ORIGINAL ARTICLE

When is it worth performing lymphadenectomy in patients with melanoma micrometastases? A 20-year experience retrospective analysis

¿Cuando merece la pena realizar una linfadenectomía en pacientes con micrometástasis de melanoma en ganglio centinela? Un análisis retrospectivo de 20 años de experiencia

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Abstract

Background: *The benefits of complete lymph node dissection (CLND) in melanoma patients with a positive sentinel lymph node biopsy (SLNB) have been recently questioned. Sentinel node (SN) tumor burden > 1 mm has been proposed as the most reliable parameter associated with positive CLND and poorer disease-free survival.* **Material and methods:** *Between June 1997 and June 2017, data from 119 melanoma patients with positive SLNB were analyzed. Patients were classified by SN burden in two groups: ≤ 1 mm and > 1 mm.* **Results:** *CLND was positive in 6 (10%) patients with SN tumor burden ≤ 1 mm and in 23 (37.7%) patients with > 1 mm (p < 0.001). In univariable analysis, SN tumor burden was the only predictive factor of positive CLND (OR 5.24 [1.94-14.13]). In multivariable analysis, SN tumor burden was the only independent factor of melanoma-specific survival (MSS).* **Conclusion:** *Although CLND should still be considered individually in patients with positive SLNB, SN tumor burden >1 mm might be a good predictive factor of additional positive non-sentinel nodes and a strong independent prognostic factor in melanoma-specific survival.*

Key words: *Melanoma. Sentinel lymph node biopsy. Lymphadenectomy. Micrometastasis. Survival analysis. Melanoma-specific survival.*

Resumen

Introducción: *Actualmente existe controversia respecto a los beneficios de realizar linfadenectomía en pacientes de melanoma con una biopsia selectiva de ganglio centinela (BSGC) positiva. La carga tumoral > 1 mm se ha propuesto como el parámetro mas relevante asociado a una linfadenectomía positiva y un deterioro de la supervivencia libre de enfermedad.* **Material y métodos:** *Se analizaron los datos de 119 pacientes de melanoma con BSGC positiva atendidos en el periodo entre Junio de 1997 y Junio de 2017. Los pacientes se clasificaron según la carga tumoral en dos grupos: ≤ 1 mm and > 1 mm.* **Resultados:** *La linfadenectomía resultó positiva en sólo 6 (10%) pacientes con una carga tumoral ≤ 1 mm, y en 23 (37.7%) pacientes con carga tumoral > 1 mm (p < 0.001). En análisis univariante, la carga tumoral fue el único factor predictivo de linfadenectomía positiva (OR 5.24 (1.94-14.13)). En análisis multivariante, la carga tumoral fue la única variable independiente de supervivencia específica de melanoma (SEM).* **Conclusion:** *Aunque la realización de linfadenectomía debe*

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individualizarse en cada caso, la carga tumoral > 1 mm puede ser un factor predictivo de la presencia de ganglios no centinelas positivos en piezas de linfadenectomía, y un factor pronostico independiente importante para la SEM.

Palabras clave: *Melanoma. Biopsia selectiva de ganglio centinela. Linfadenectomía. Micrometastasis. Análisis de supervivencia. Supervivencia específica de melanoma.*

Background and Objectives

Complete lymph node dissection (CLND) has been a cornerstone in the management of melanoma patients with a positive sentinel lymph node biopsy (SLNB) for many years. Since the outcomes from the DeCOG (German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy)[1] and MSLT-II (Multicenter Selective Lymphadenectomy Trial)[2] studies were published, the benefits of CLND have increasingly been questioned. In recent years, we have observed a tendency toward performing fewer CLND in patients with positive SLNB. Every time we face a patient with a positive SLNB, we still have the responsibility to decide whether to perform a CLND or not.

Sentinel node (SN) tumor burden > 1 mm has been proposed previously as the most reliable and consistent parameter independently associated with positive CLND and poorer disease-free survival[3,4].

The aim of this study was to analyze how SN burden predicts additional positive non-sentinel nodes (NSN) in CLND and survival in patients with a positive SNLB melanoma.

Methods

Between June 1997 and June 2017, a retrospective study to evaluate epidemiological, histological, and survival characteristics in a sample of melanoma patients with positive SLNB was performed. According to clinical guidelines of that time period before the AJCC 8th edition for staging of melanoma, SLNB was considered and discussed with patients presenting melanoma thickness ≥ 0.75 mm. Histological reports of excised nodes described SN tumor burden by measuring the sum of the maximum diameter of nodal involvement. Our patients were classified in two categories according to SN tumor burden maximum diameter (≤ 1 mm and > 1 mm). In patients with positive SLNB, a subsequent completion lymph node dissection (CLND) was performed.

Descriptive statistics for the variables of patients with positive SLNB were collected. To study the associations between SN burden and these variables, a *Student's* t-test was performed for quantitative variables (age at diagnosis, Breslow index) and a *Chi-square* test was performed for qualitative variables. $P < 0.05$ was considered statistically significant. A Kaplan–Meier method with a 95% confident interval (CI) was performed to analyze impact of SN burden on recurrence-free survival (RFS) and melanoma-specific survival (MSS). The descriptive and analytical studies of the data were performed with SPSS® software, version 22.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 1358 melanoma patients were treated during the study period. A SLNB was performed in 440 of these patients (32.4%).

In 119 (27%) patients with positive SLNB, an immediate CLND was performed. Mean age at diagnosis was 55 years. Fifty-nine (49.5%) were women and 60 (50.5%) were men. The melanomas were located as follows: head and neck (9; 7.4%), trunk (57; 46.7%), and limbs (56; 45.9%). The median follow-up period was 48 months. Immediate complications after lymphadenectomy were lymphedema (22%), seroma (15%), hematoma (5%), infection (4%), and thrombosis (3%).

Associations between SN burden subgroups and clinical-pathological features are presented in Table 1. Fifty-eight (49%) patients had a total SN burden ≤ 1 mm and 61 (51%) patients had a SN burden > 1 mm. CLND was positive in only 6 (10%) patients with a SN tumor burden ≤ 1 mm and in 23 (37.7%) patients with SN tumor burden > 1 mm ($p < 0.001$). SN tumor burden > 1 mm was associated with a higher number of deaths by melanoma and lower recurrence-free survival and melanoma-specific survival (Table 2). In multivariable analysis, including sex, age, tumor thickness, histological subtype, ulceration, and SN burden (Table 3), SN burden was the only independent factor of melanoma-specific survival (OR 5.24; 1.94-14.13; $p < 0.001$) (Fig. 1).

Discussion

Sentinel lymph node biopsy is still a recommended procedure in most national and international

Table 1. Predictive factors of non-sentinel node status in CLND

	All (n=119)	Negative CLND (n=90)	Positive CLND (n=29)	p
Sex, n (%)				0.31
Women	59 (49)	47 (80)	12 (20)	
Men	60 (51)	43 (72)	17 (28)	
Age at diagnosis (y)				0.74
Mean ± standard deviation	56 ±14.61	55.8 ± 14.9	56.8 ± 14	
Histological type of melanoma, n (%)				0.75
Nodular	29 (24)	19 (65)	10 (35)	
Others	90 (76)	56 (62)	34 (38)	
Mitoses/mm^2				0.45
0	9 (8)	7 (78)	2 (22)	
1	30 (25)	22 (73)	8 (27)	
2-5	55 (46)	39 (71)	16 (29)	
≥6	25 (21)	15 (60)	10 (40)	
Breslow index (mm)				0.39
Mean ± standard deviation	3.83 ±4.95	3.61 ±4.97	4.52 ±4.91	
Tumoral thickness (T stage)				0.13
T1 (≤ 1 mm)	11 (9)	9 (82)	2 (18)	
T2 (1.01-2 mm)	34 (29)	28 (82)	6 (18)	
T3 (2.01-4 mm)	41 (34)	33 (81)	8 (19)	
T4 (> 4 mm)	33 (28)	20 (61)	13 (39)	
Histological ulceration				0.092
Absent	90 (76)	60 (79)	16 (21)	
Present	29 (24)	30 (70)	13 (30)	
SN tumor burden				<0.001
≤1 mm	58 (49)	52 (90)	6 (10)	
>1 mm	61 (51)	38 (62)	23 (37.7)	

CLND: complete lymph node dissection. SN: sentinel node

Table 2. Associations between SN burden and survival outcomes (%)

	SN burden ≤ 1 mm (n=58)	SN burden > 1 mm (n=61)	p
Deaths by melanoma	6/58 (19)	36/61 (59)	<0.0001
RFS (months)			<0.0001
Mean ± SD	190.42±21.91	74.57±11.87	
95% CI	147.47-233.38	51.30-97.85	
MSS (months)			<0.0001
Mean ± SD	185.75±23.50	85.04±11.20	
95% CI	139.65-231.84	63.07-107.01	

RFS: recurrence-free survival; MSS: melanoma-specific survival.

Table 3. Multivariate Cox's analysis of melanoma disease-specific survival

	HR (95% CI)	p
Sex	1.88 (0.90-3.57)	0.054
Age	0.98 (0.96-1.00)	0.194
Histologic type	0.97 (0.49-1.92)	0.935
Histologic ulceration	1.10 (0.58-2.11)	0.766
Breslow index	2.18 (0.94-5.01)	0.071
SN tumor burden	5.66 (2.28-14.02)	<0.001

HR: hazard ratio; SN: sentinel node.

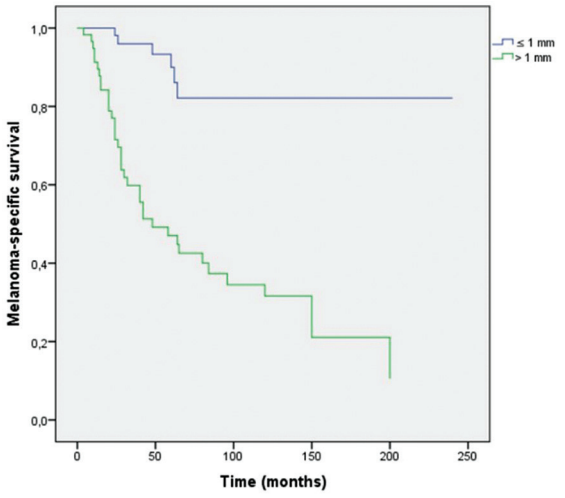

Figure 1. *Melanoma-specific survival differences according to SN tumor burden.*

guidelines for the staging and treatment of melanoma. Sentinel node tumor burden has been reported to predict additional positive non-sentinel lymph nodes and survival in patients with melanoma[5,6]. Two classifications of SLNB tumor burden using micromorphometric criteria have been proposed: the Rotterdam classification of maximum tumor diameter (< 0.1 mm, 0.1-1.0 mm, and > 1.0 mm) and the Starz classification of SN depth of invasion[7,8]. In line with our study, both methods estimate additional NSN metastases, correlate tumor burden with tumor thickness, and associate tumor burden with poorer recurrence-free survival (RFS) and disease-specific survival (DSS).

In patients with sentinel-node micrometastases, the value of CLND remains controversial to this date. Arguments against CLND include the cost and morbidity related to the procedure[9]. Nevertheless, the presence of microscopic NSN metastases portends a markedly worse prognosis similar to patients with clinically diagnosed metastases[10,11]. As only about 20% of

positive SN melanoma patients have additional NSN involvement in the CLND pathological analysis, we tried to identify a subgroup within SN-positive patients which could be spared of CLND.

Our results show that SN tumor burden > 1 mm might be a strong independent prognostic factor in melanoma-specific survival. In DeCOG trial, 66% of cases had micrometastases < 1.0 mm in SLNB; in MSLT-II trial, almost 67% of patients in lymphadenectomy group and almost 90% of patients in the observation group had a SN burden < 1 mm[1,2]. The small number of patients with larger SN tumor burden in both trials limited the statistical significance regarding the impact of CLND in survival. A recent meta-analysis[12] showed that MSS was higher after immediate CLND compared with delayed CLND in patients with nodal metastasis, suggesting that there is a time-dependent disease-specific survival benefit for immediate lymph node surgery.

Our study may also help to establish when it is worth performing CLND after a positive SLNB. However, the present study does not directly compare survival for patients who received CLND versus those who did not, so there is a lack of direct evidence of improved survival with CLND. Another limitation in our study is that all patients come from a single institution.

Even in patients with micrometastases ≤ 1 mm, it seems reasonable to explain to patients, the advantages and disadvantages of CLND versus nodal observation. Patients should decide after being adequately informed and advised by their physician. In this scenario, physicians should also discuss with their patients the benefits and risks of currently available adjuvant therapies, or, taking part in a clinical trial of a new therapeutic alternative.

In conclusion, although CLND should still be considered individually in patients with positive SLNB, SN tumor burden >1 mm might be a good predictive factor of additional positive non-sentinel nodes and a strong independent prognostic factor in melanoma-specific survival.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical responsibilities

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of the data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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