Martín-Cuevas P, et al. Is mitotic rate still useful in the management of patients with thin melanoma? J Eur Acad Dermatol Venereol. 2017;31:2025–9, http://dx.doi.org/10.1111/jdv.14485.
24. van der Ploeg APT, van Akkooi ACJ, Rutkowski P, Nowecki ZI, Michej W, Mitra A, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and dewar topography criteria. J Clin Oncol. 2011;29:2206–14, http://dx.doi.org/10.1200/JCO.2010316760.
25. Tejera-Vaquerizo A, Barrera-Vigo MV, Fernández-Canedo I, Blázquez-Sánchez N, Mendiola-Fernández M, Fernández-Orland A, et al. Longitudinal study of different metastatic patterns in the progression of cutaneous melanoma. Actas Dermosifiliogr. 2007;98:531–8, http://dx.doi.org/10.1016/S0001-7310(07)70128-X.
26. Meier F, Will S, Ellwanger U, Schlagenhauff B, Schittek B, Rassner G, et al. Metastatic pathways and time courses in the orderly progression of cutaneous melanoma. Br J Dermatol. 2002;147:62–70, http://dx.doi.org/10.1046/j.1365-2133.2002.04867.x.
27. Richter K, Stefura T, Macheta K, Tempski J, Kazoń J, Szeremeta M, et al. Does it really pay-off? Comparison of lymphadenectomy versus observational approach in skin melanoma with positive sentinel node biopsy: systematic review and meta-analysis. J Clin Med. 2022;11:3880, http://dx.doi.org/10.3390/jcm11133880.
28. Ziętek M, Teterycz P, Wierzbicki J, Jankowski M, Las-Jankowska M, Zegarski W, et al. The current treatment trends and survival patterns in melanoma patients with positive sentinel lymph node biopsy (SLNB): a multicenter nationwide study. Cancers (Basel). 2023;15:2667, http://dx.doi.org/10.3390/cancers15102667.
29. Smith VA, Cunningham JE, Lentsch EJ. Completion node dissection in patients with sentinel node-positive melanoma of the head and neck. Otolaryngol Head Neck Surg. 2012;146:591–9, http://dx.doi.org/10.1177/0194599811432672.
30. Fritsch VA, Cunningham JE, Lentsch EJ. Completion lymph node dissection based on risk of nonsentinel metastasis in cutaneous melanoma of the head and neck. Otolaryngol Head Neck Surg. 2016;154:94–103, http://dx.doi.org/10.1177/0194599815605494.
31. Huang K, Misra S, Lemini R, Chen Y, Speicher LL, Dawson NL, et al. Completion lymph node dissection in patients with sentinel lymph node positive cutaneous head and neck melanoma. J Surg Oncol. 2020;122:1057–65, http://dx.doi.org/10.1002/jso.26119.
32. Schmalbach CE, Bradford CR. Completion lymphadenectomy for sentinel node positive cutaneous head & neck melanoma. Laryngoscope Investig Otolaryngol. 2018;3:43–8, http://dx.doi.org/10.1002/lio2.136.
33. de Vries M, Vonkeman WG, van Ginkel RJ, Hoekstra HJ. Morbidity after inguinal sentinel lymph node biopsy and completion lymph node dissection in patients with cutaneous melanoma. Eur J Surg Oncol. 2006;32:785–9, http://dx.doi.org/10.1016/j.ejso.2006.05.003.