ISSN 1669-9106 MEDICINA (Buenos Aires) 2024: 84: 279-288

Original article

RECURRENCE FACTORS IN PATIENTS WITH CUTANEOUS MELANOMA AND POSITIVE SENTINEL LYMPH NODE TREATED IN A SINGLE REFERENCE UNIT IN BUENOS AIRES

WALTER S. NARDI[1,2], MARIANA TOFFOLO PASQUINI[1], FLORENCIA TOMÉ[1], FÉLIX VIGOVICH[3], MARIA FLORENCIA CORA[3], SERGIO D. QUILDRIAN[1,2]

[1]Departmento de Cirugía General, [2]Unidad de Sarcomas y Melanoma, Departamento de Cirugía General, [3]Departmento de Anatomía Patológica, Hospital Británico de Buenos Aires, Argentina

Postal address Walter S. Nardi, Unidad de Sarcomas y Melanoma, Departamento de Cirugía General, Hospital Británico de Buenos Aires, Perdriel 74, 1280 Buenos Aires, Argentina
E-mail: nardi.ws@gmail.com
Received: 20-VI-2023
Accepted:31-X-2023

Abstract

Introduction: Although therapeutic advances have improved results of cutaneous melanoma (CM), sentinel node-positive patients still have substantial risk to develop recurrent disease. We aim to investigate prognostic indicators associated with disease recurrence in positive-sentinel lymph node biopsy (SLNB) patients in a Latin-American population.

Methods: Retrospective analysis of CM patients and positive-SLNB (2010-2020). Patients were divided into two groups: Group A (completion lymph node dissection, CLND), Group B (active surveillance, AS). Association of demographics, tumor data and SLN features with recurrence-free (RFS), distant metastases-free (DMFS) and melanoma specific (MSS) survival was analyzed.

Results: Of 205 patients, 45 had a positive SLNB; 27(60%) belonged to Group A and 18(40%) to Group B. With a median follow-up of 36 months, 16 patients (12 in Group A and 4 in Group B) developed recurrent disease and estimated 5-yr RFS at any site was 60% (CI95%, 0.39 – 0.77) (44.5% in CLND group vs. 22% in AS group; P = 0.20). Estimated 5-yr DMFS and MSS: 65% (CI 95%, 0.44 – 0.81) and 73% (CI 95%, 0.59 – 0.89) with no differences between groups (p = 0.41 and 0.37, respectively). Independent predictors of poorer MSS were extranodal extension (ENE) and MaxSize > 2 mm of melanoma deposit in SLN. Factors independently associated with DMFS: Breslow depth > 2 mm, ENE, number (≥ 2) of positive SN and CLND status.

Conclusion: Primary tumor and SN features in melanoma provide important prognostic information that help optimize prognosis and clinical management. AS is now the preferred approach for most positive-SLNB CM patients.

Key words: cutaneous melanoma, positive sentinel lymph node, prognostic factors, survival, active surveillance, adjuvant therapy

Resumen

Factores de recurrencia en pacientes con melanoma cutáneo y ganglio centinela positivo

Introducción: Si bien los avances terapéuticos han permitido mejorar los resultados del melanoma cutáneo (MC), los pacientes con ganglio centinela positivo (BGCP) aún tienen riesgo elevado de desarrollar recurrencia de la enfermedad. Nuestro objetivo fue investigar indicadores pronósticos asociados a dicho evento en una población latinoamericana.

Métodos: Análisis retrospectivo de pacientes con MC y BGCP entre 2010-2020. Los pacientes se dividieron en 2 grupos: Grupo A (linfadenectomía terapéutica) y Grupo B

(Vigilancia activa, VA). Se analizaron datos demográficos, tumorales y características del GC junto con sobrevida-libre de recurrencia (SLR), libre de metástasis a distancia (SLMD) y específica de melanoma (SEM).

Resultados: De 205 pacientes, 45 presentaron BGCP; 27 (60%) perteneció al Grupo A y 18 (40%) al Grupo B. Con una mediana de seguimiento de 36 meses, 16 pacientes (12 en Grupo A y 4 en Grupo B) desarrollaron enfermedad recurrente con una SLR a 5 años de 60% (IC95%: 0.39-0.77) (44.5% en Grupo B vs. 22% en Grupo A; P = 0.20). Las SLMD y SEM estimadas a 5 años fueron de 65% (CI 95%, 0.44 – 0.81) y 73% (CI 95%, 0.59 – 0.89) sin diferencias entre ambos grupos (p = 0.41 y 0.37, respectivamente). Los predictores independientes de peor SEM fueron: extensión extranodal (ENE) y MaxSize > 2mm de depósito tumoral en GC. Los factores asociados de forma independiente con SLMD fueron Breslow >2mm, ENE, número (≥ 2) de GC positivos y el status (positividad) de la linfadenectomía.

Conclusión: Características del tumor primario y del GC brindan información importante que ayuda a optimizar el pronóstico y manejo clínico de los pacientes con MC. La VA es actualmente el abordaje de elección para la mayoría de los pacientes con BGCP.

Palabras clave: melanoma cutáneo, biopsia de ganglio centinela (positivo), factores pronósticos, vigilancia activa, sobrevida

Abbreviations: cutaneous melanoma (CM), sentinel node (SN), sentinel lymph node biopsy (SLNB), completion lymph node dissection (CLND), active surveillance (AS), sentinel lymph node (SLN), recurrence-free survival (RFS), distant metastases-free survival (DMFS), melanoma specific survival (MSS), American Joint Committee on Cancer (AJCC), Multicenter Selective Lymphadenectomy Trial (MSLT), non-sentinel lymph nodes (NSNs), Multidisciplinary tumor board (MDT), maximum size of largest melanoma deposit (MaxSize), extranodal extension of tumor (ENE), isolated nodal recurrence (INR)

KEY POINTS
Current knowledge

- For patients with melanoma and positive-SLNB risk of recurrent disease is still substantial. Also in those patients, monitoring with ultrasound (active surveillance) has recently been adopted as an alternative to immediate lymphadenectomy.

Article contribution

- This study confirms prognostic indicators that impact on survival of CM patients. Most importantly adds real-world data of results on (actually preferred strategy) active surveillance in positive-SLN melanoma patients in a reference specialized center in Argentina.

Tumor progression has been reported in about one third of all patients diagnosed with clinically localized primary cutaneous melanoma (CM) as locorregional nor distant recurrences[1]. Different factors have been recognized and used in scoring systems to predict the risk of recurrence. Anatomic location, ulceration, age, mitotic rate and positive-SN represent some of those variables evaluated in different series. Some studies also have investigated the positive sentinel node characteristics and correlated them with outcomes and patient survival. Moreover, there is a historically wide range of survival for stage III melanoma patients and this trend increased even more in the current 2017 American Joint Committee on Cancer (AJCC) eight edition[2].

Status of the regional lymph nodes in patients with clinically localized CM is the most important prognostic factor[3-7]. Sentinel lymph node biopsy (SLNB) is the best-known and precise procedure to assess the lymph node status in these patients as demonstrated in the first Multicenter Sentinel Lymphadenectomy Trial (MSLT-1)[8, 9]. Moreover, with an accountable less morbidity than elective completion lymph node dissection (CLND) which was previously the strategy of choice for staging regional lymph nodes in clinically node-negative patients[10,11]. Only approximately 20% of the patients with positive sentinel lymph node (SLN) have metastatic tumor cells in the other non-sentinel lymph nodes (NSNs). Results of two randomized controlled trials (MSLT-2 and DeCOG-SLT) posteriorly showed that immediate CLND did not increase melanoma-specific survival and proposed a change in the timing of that intervention for those patients with subclinical metastatic-NSNs; establishing that the active surveillance with ultrasound and without immediate CLND is a safe and less

morbid option in these patients[12,13]. In addition, several trials have established the utility of adjuvant systemic therapy in patients with stage III cutaneous melanoma[14-16].

We aimed to investigate prognostic indicators associated with disease recurrence (regional and distant) and survival in positive-SLNB patients treated at our Institution before and after MSLT-2 era.

Material and methods

A retrospective evaluation of patients with positive-SLNB for cutaneous melanoma between January 2010 and December 2020 at the Sarcoma and Melanoma Unit of our General Surgery Department was carried out. We included patients who had a clinically localized and node-negative cutaneous melanoma of trunk and extremities, aged ≥18 years and had at least 1 positive (metastatic) SLN. Patients who had loco-regional or distant disease during the preoperative staging were excluded. Institutional Review Board permission was obtained for this study.

Multidisciplinary institutional melanoma tumor board (MDT) meets once every week and all patients are discussed at initial consultation and previous to start definitive treatment. We recommended SLNB in all patients with cutaneous melanoma and a Breslow thickness ≥1mm or ≥0.75mm with associated risk factors (ulceration, high mitotic count or Clark level invasion IV/V). Since 2020 we discussed the indication in thin melanomas when the probability of nodal metastasis was ≥10% (using the Sentinel Node Metastasis Risk Prediction Tool developed by Melanoma Institute Australia based on a published risk prediction model)[17,18]. The SLN was defined as the lymph node (or nodes) that first receives direct lymphatic drainage (evaluated with blue dye and/or radioactive isotope) from the primary melanoma. All patients underwent surgical procedure as described by Morton[19]. In the same surgical procedure definitive treatment of primary lesion was done as appropriate (wide local excision of primary tumor with proper margins or wide excision of scar of previous incomplete surgery).

Clinical features (age at diagnosis and sex) and primary tumor features (histologic subtype, Breslow thickness divided as < 2 or ≥ 2 mm, ulceration, mitotic rate, lymphovascular invasion) were recorded. Meticulous pathologic examination was done in all SLNs using H&E analysis and immunohistochemistry (with S-100 and HMB-45) by the same expert pathologist (FV). Some SLN specimens were re-examined and if necessary further sections were cut and stained ensuring that all the patients were assessed under the same protocol. Sentinel node (SN) features analyzed were: number of SN harvested during SLNB, maximum size of largest melanoma deposit (MaxSize) categorized as ≤ 2 mm or > 2 mm, intranodal location of melanoma deposits as described by Dewar et al[20] and presence of extranodal extension of tumor (ENE).

According to the evidence published in literature we started our active surveillance (AS) protocol without CLND in positive-SLNB patients in June 2017. Previously, all patients were offered CLND. Hence, depending on management, we divided the cohort into two groups: Group A (CLND) and Group B (active surveillance, AS). All patients were followed-up according to usual protocol which is every 3 months the first 2 years, then every 6 months until the 5th year and then annually with physical examination, chest radiography and hepatic ultrasound. AS protocol adds an ultrasound of the mapped node basin. The indication for systemic adjuvant treatment was discussed with the patients after multidisciplinary tumor board evaluation. The immediate CLND was not a requirement to deliver adjuvant treatment.

Any-site recurrence free survival (RFS) was defined as first recurrence of melanoma at any site from time of SLNB, diagnosed by clinical and/or imaging studies and confirmed on biopsy when feasible. Isolated nodal recurrence (INR) was defined as recurrence in SLN-basin without other affected site. Distant metastasis-free survival (DMFS) was defined as distant recurrence beyond the regional node field identified during follow-up as either first or subsequent recurrence. Melanoma-specific survival (MSS) was defined as melanoma-related death from time of SLNB.

The relationship of categorical clinic-pathologic parameters between the different groups was assessed initially. Qualitative variables were compared using χ^2 and Fisher's exact test, when applicable, while Student's t-test was used for quantitative variables. Quantitative variables are described as mean and standard deviation (SD) or median and interquartile range (IQR) and qualitative variables as percentages. Patients were compared according to systemic recurrence, performing a univariate analysis to identify the factors associated with it. MANOVA was used for multivariate analysis, including variables identified as p <0.25 in univariate analysis. All statistical analyses were done by use of XLSTAT 2020, 4.1.1023. An arbitrary p value of less than 0.05 was considered as significant.

Consent to participate: Due to the retrospective nature of this study, the Ethics Committee waived the require-

ment for written informed consent: however, all patients signed the surgical consent form.

Results

During the study period we performed 205 SLNBs. Among these, 45 patients (22%) had at least one positive SLN. Twenty-seven patients (60%) underwent CLND (Group A) while the remaining 18 (40%) had an active surveillance (Group B) (Fig. 1). Characteristics of patients in both groups are listed in Table 1.

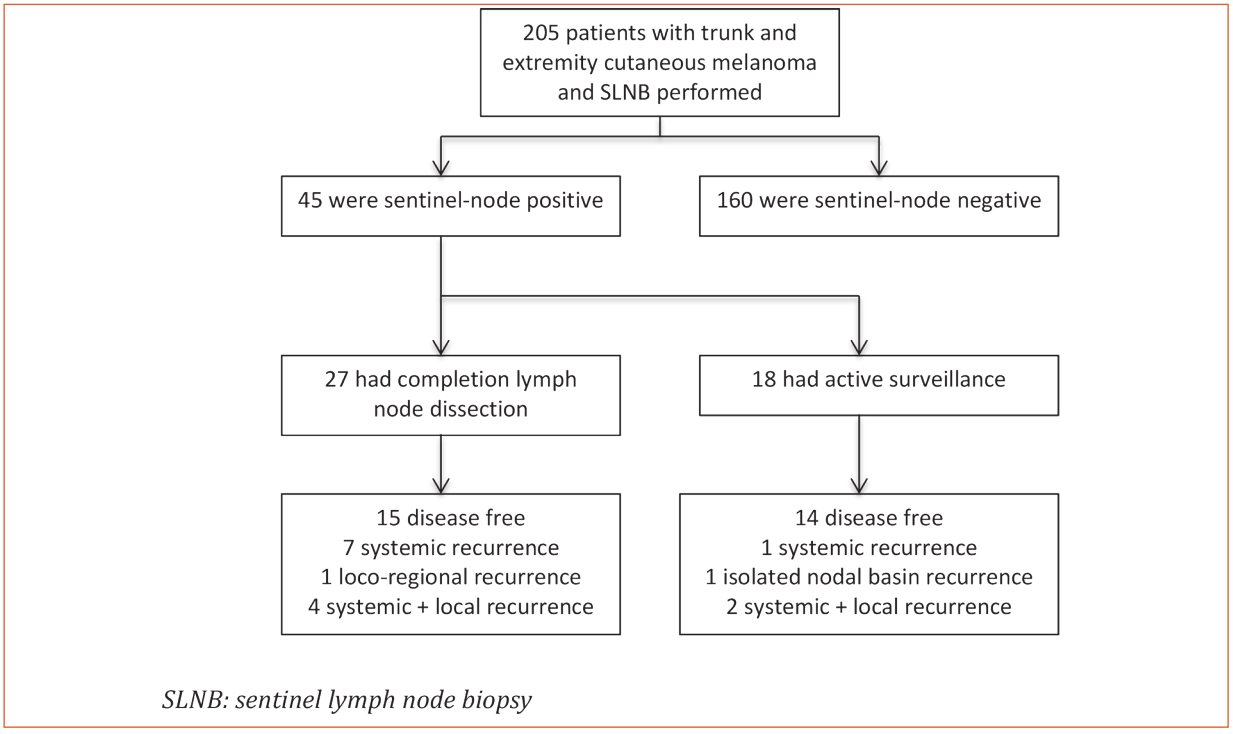
Among the patients in Group A, 10 (37%) had metastatic disease in the completion specimen: 5 patients one positive non-SLN and 5 patients had ≥ 2 positive non-SLNs. CLND resulted in upstaging, according to the American Joint Committee on Cancer 8th edition cancer staging manual, in 4 of 10 cases (40%).

The median follow-up of the whole cohort was 36 months (25th to 75th interquartile, 16.5-66.5 months). We observed a total of 16 (35%) recurrences at any site (10 patients having disease recurrence before year one of follow-up; median time to disease recurrence was 10 months) and estimated 5-yr RFS at any site was 60% (CI95%, 0.39-0.77). Of them, only 50% (8/16 patients) received adjuvant treatment and had Stage III C/D disease. We observed 44.5% recurrences in Group A (12/27, median follow-up 41 months) and 22% in Group B (4/18, median follow-up 28.5 months); p = 0.20.

There were two (2/45; 4%) exclusive loco-regional recurrences: one tumor satellite near surgical scar of primary tumor that was resected and, in Group B, an isolated nodal basin recurrence detected by ultrasound during follow-up. That patient (stage IIIB without adjuvant treatment) underwent complete nodal basin dissection without post-operative morbidities. Both patients are alive and without evidence of disease at last follow-up.

Estimated 5-yr DMFS of the whole cohort was 65% (CI 95%, 0.44-0.81) with no differences between groups (p = 0.41). We observed eight (18%) exclusive systemic recurrences and six (13%) patients had both systemic and loco-regional disease recurrence. When analyzed, we observed age ≥ 50, Breslow depth > 2 mm, MaxSize of melanoma deposit > 2 mm, ENE and CLND status (positive) to be associated with occurrence of systemic disease on univariate analysis. Multivariate analysis showed Breslow

Figure 1 | Patient flow chart and outcomes



SLNB: sentinel lymph node biopsy

Table 1 | Characteristics of patients undergoing complete lymph node dissection (Group A) and active surveillance (Group B)

Parameter	Group A n = 27	Grupo B n = 18	p
Male sex (%)	15 (55)	9 (50)	ns
Age: mean SD, yr.	56 (42-68)	53 (39-67)	ns
Tumor location (%)			ns
Trunk	13 (50)	9 (50)	
Upper extremity	6 (21)	3 (17)	
Lower extremity	8 (29)	6 (33)	
Breslow thickness, mm	2 (1-6)	3 (2-6.5)	ns
Tumor ulceration (%)	11 (39.5)	10 (55)	ns
Mitotic rate			ns
0	4	3	
1-2 /mm^2	22	11	
≥ 3 /mm^2	1	4	
LVI	2	3	ns
AJCC8 Stage			
IIIA	10	4	
IIIB	7	5	
IIIC	8	8	
IIID	2	1	ns
Adjuvant systemic therapy	10 (35)	11 (61)	ns
Follow up (months), median	41 (15-83)	28.5 (17-39)	-
Pattern of recurrence (%)	12 (46.5)	4 (22)	ns
Loco-regional	1	1	
Systemic	7	1	
Both	4	2	

AJCC8: American Joint Committee on Cancer 8th Edition

depth > 2 mm, ENE, number (≥ 2) of positive SN and CLND status as independent risk factors of DMFS (Table 2).

During the study period eight patients died of melanoma while other three died for other not related causes and were excluded from the analysis of MSS. Estimated 5-yr MSS was 73% (CI 95%, 0.59-0.89) with no differences between CLND and AS groups (log-rank p = 0.37). Factors associated with MSS were sex (male), Breslow thickness, ENE and MaxSize of melanoma deposit in SLN, CLND status (positive) and use of adjuvant systemic therapy. Multivariate analysis showed ENE and MaxSize > 2 mm of melanoma deposit were independent predictors of MSS (Table 3).

Discussion

SN-positive patients have a significantly increased risk of developing any form of recurrence compared to SN-negative patients. In the past, several studies have identified parameters predictive of clinical outcomes in SN-positive patients. Breslow thickness, older age and Non-SN positivity (but not number of nodes) in CLND demonstrated to be independent predictors of survival. But additionally, management of patients with cutaneous melanoma has had several changes in the last decades[21]. Despite its retrospective nature and small sample size, the results of our study are in line with previous studies and analyses the outcomes of positive-SN patients (with a signifi-

Table 2 | Analysis of factors related to systemic recurrence

Parameter	No Recurrence n = 29	Systemic Recurrence n = 14	Univariate p value	Multivariate p value
Male sex	16	9	0.74	-
Age, years			0.18	0.076
< 50	13	3		
≥ 50	16	11		
Breslow thickness, mm			0.04	0.018
< 2	14	2		
≥ 2	15	12		
Tumor ulceration			0.32	-
Present	11	8		
Absent	18	6	0.14	-
Mitotic rate				
0	3	0		
1-2 /mm^2	19	13		
≥ 3 /mm^2	7	1		
LVI	4	1	1	-
SN tumor features				
N of positive SN:			0.11	0.014
1	24	8		
2	5	6		
MaxSize of melanoma deposit:			0.04	0.337
≤ 2 mm	19	4		
> 2 mm	10	10		
Intranodal location of tumor:			0.9	-
Subcapsular	13	7		
Combined	1	0		
Parenchymal	3	2		
Multifocal	5	1		
Extensive	7	4		
ENE	0	3	0.02	0.006
AJCC8 Stage			0.09	0.932
III A	12	2		
III B-C-D	17	12		
Nodal Management			0.11	0.308
Dissection	15	11		
Surveillance	14	3		
CLND Status (n = 26)			0.03	0.048
Positive	3	8		
Negative	13	2		
Adjuvant systemic therapy			1	-
Yes	13	7		
No	16	7		

LVI: lympho-vascular invasion; ENE: extranodal extension; AJCC8: American Joint Committee on Cancer 8th Edition; CLND: completion lymph node dissection

Table 3 | Analysis of factors related to melanoma specific survival

Parameter	Alive n = 34	Death of disease n = 8	Univariate p value	Multivariate p value
Male sex	17	6	0.25	0.075
Age, years			0.42	-
< 50	14	2		
≥ 50	20	6		
Breslow thickness, mm			0.11	0.055
< 2	16	1		
≥ 2	18	7		
Tumor ulceration			1	-
Present	15	4		
Absent	19	4		
Mitotic rate			0.55	-
0	4	0		
1-2 / mm^2	23	7		
≥ 3 /mm^2	7	1		
LVI	4	1	1	-
SN tumor features				
N of positive SN:			0.29	-
1	8	5		
2	26	3		
MaxSize of melanoma deposit:			0.002	0.007
≤ 2 mm	22	0		
> 2 mm	12	8		
Intranodal location of tumor:			0.42	-
Subcapsular	16	3		
Combined	2	0		
Parenchymal	4	1		
Multifocal	5	0		
Extensive	7	4		
ENE	0	3	0.005	< 0.0001
AJCC8 Stage			0.23	0.5
III A	13	1		
III B-C-D	21	7		
Nodal Management			0.11	0.14
Dissection	18	7		
Surveillance	16	1		
CLND Status (n = 26)			0.002	0.07
Positive	4	5		
Negative	15	2		
Adjuvant systemic therapy			0.25	0.051
Yes	17	2		
No	17	6		

LVI: lympho-vascular invasion; ENE: extranodal extension; AJCC8: American Joint Committee on Cancer 8th Edition; CLND: completion lymph node dissection

cant number of clinicopathologic parameters assessed) before and after MSLT-II era and adjuvant therapies in a Latin-American population where information is still scarce[22,23].

We found that some primary tumor (Breslow > 2 mm) and SN tumor (extranodal extension and ≥ 2 positive SN) features as well as CLND status (positive) were independent risk factors of DMFS. Non SN positivity in CLND has been shown to be a significant predictor of survival and poor DMFS; this last parameter being a more reliable measure because it takes into account as an endpoint a clinical situation that could be life-threatening and might lead to patient's death by disease. Results of MSLT-II and DeCOG-SLT showed that immediate CLND in patients with a low tumor burden in the SLN was not associated with improved melanoma specific survival. As a result, active nodal surveillance emerged as an option delaying the CLND in the true 20% positive-NSN group without adverse oncologic impact and avoiding it in the rest of the patients. In the present study positive immediate CLND (majority performed prior MSLT-II era) was an independent risk factor of DMFS as in other studies; but we saw no impact in disease specific survival nor DMFS when we analyzed the management of nodal basin (active surveillance vs. lymphadenectomy) according to the actual evidence in the literature[12, 13, 24, 25].

Moreover, SN tumor characteristics such as MaxSize or tumor penetrative depth have proven to be associated with clinical outcomes[26-28]. Optimal MaxSize cutoff for prognostic stratification is not well standardized given the fact that histologic protocols for sampling SNs vary between studies. Nonetheless, MaxSize is predictive of survival as shown in different studies even with different cutoffs. The Rotterdam Group[29,30] showed association with disease survival when categorized into <0.1 mm, 0.1-1 mm and >1 mm while the 2 mm cutoff was a significant predictor of DFS and DMFS in the study by Murali et al[28]. In our study we found a statistical significant association of this value (2 mm) with DMFS and MSS. Some studies argue against the use of size of tumor deposits as a criterion to estimate prognosis. We had 6 patients with MaxSize < 1 mm (micrometastases) and, after a median follow-up of 58.5 (IQR, 16-93) months, all are alive without disease recurrence. Due to the small size of this subgroup we cannot determine the clinical significance of melanoma micrometastases in SNs.

Although not statistically significant, a trend towards worse DMFS and MSS was observed in older patients and male sex respectively. Nonetheless, in a previous report of the role of SLNB for cutaneous melanoma in elderly patients we described poorer overall survival in patients ≥ 70 years[31]. Age > 50 years has been associated with poorer MSS in other studies[28].

Given the results of the nivolumab, pembrolizumab and dabrafenib-trametinib trials and, in light of the results of MSLT-II and DeCOG trials, adjuvant therapy is a reasonable strategy even in those patients not undergoing CLND. But real world data show different percentages of patients actually receiving it. Broman et al. described that adjuvant systemic therapy was given in 39% of patients who underwent CLND and 38% who underwent active surveillance[28]. Nijhuis et al[32] reported a higher use of adjuvant therapy in AS patients (52%, 32/61) while Farrow et al. reported 68.8%[33]. In our series, 46% (21/45) of our cohort received adjuvant systemic therapy and specifically 61% of patients under AS. The most frequent indication was single-agent anti-PD-1 immunotherapy (62%). Active surveillance approach is nowadays the preferred strategy in SN-positive patients. In fact, we have chosen AS in more than 80% of our patients since we started our protocol in June 2017 without an impact in RFS at any site, DMFS or MSS.

There are limitations in this current study. The most important is its retrospective nature and relative small number of patients. Ulceration of primary tumor was not a strong factor, but should be in a larger future cohort. However, this study analyses a wide range of clinicopathologic parameters and its impact on survival. To the best of our knowledge, is the first national study to report this information in a Latin American population.

The results of this study in a SN-positive Argentinian cohort shows that primary tumor and SN (tumor deposit) features in melanoma give important prognostic information. Active surveillance strategy has been adopted for most positive-SLNB cutaneous melanoma patients[25].

Conflict of interest: None to declare

References

1. Leiter U, Meier F, Schittek B, et al. The natural course of cutaneous melanoma. *J Surg Oncol* 2004; 86: 172-8.
2. Gershenwald JE, Scoyler RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eight edition cancer staging manual. *CA Cancer J Clin* 2017; 67: 472-92.
3. Morton DL, Thompson JF, Essner et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg* 1999; 230: 453-63.
4. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999; 17: 976-83.
5. Thompson JF. The Sydney Melanoma Unit experience of sentinel lymphadenectomy for melanoma. *Ann Surg Oncol* 2001; 8: 44S-47S.
6. Thompson JF, Stretch JR, Uren RF, et al. Sentinel node biopsy for melanoma: where have we been and where are we going? *Ann Surg Oncol* 2004; 11: 147S-151S.
7. Balch CM, Morton DL, Gershenwald JE, et al. Sentinel node biopsy and standard of care for melanoma. *J Am Acad Dermatol* 2009; 60: 872-5.
8. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006; 355: 1307-17.
9. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014; 370: 599-609.
10. Roulin D, Matter M, Bady P, et al. Prognostic value of sentinel node biopsy in 327 prospective melanoma patients from a single institution. *Eur J Surg Oncol* 2008; 34: 673-9.
11. Ling A, Dawkins R, Bailey M, et al. Short-term morbidity associated with sentinel lymph node biopsy in cutaneous malignant melanoma. *Australas J Dermatol* 2010; 51: 13-7.
12. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med* 2017; 376: 2211-22.
13. Leiter U, Stadler R, Mauch 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.
14. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF -mutated melanoma. *N Engl J Med* 2017; 377: 1813–23.
15. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018; 378: 1789–801.
16. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017; 377: 1824–35.
17. Lo SN, Ma J, Scolyer RA, et al. Improved risk prediction calculator for sentinel node positivity in patients with melanoma: The Melanoma Institute Australia nomogram. *J Clin Oncol* 2020: JCO1902362.
18. El Sharouni MA, Varey AHR, Witkamp AJ, et al. Predicting sentinel node positivity in patients with melanoma: external validation of a risk-prediction calculator (the Melanoma Institute Australia nomogram) uring a large European population-based patient cohort. *Br J Dermatol* 2021; 185: 412-8.
19. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127: 392-9.
20. Dewar DJ, Newell B, Green Ma, et al. The microanatomic location of metastatic melanoma in sentinel lymph nodes predicts nonsentinel lymph node involvement. *J Clin Oncol* 2004; 22: 3345-9.
21. Curti BD, Faries MB. Recent advances in the treatment of melanoma. *N Engl J Med* 2021; 384: 2229-40.
22. Schmerling RA, Loria D, and Cinat G, et al. Cutaneous melanoma in Latin america: the need for more data. *Rev Panam Salud Publica* 2011; 30: 431–8
23. Nova JA, Sanchez-Vanegas G, and Gamboa M, et al. Melanoma risk factors in a Latin American population. *Ann Bras Dermatol* 2020; 95: 531–3.
24. Broman KK, Hughes T, Dossett L, 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.
25. Quildrian SD, Nardi WS, Scasso V, et al. Current management of patients with cutaneous melanoma with a positive sentinel lymph node. *Medicina (B Aires)* 2023; 83: 376-83.
26. Starz H, Balda BR, Kramer KU, et al. A micromorphometry-based concept for routine classification of sentinel lymph node metastases ans its clinical

relevance for patients with melanoma. *Cancer* 2001; 91: 2110-21.
27. Starz H, Siedlechi K, Balda BR. Sentinel lymphonodectomy and s-classification: a successful strategy for better prediction and improvement of outcome of melanoma. *Ann Surg Oncol* 2004; 11: 162S-168S.
28. Murali R, Desilva C, Thompson JF, et al. Factors predicting recurrence and survival in sentinel lymph node-positive melanoma patients. *Ann Surg* 2011 Jun; 253: 1155-64.
29. van Akkooi AC, Nowecki ZI, Voit C, et al. Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. *Ann Surg* 2008; 248: 949-55.
30. van Akkooi AC, Spatz A, Eggermont AM, et al. Expert opinion in melanoma: the sentinel node; EORTC Melanoma Group recommendations on practical methodology of the measurement of the microanatomic location of metastases and metastatic tumour burden. *Eur J Cancer* 2009; 45: 2736-42.
31. Featherston C, Nardi WS, Tomé F. Role of sentinel lymph node biopsy for cutaneous melanoma in elderly patients: preliminary results in a Latin-American population. *eCancer* 2021; 15:1167.
32. Nijhuis AAG, Spillane AJ, Stretch JR, et al. Current management of patients with melanoma who are found to be sentinel node-positive. *ANZ J Surg* 2020 Apr; 90: 491-496.
33. Farrow NE, Raman V, Williams TP, et al. Adjuvant Therapy is Effective for Melanoma Patients with a Positive Sentinel Lymph Node Biopsy Who Forego Completion Lymphadenectomy. *Ann Surg Oncol* 2020 Dec; 27: 5121-5.