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Original article

CURRENT MANAGEMENT OF PATIENTS WITH CUTANEOUS MELANOMA WITH A POSITIVE SENTINEL LYMPH NODE

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Abstract

Introduction: Immediate completion lymph node dissection (CLND) performed in patients with a positive sentinel lymph node biopsy (SLNB) cutaneous melanoma is not associated with improved melanoma specific survival versus active surveillance (AS) using nodal ultrasound. Clinical practice experience and outcomes of AS and adjuvant therapy is now starting to be published in literature.

Methods: Retrospective analysis of patients with a positive-SLNB between June/2017-February/2022. Impact of management on any-site recurrence free survival (RFS), isolated nodal recurrence (INR), distant metastasis-free survival (DMFS) and melanoma-specific survival (MSS) was evaluated.

Results: From 126 SLNB, 31 (24.6%) were positive: 24 received AS and 7 CLND. Twenty-one (68%) received adjuvant therapy (AS, 67% and CLND, 71%). With a median follow-up of 18 months, 10 patients developed recurrent disease with an estimated 2-yr RFS of 73% (CI95%, 0.55-0.86) (30% in AS group vs. 43% in dissection group; P = 0.65). Four died of melanoma with an estimated 2-yr MSS of 82% (CI 95%, 0.63-0.92) and no differences between AS and CLND groups (P = 0.21). Estimated 2-yr DMFS of the whole cohort was 76% (CI 95%, 0.57-0.88) with no differences between groups (P = 0.33).

Conclusion: Active surveillance strategy has been adopted for most positive-SLNB cutaneous melanoma patients. Adjuvant therapy without immediate CLND was delivered in nearly 70% of patients. Our results align with outcomes of randomized control trials and previous real-world data.

Key words: cutaneous melanoma, positive sentinel lymph node biopsy, active surveillance, follow-up studies, immunotherapy

Abbreviations: completion lymph node dissection (CLND), sentinel lymph node biopsy (SLNB), active surveillance (AS), recurrence free survival (RFS), isolated nodal recurrence (INR), distant metastasis-free survival (DMFS), melanoma-specific survival (MSS), Multicenter Selective Lymphadenectomy Trial (MSLT), sentinel lymph node (SLN), German Dermatologic Cooperative Oncology Group sentinel lymph-node Trial (DeCOG-SLT)

Resumen

Tratamiento actual de pacientes con melanoma cutáneo y ganglio centinela positivo

Introducción: La linfadenectomía inmediata (LI) realizada en pacientes con biopsia de ganglio centinela (BGC) positivo por melanoma cutáneo no está asociada a mejoría en la supervivencia libre de enfermedad vs. vigilancia activa (VA). Resultados oncológicos y experiencia en la práctica clínica con dicha conducta asociados

a tratamiento adyuvante comienzan a ser publicados en la literatura.

Métodos: Análisis retrospectivo incluyendo pacientes con BGC-positiva por melanoma cutáneo entre junio/2017-febrero/2022. Se evaluó impacto del manejo en: supervivencia libre de recurrencia (SLR), recurrencia ganglionar aislada (RGA), supervivencia libre de metástasis a distancia (SLMD) y supervivencia libre de enfermedad (SLE).

Resultados: De 126 pacientes, 31 (24.6%) fueron positivos: en 24 se realizó VA y en 7 LI. Veintiún pacientes (68%) recibieron tratamiento adyuvante (VA, 67% y LI, 71%). Con una media de seguimiento de 18 meses, 10 pacientes presentaron recurrencia de la enfermedad con una SLR estimada a 2 años del 73% (CI95%, 0.55-0.86) (30% en VA vs. 43% en LI; P = 0.65). Cuatro murieron de melanoma con una SLE a 2 años del 82% (CI 95%, 0.63-0.92); sin diferencia entre ambos grupos (P = 0.21). La SLMD a 2 años de toda la cohorte fue de 76% (CI 95%, 0.57-0.88; P = 0.33).

Conclusión: La vigilancia activa se ha adoptado como conducta para la mayoría de los pacientes con BGC-positivo. El tratamiento adyuvante sin linfadenectomía inmediata se realizó en cerca del 70% de nuestra serie. Los resultados de nuestra serie son similares a los reportados en la literatura.

Palabras clave: melanoma cutáneo, biopsia de ganglio centinela, vigilancia activa, seguimiento, inmunoterapia

Abreviaturas: linfadenectomía inmediata (LI), biopsia de ganglio centinela (BGC), vigilancia activa (VA), supervivencia libre de recurrencia (SLR), recurrencia ganglionar aislada (RGA), supervivencia libre de metástasis a distancia (SLMD) y supervivencia libre de enfermedad (SLE)

KEY POINTS
Current knowledge

- For patients with melanoma microscopic spread to lymph nodes, monitoring with ultrasound has recently been adopted as an alternative to immediate lymphadenectomy. Outcomes of this strategy with adjuvant therapy are now starting to being published in the literature.

Article contribution

- This study provides real-world data of active surveillance in positive-SLN melanoma patients in a reference center in Argentina. Active nodal surveillance was the preferred strategy (almost 80% of our patients) and in case of isolated nodal recurrence, delayed surgery could be performed without post-operative morbidities.

The management of patients with cutaneous melanoma has dramatically changed in the recent decades. Since the first description by Morton in 1992, the use of sentinel lymph node biopsy (SLNB) in cutaneous melanoma has become accepted worldwide[1]. The results of the Multicenter Selective Lymphadenectomy Trial I (MSLT-1) established the SLNB as a highly prognostic staging procedure in localized and clinically node-negative cutaneous melanomas[2,3]. This technique allowed clinicians to avoid the complications associated with completion lymph node dissection (CLND) in nearly 80% of patients who had a localized cutaneous melanoma and clinically negative regional lymph nodes. Nevertheless, knowing that 80-85% of those with a positive sentinel lymph node (SLN) did not have additional positive nodes after CLND, the indication of immediate surgery began to be questioned.

To address this issue, two randomized control trials, the Multicenter Selective Lymphadenectomy Trial II (MSLT-2) and German Dermatologic Cooperative Oncology Group sentinel lymph-node Trial (DeCOG-SLT) were conducted. Both demonstrated that immediate CLND performed after a positive sentinel lymph node biopsy was not associated with improved melanoma specific survival[4,5]. Patients underwent ultrasonography in the mapped nodal basin and a therapeutic (delayed) lymph node dissection was indicated only in case of nodal recurrence. These trials support a less aggressive approach in stage III cutaneous melanoma with low tumor burden in the regional lymph nodes. As a result, active nodal surveillance emerged as an option. It is noteworthy that patients included in these clinical trials did not have adjuvant systemic treatment after lymph node biopsy.

In addition, several trials have evaluated the outcomes of adjuvant systemic therapy in stage III disease. These landmark trials found an improvement in relapse-free survival with the use of anti-programmed death 1 (anti-PD-1) immu-

notherapy or BRAF/MEK inhibitors but only after complete lymph node dissection[6-8].

At this point, a new scenario has arisen in the daily clinical practice in which clinicians need decide to initiate adjuvant therapy and avoid immediate complete lymph node dissection. This treatment strategy is becoming more accepted nowadays. In our study, the first objective was to describe the management and adoption of active surveillance in SLN-positive patients since the publication of MSLT-2 Trial. Second, we sought to compare early oncological outcomes; namely, local and systemic recurrence between those who underwent AS and CLND.

Material and methods

Multidisciplinary institutional melanoma tumor board meeting takes place once every week and all cases are discussed. 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)[9-10]. The surgery requires a preoperative lymphoscintigraphy (involving injection of radioactive colloidal isotope); and the use of blue dye and gamma probe during the surgical procedure as described by Morton[1]. The SLN was defined as the lymph node (or nodes) that first receives direct lymphatic drainage (dye and/or radioactive isotope) from the primary melanoma.

A retrospective evaluation of all procedures between June 2017 and February 2022 at the Sarcoma and Melanoma Unit of our General Surgery Department was carried out. We included patients who had a localized and clinically node-negative cutaneous melanoma, were aged ≥18 years, underwent SLNB in primary cutaneous melanoma of the trunk and extremities and had at least 1 positive (metastatic) SLN. Those with loco-regional or distant disease during the preoperative staging were excluded.

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. Active surveillance (AS) consisted of physical examination and ultrasound of the mapped node field. Cross-sectional images were performed during surveillance upon discretion of treating clinicians. All patients were followed-up according to a usual surveillance protocol performed every 3 months throughout the first 2 years; after that, every 6 months until the 5th year, and then annually.

The main outcome variables were: any-site recurrence free survival (RFS) defined as recurrent melanoma at any site from the time of SLNB, diagnosed by clinical and/or imaging studies and confirmed on biopsy when feasible; isolated nodal recurrence (INR), defined as recurrence in SLN-basin without other affected sites; distant metastasis-free survival (DMFS), defined as distant metastasis identified during follow-up as either first or subsequent recurrence; and melanoma-specific survival (MSS) defined as survival until death by disease from time of SLNB.

Approval from the Institutional Review Board was obtained for this study in view of retrospective nature of the study and all the procedures being performed as part of the routine care. Requirement for specific written informed consent was waived: however, all patients signed the surgical consent form.

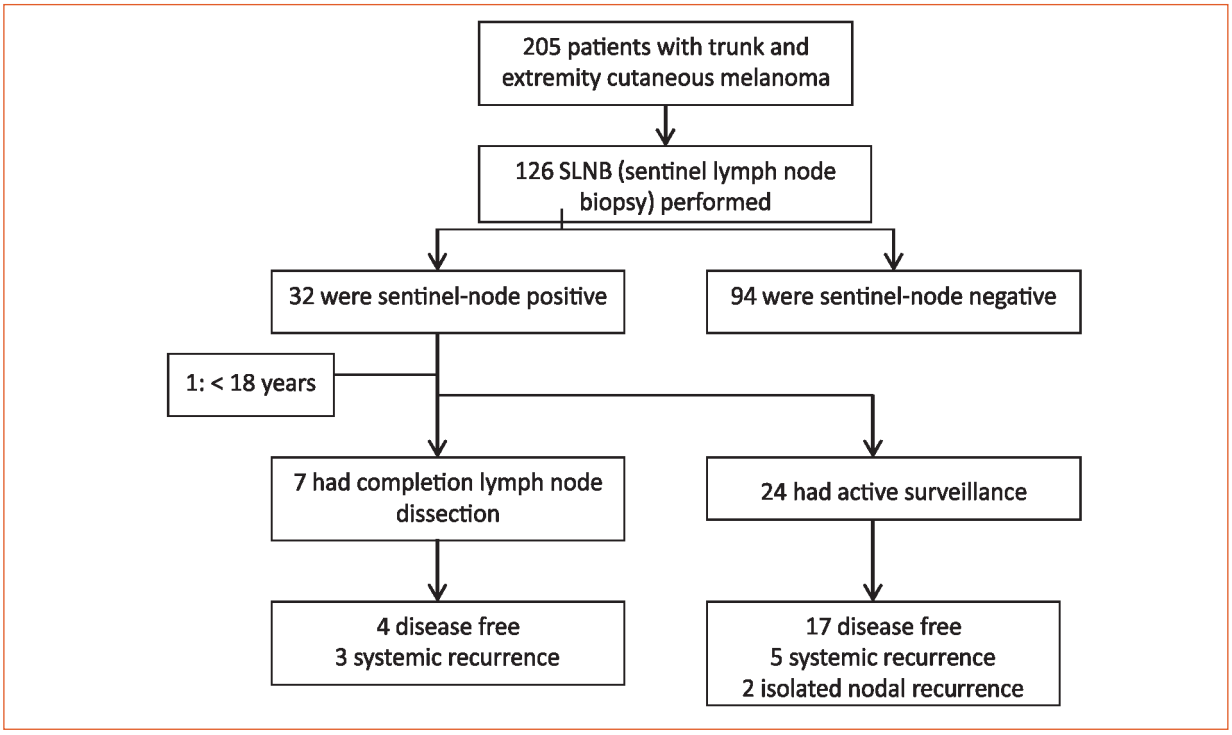
Statistical analysis was carried out with Statistix® and included X^2 independence tests and t test for comparison between groups, and a p value <0.05 was considered as statistical significant. Quantitative variables are described as mean and standard deviation (SD) or median and interquartile range (IQR) and qualitative variables as percentages. Survival analysis was performed using the Kaplan-Meier method.

Results

We performed 126 SLNB during the time interval of our study. Among these, 32 patients (25.4%) had at least 1 positive SLN. We excluded 1 patient due to age < 18 years, leaving a total of 31 patients analyzed. Seven patients (22.5%) underwent CLND and the remaining 24 (77.5%) received active surveillance (Fig. 1). Characteristics of patients in both groups are listed in Table 1.

The indication for immediate CLND was high tumor burden in 5 patients and due to multidisciplinary tumor board recommendation after case discussion in 2 patients. Among the patients who required immediate surgery, 3 (42.8%) of those 7 had at least 1 positive non-SLN in the completion specimen, which resulted in upstaging, according to the American Joint Committee on Cancer 8th edition cancer staging manual, in 1 of 7 cases (14%). That patient had a T4b lesion with additional positive non-SLNs on CLND and was consequently upstaged from IIIC to IIID.

Figure 1 | Patient flow chart and outcomes



For patients receiving active surveillance we primarily indicated nodal basin ultrasound every 3 months besides strict physical exam; 16 of the 24 patients (66%) had at least 1 ultrasound during the first 6 months of follow-up. The median number of nodal basin ultrasound per patient in active surveillance during follow-up was 3 (IQR, 1-6). Moreover, twelve patients (12/24, 50%) had also cross-sectional images during follow-up and all of them where receiving adjuvant therapy.

The median follow-up of the whole cohort was 18 (12-32) months. At the final follow-up: 21 patients (68%) were disease-free, 4 patients were alive with disease recurrence and 6 (19%) patients had died (4 of disease progression and 2 of unrelated causes). Estimated 2-yr melanoma-specific survival was 82% (CI 95%, 0.63 – 0.92) with no differences between CLND and AS groups ($P = 0.21$).

There were 10 (32%) recurrences at any site (Table 2). Estimated 2-yr recurrence free survival was 73% (CI95%, 55-86). The proportion of patients who had a recurrence at any site between groups was: 43% in the dissection group (3 of 7 patients; median follow-up 15 months) vs. 30% in the AS group (7 of 24 patients; median follow-up 18 months). Of the two patients who had isolated nodal basin recurrence, one was detected on clinical assessment and the other detected only by ultrasound. These two patients were receiving active surveillance (2 of 24 patients, 8.3%) without adjuvant therapy and undergone complete (delayed) nodal resection without post-operative morbidities. Estimated 2-yr distant metastases free survival of the whole cohort was 76% (CI 95%, 0.57-0.88); 2 of 7 in dissection group vs. 5 of 24 in AS group. Of the patients with multiple sites recurrences, all but two (5 of 7 patients) were being treated with systemic therapy. Moreover, of those 5 patients, 3 had intra-adjuvant recurrences (2/3 were in the active surveillance arm).

Five of 7 patients (71%) in CLND group and 16 of 24 (67%) patients in active surveillance received adjuvant systemic therapy while 10 patients did not, being the main reasons financial issues or lack of approval by the health insurance (Table 3). Of the patients who had adju-

Table 1 | Characteristics of patients undergoing active surveillance vs. completion lymph node dissection

Characteristic	Surveillance (n = 24)	Dissection (n = 7)	p
Age: mean SD,	54.8 ± 17.6	60.4 ± 11	.43
Men, n (%)	12 (50)	6 (85)	.19
Tumor location, n (%)			1
Trunk	13 (54)	4 (57)	
Upper extremity	3 (13)	2 (29)	
Lower extremity	8 (33)	1 (14)	
Breslow thickness, mm, n (%)			1
≤ 1.0	1 (4)	1 (14)	
> 1.0 to 2.0	6 (25)	1 (14)	
> 2.0 to 4.0	6 (25)	1 (14)	
> 4.0	8 (33)	2 (29)	
Size of SLN metastasis: median [25th-75th percentile], mm	1.8 [1-3]	1.3 [0.6-4.0]	.6
Extranodal extension, n (%)	2 (8)	2 (29)	.21
AJCC8 stage, n (%)			
IIIA	6 (25)	2 (28.6)	1
IIIB	7 (29)	2 (28.6)	1
IIIC	11 (46)	2 (28.6)	1
IIID	0	1 (14)	-
BRAF mutation status, n (%)			.67
Mutant	10 (42)	4 (58)	
Wild type	14 (58)	3 (42)	
Adjuvant systemic therapy	16 (67)	5 (71)	1

SLN: sentinel lymph node; AJCCC: American Joint Committee on Cancer, eight edition

Table 2 | Patterns of recurrence

Site of recurrence	Nodal Management		Systemic therapy	
	Dissection (n = 7)	Surveillance (n = 24)	Yes (n = 21)	No (n = 10)
No recurrence, n (%)	4 (57)	17 (70)	16 (76)	5 (50)
Recurrence, n (%)	(43)	7 (30)	5 (24)	5 (50)
Local-regional only	0	0	0	
SLN basin only	0	2	0	2
Distant only	0	1	1	0
Multiple sites	3	4	4	3
Including nodal	2	3	4	1
No including nodal	1	1	0	2

SLN: sentinel lymph node

vant therapy: 15 completed one year therapy, 3 are presently on treatment and the remaining 3 (13.5%) patients discontinued treatment due to toxicity (fever and severe chills, hepatotoxicity with elevated alanine-aspartate aminotransferase and immuno-mediated nephritis).

Single-agent anti-PD-1 immunotherapy was the most common adjuvant treatment (16 of 21 patients, 76%); being nivolumab the most frequent drug used (13 patients [62%] vs. pembrolizumab, 3 patients [14%]). The remaining 5 (24%) patients received BRAF/MEK inhibitors.

Table 3 | Characteristics of patients who received systemic therapy vs. no systemic treatment

Characteristic	No Adyuvant Therapy (n = 10)	Adyuvant Therapy (n = 21)	p
Age: Mean SD	57 ± 16	57.8 ± 13.8	.88
Men, n (%)	5 (50)	13 (61)	.43
Tumor location, n (%)			1
Trunk	5 (50)	12 (57)	
Upper extremity	2 (20)	2 (10)	
Lower extremity	3 (30)	7 (33)	
Breslow thickness, median	2 [1.35-4.7]	3 [1.8-4.9]	.37
Tumor ulceration, n (%)	4 (40)	11 (52)	.43
Presence of microsatellites	0	1 (14)	1
Positive nodes, median	1	1	1
Size of SLN metastasis: median [25th-75th percentile], mm	1.8 [0.3-2.1]	1.5 [01.1-3.15]	.57
Extranodal extension, n (%)	2 (20)	2 (9.5)	.55
AJCC8 stage			
IIIA	3 (30)	5 (24)	.65
IIIB	4 (40)	5 (24)	.38
IIIC	3 (30)	10 (47)	.23
IIID	0	1 (5)	1
BRAF mutation status			.45
Mutant	3 (30)	11 (53)	
Wild type	7 (70)	10 (47)	
Nodal management			
Active surveillance	8 (80)q	16 (76)	
CLND	2 (20)	5 (24)	1

ASLN: sentinel lymph node; AJCCC: American Joint Committee on Cancer, eight edition; CLND: completion lymph node dissection

Discussion

In this study of patients with cutaneous melanoma and positive SLNB, only 22% underwent lymphadenectomy while the rest underwent active nodal surveillance. The percentages of patients with recurrence (any site recurrence- or distant metastases- free survival) and disease specific survival were similar between groups; it was noteworthy that almost 70% of patients in AS received adjuvant systemic treatment. We had a low rate of isolated nodal recurrence with AS and all could be salvaged with therapeutic (delayed) lymph node dissection. This big change in the clinical practice started following MSLT-2 Trial publication and we report the real-world experience in a cohort in Argentina.

The management of patients with cutaneous melanoma has changed drastically after the results seen in large Phase III clinical trials of cutaneous melanoma patients without clinical evidence of regional node metastases. First, the MSLT-1 trial established the prognostic value of SLNB in patients with intermediate thickness cutaneous melanoma without clinically detected node disease. Hence, more than 80% of patients with localized disease could avoid an immediate lymphadenectomy and its associated morbidity after a negative SLNB[2,3]. The possibility to find patients with microscopic node metastases allowed selecting patients for immediate CLND. Nonetheless, only 15-20% of patients with a positive-SLN had another metastatic node (non-SLN) in the specimen of lymphadenectomy. These findings led to evaluate the selection of patients in whom to avoid CLND without a negative impact on oncological outcomes and thus reduced morbidity rates[11-15].

Results of De-COG SLT and MSLT-2 trials added more information about the clinical impact of delayed CLND in patients with positive-SLN. Both randomized clinical trials showed no difference in melanoma-specific survival in patients with immediate lymphadenectomy vs control with active surveillance and delayed surgery after the appearance of nodal recurrence[4,5]. In addition, three randomized control trials evaluated the outcomes of adjuvant systemic therapy in patients with stage III cutaneous melanoma showing improvement in disease free survival with immunotherapy or target therapy. Those studies randomized only patients with previous CLND[6-8]. At this point, the results of all these trials created a controversy: is there a clinical benefit to undergo immediate CLND in all patients with positive-SLNB before starting adjuvant treatment? Different reports have been published evaluating the current management in referral centers.

Broman et al. evaluated 1154 patients with positive SLNB in an international multi-institutional study; 189 (16%) underwent lymphadenectomy and 965 (84%) received active surveillance. On multivariable analysis, head and neck location, higher number of positive nodes, larger nodal tumor burden and location of the treating center (more frequent in USA and Europe than Australia) were associated with immediate CLND. Reasons for surgery were patient preference (41%), surgeon recommendation (18%), burden of disease (32%), difficult in active surveillance (24%) and for prognostic information (14%). After a follow-up of 11 months, 19% of patients developed recurrence of disease: 19% in the active surveillance group and 22% in the immediate CLND group (p=0.31). There were no differences in distant metastases-free survival according to nodal management or the use of adjuvant treatment[15]. In another study including 61 positive-SLNBs only 3% of patients underwent immediate CLND and all remained without disease recurrence. A 13% of recurrence was informed in the active surveillance group[16]. Bartlett et al. reported 42% of recurrence in 370 patients with positive sentinel node who did not undergo immediate CLND and isolated nodal recurrence in 13.2%[12]. Farrow et al. reported a recurrence rate of 21.9% (7/32) under active surveillance and adjuvant therapy[17]. The differences in recurrence rates observed in the previous series may be due to differences in sample size and time of follow-up between them[12,15-17]. In our series, seven patients of the cohort (22.5%) had immediate CLND and we registered 32% of recurrences at any site without differences between groups. This value is higher than those reported in the literature but may be due to our smaller number of patients.

Broman et al. described that adjuvant systemic therapy was given in 39% of patients who underwent CLND and 38% who underwent active surveillance. A single agent anti-PD-1 regimen was the most frequent indication. Adjuvant therapy was indicated in patients with high risk of recurrence and was associated with a 48% reduction in all-site recurrence[15]. Nijhuis et al. reported a higher use of adjuvant therapy (52%, 32/61 patients) while Farrow et al. reported its use in 22/32 patients (68.8%)[16]. In our study, 68% of patients (21 out of 31) received adjuvant systemic therapy and the most frequent indication was single-agent anti-PD-1 immunotherapy (77%).

Immediate CLND is associated with some theoretical advantages: best nodal staging and the possibility of avoiding strict nodal follow up with ultrasound. Nevertheless, the upstaging is as low as 5-6% after CLND with more than 80% of patients not having additional positive non-SNs and being exposed to postoperative morbidity. More important is that there is no evidence that immediate CLND is correlated with survival benefit[4, 5, 18]. In addition, unresectable nodal disease after active surveillance seems to be extremely rare[12, 15]. Finally, nowadays a new clinical dilemma emerges when a patient under active surveillance and adjuvant treatment develops nodal recurrence. These patients will undergo a therapeutic delayed CLND but the indication for discontinuing or resuming the adjuvant treatment is not yet clearly determined.

Although we have provided some real-world information regarding active surveillance in positive-SLN patients, findings of our study should be taken with caution. The main limitation of this study is the small size of the cohort and its retrospective design. Also, given the relatively new strategy in this scenario,

studies have a short follow-up, and this also limits the ability to draw firm conclusions on the long-term oncologic outcomes. Nevertheless, our findings are similar to those reported in larger retrospective studies that evidence an increasing number of patients in whom an active surveillance approach is preferred after a positive-SLNB.

Conflict of interest: None to declare

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