The Oncologist, 2025, **30**, oyaf212
https://doi.org/10.1093/oncolo/oyaf212
Advance access publication 17 July 2025
Original Article

Conservative lymph node surgery for patients with stage III melanoma: a prospective longitudinal cohort

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Abstract

Background: Therapeutic lymph node dissection has shown no clear benefits in terms of overall survival. However, appropriate regional control has repeatedly been reported in patients with lymph node metastasis.

Objective: The objective of the study was to analyze the outcomes of a conservative surgical approach to patients with melanoma and lymph node metastasis detected either clinically or by imaging tests.

Methods: A multicenter, prospective, longitudinal, single-arm cohort was conducted to recruit patients with melanoma who had 1-3 non-matted regional lymph node metastases (N1b, N2b) and were treated with conservative nodal surgery (conservative NS). The surgical procedure entailed resection of the metastatic lymph nodes identified, while preserving uninvolved lymph nodes in the regional basin. The patients received post-operative adjuvant immunotherapy according to routine clinical recommendations. The primary end-point was the 2-year regional lymph node recurrence-free survival (RRFS).

Results: A total of 25 patients with lymph node metastasis underwent conservative NS to remove inguinal (44.00%) and axillary (56.00%) lymph node metastasis. During the follow-up, 36.00% ($n=9$) of the patients developed recurrence in the regional basin treated with conservative NS. The 2-year RRFS was 65.70% (95% CI 46.30%-85.10%), and MSS was 78.10% (95% CI 60.85%-95.35%) at 2 years. Stage IIIB patients exhibited no statistically significant improvement in 2-year RRFS (83.30%) (log-rank $P=.238$). The short-term surgical complications reported were seroma (32%, $n=8$), hematoma (8%, $n=2$), and wound infection (4%, $n=1$). No cases of lymphedema were observed.

Conclusion: Conservative NS has the potential to prevent unnecessary complete lymph node dissections, particularly in clinical settings where neoadjuvant immunotherapy is not a suitable first-line therapeutic option.

Key words: cutaneous melanoma; lymph node metastasis; stage III melanoma; lymph node dissection; oncologic surgery; recurrence-free survival.

Implications for Practice

Therapeutic lymph node dissection has shown no clear benefits in terms of overall survival. In melanoma patients with lymph node metastasis, conservative lymph node surgery could avoid more than half of complete lymph node dissections performed.

Introduction

To date, therapeutic lymph node dissection (TLND) has been the first-line treatment for patients with malignant melanoma (MM) who have resectable lymph node metastasis detected clinically or by imaging.[1] However, a shift in approach is emerging, precipitated by the encouraging outcomes observed in clinical trials of neoadjuvant immunotherapy, which involves the administration of immunotherapy before TLND.[2,3] While this strategy is poised to become universally accessible, there will continue to be debate regarding treatment modalities for patients not eligible for neoadjuvant therapy because of formal contraindications or who simply decline this approach, for whom TLND would remain the treatment of choice.

Moreover, recent hypotheses regarding parallel tumor progression,[4] coupled with a lack of definitive evidence regarding the correlation between the extent of nodal surgery and patient

Received: 14 January 2025; Accepted: 10 July 2025.
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survival, as well as the morbidity associated with radical lymph node dissection, suggest the need to explore more conservative surgical procedures in this clinical setting.[5] A conservative approach could facilitate customization of surgery and consequently achieve a better balance between oncological outcomes and surgical morbidity. Although retrospective studies have not shown survival differences between patients treated with radical or conservative nodal surgery, this conservative approach has not previously been evaluated in a prospective cohort of patients with stage III melanoma.[6]

The aim of this study was to describe and analyze the oncological outcomes yielded by conservative nodal surgery (Conservative NS) of patients with melanoma and lymph node metastasis detected clinically or by imaging test.

Methods

This was a multicenter, prospective, longitudinal, single-arm cohort of patients with melanoma who had lymph node metastasis treated with conservative NS between January 2021 and September 2022 in the following Spanish Centers: Hospital Universitario Virgen Macarena (Sevilla), Hospital Universitari i Politècnic La Fe (Valencia), Hospital Clínico San Cecilio (Granada), and Hospital Germans Trias i Pujol (Barcelona).

Eligible patients met the following inclusion criteria: age 18 years or older, Eastern Cooperative Oncology Group performance status 0-2, 1-3 non-matted regional lymph node metastases (N1b, N2b) in a single axillary or inguinal regional basin detected clinically or by imaging (ultrasound, computed tomography [CT]-scan, positron emission tomography [PET]-scan) at the time of primary melanoma diagnosis or during the follow-up after treatment for a primary MM. The presence of lymph node metastasis, whether identified through clinical observation or imaging tests, required confirmation through fine-needle aspiration and subsequent cytologic study.

Exclusion criteria applied were as follows: single lymph node metastasis in more than 1 regional basin, multiple primary melanoma (with the exception of limb melanoma), primary occult melanoma, previous nodal metastasis, previous TLND, previous or simultaneous locoregional or distant metastasis, or intraoperative finding of additional metastatic lymph nodes, matted nodes, or any regional basin involvement leading to TLND. Cervical lymph node metastases were excluded from this study due to methodological concerns (ie, the incidence of head-and-neck melanoma is less than 20%), as well as the uncertainty about the feasibility and risks of second surgeries to treat potential recurrences after conservative dissections. Perioperative management—including the use of drains, duration of hospital stay, wound care recommendations, etc—was conducted according to the local protocols of each participating center.

Prior to inclusion, patients underwent a comprehensive evaluation that involved a full-body CT or PET-scan, and brain MRI. Surgery had to be performed within a period of 30 days from the first suspicion of lymph node metastasis. The final recommendation for conservative NS had to be approved by consensus of the local multidisciplinary melanoma board. Following this determination, eligible patients were informed, and a signed consent document was obtained.

Conservative NS involves the surgical resection of the metastatic lymph nodes, while preserving uninvolved lymph nodes in the regional basin. To ensure the complete removal of the metastatic nodes, in cases of non-palpable or deep nodal metastasis, guided surgical techniques were employed (radio-guided, ultrasound-guided, and radioscopy-guided with hook wire localization).

After surgery, the patient received postoperative adjuvant immunotherapy as directed by the local multidisciplinary melanoma board, following current recommendations aligned with international guidelines, patient preferences, and reimbursement conditions. In this regard, the reimbursement of adjuvant immunotherapy has been granted in Spain for patients with stage IIIC-IIID, while stage IIIB patients were not offered postoperative immunotherapy.

Follow-up procedures during the study period involved clinical examination and regional ultrasound every 3 months, and cross-sectional imaging (CT or PET-CT) every 6 months, or in cases concerning US-lymph node images identified clinically or by regional ultrasound.

The following study variables were recorded during the screening, intervention, and follow-up phases: demographics (age at conservative NS, sex), primary tumor (T stage), sentinel lymph node biopsy (SLNB) performance, lymph node metastases (location, N stage), surgical procedure (non-guided, radio-guided, radioscopy-guided, ultrasound-guided), postoperative N and tumor-node-metastasis stage, regional lymph node recurrence, recurrence treatment, further progression (in-transit, distant metastasis), hospital stay, short-term complications (wound infection, seroma, hematoma), long-term complications (lymphedema), and melanoma-related death. The primary tumor and nodal staging were assigned following the American Joint Committee on Cancer 8th edition staging classification.[7] Postoperative complications were assessed during the initial inpatient stay and at every follow-up visit, and they were classified according to the Clavien-Dindo grading system.[8]

The primary endpoints analyzed were the frequency of regional recurrence and the 2-year regional lymph node recurrence-free survival (RRFS), defined as any recurrence in the same regional basin managed with conservative NS. As secondary endpoints, the 2-year melanoma-specific survival (MSS), hospital stay, and surgical complication rates were analyzed. In addition, an effort was made to identify potential independent variables that may contribute to regional recurrence.

The statistical analysis was conducted using SPSS software (v24.0; IBM Corp., Armonk, NY, USA). For the quantitative data analysis, Student's *t*-test and analysis of variance were applied. For qualitative data analysis, the chi-squared test was employed, using Fisher's exact test when the expected count was less than 5. A multivariate analysis was performed to identify predictors of regional recurrence through logistic binary regression. Variables with $P < .25$ in the univariate analysis were incorporated into the multivariate model. The results of the univariate and multivariate analyses were expressed as hazard ratios and corresponding 95% confidence intervals. The RRFS and the mean survival time (MSS) were estimated using the Kaplan-Meier method, with the log-rank test employed to compare survival curves by independent factors. All significance tests were 2-sided, and $P < .05$ was considered statistically significant.

The study was approved by the Institutional Review Board (2385-N-20), and all patients provided written informed consent (www.clinicaltrials.gov. Identifier: NCT05445752).

Results

A total of 25 patients with lymph node metastasis detected clinically or by imaging studies and fulfilling the inclusion criteria were recruited (Figure 1). The patient population was predominantly male, with 52.00% of the subjects being male ($n = 13$). Fifty-two percent ($n = 13$) of these subjects were identified during the initial screening at the time of primary melanoma diagnosis, while the remaining 48% ($n = 12$) were identified during routine follow-up after primary melanoma treatment. The mean age of the cohort was 65.64 years (95% CI 58.62-72.66) at the time of conservative NS, with a sex distribution of 56.00% men and 44.00% women. The median follow-up period was 25.90 months (IQR 20.42, mean 22.83 months, 95% CI 17.92-27.75). A total of 68% of the patients ($n = 17$) had a primary tumor stage IIB/IIC. The clinical and pathological features of the primary tumors and the regional lymph node metastases are outlined in Table 1 (Table 1).

Regarding the surgical procedure, 48.00% ($n = 12$) of conservative dissections were radio-guided with radioactive seeds, 24.00% ($n = 6$) were ultrasound-guided, and 8.00% ($n = 2$) were guided by fluoroscopy and hookwire localization. In 20% ($n = 5$) of the patients, conservative NS was performed as a conventional, open, non-guided surgery. A surgical drain was placed in 20% of patients ($n = 5$) at the discretion of the operating surgeon.

Postoperative hospital stay duration was found to be 1.04 days on average (95% CI 0.50-1.58), with a median inpatient duration of 1 day (IQR 2). Furthermore, 44.00% of patients underwent outpatient surgery and were discharged on the same day as their procedure.

Post-conservative NS, 24.00% ($n = 6$) of the patients enrolled were stage IIIB, 68.00% ($n = 16$) stage IIIC, and 8.00% ($n = 2$) stage IIID, the latter due to microsatellites in the primary tumor and 2-3 non-matted lymph node metastases.

At the conclusion of the study period, 36.00% ($n = 9$) of the patients developed recurrence in the regional basin treated with conservative NS, whereas 64.00% ($n = 16$) did not. The univariate and multivariate analyses revealed no independent predictors of regional basin recurrence (Table 1). Although recurrence rates were higher in patients with high-risk primary tumors (IIB/IIC) and more advanced stage III disease, these differences did not reach statistical significance (Table 1). Furthermore, recurrence rates were similar between patients who received adjuvant immunotherapy after conservative nodal surgery and those who did not (35.70% vs. 36.50%, $P = .648$).

Among patients who developed regional basin recurrence, 77.80% ($n = 7$) developed further distant or in-transit progression, whereas 22.20% ($n = 2$) remained disease-free following surgical intervention for regional recurrence. Conversely, among patients who did not develop regional recurrence, 62.50% ($n = 10$) also did not develop distant progression, remaining disease-free after the study. Despite this difference, a statistical analysis revealed no significant difference in the frequency of distant and in-transit progression in patients who developed regional recurrence and those who did not ($P = .063$). Additionally, although a higher frequency of stages IIB/IIC was observed among patients who developed further progression (76.90%) compared with those who remained disease-free (58.30%), this difference was not statistically significant ($P = .411$).

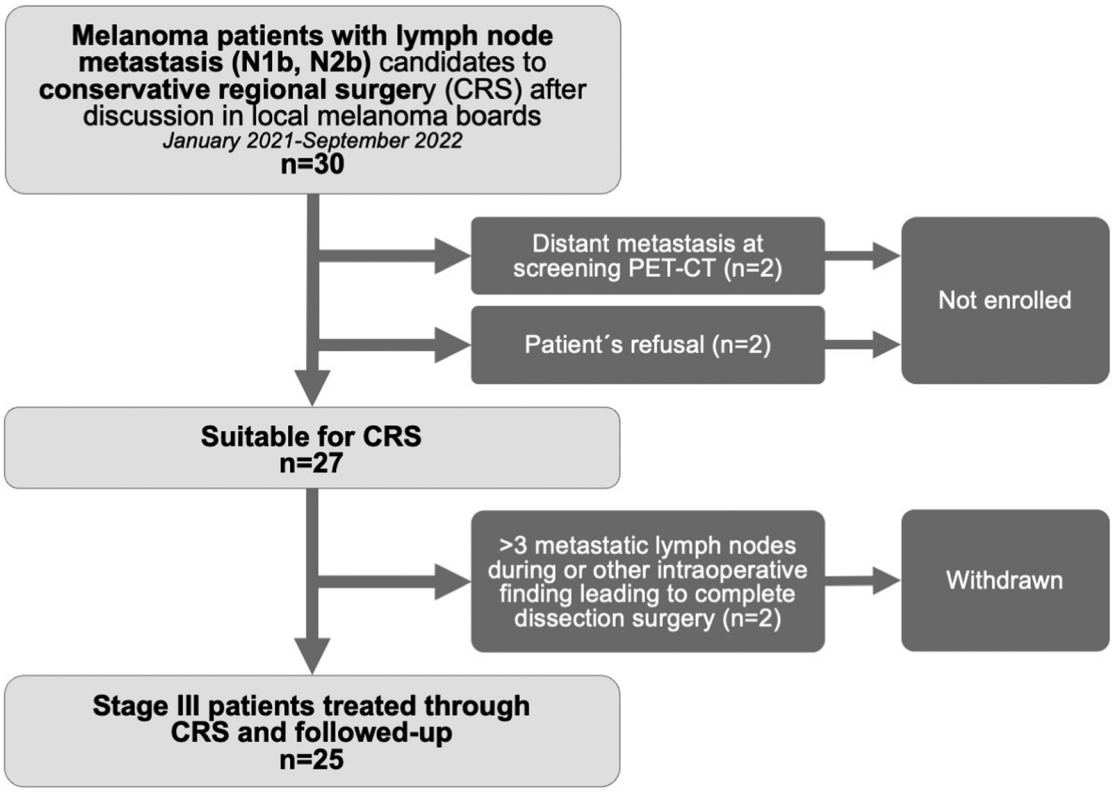

Figure 1. Flowchart of study patients' enrollment.

Table 1. Basal features of the cohort and univariate analysis for the risk of regional recurrence.

		Basal features sample		Univariate analysis				
				No regional recurrence, %	Regional recurrence, %	OR	95%CI	*P*
Gender	Men	14	56.00	64.30	35.70	1.03	0.20-5.33	.648
	Women	11	44.00	63.60	36.40			
Age	<75 years	15	60.00	73.30	26.70	2.75	0.51-14.86	.397
	≥75 years	10	40.00	50.00	50.00			
Primary tumor	IA-IIA	8	32.00	75.00	25.00	0.48	0.07-3.09	.661
	IIB-IIC	17	68.0	58.80	41.20			
Regional basin	Axilla	14	56.00	64.30	35.70	1.03	0.20-5.33	.648
	Groin	11	44.00	63.60	36.40			
Metastasis diagnosis	At diagnosis of primary tumor	13	52.00	61.50	38.50	0.80	0.16-4.12	.560
	During follow-up	12	48.00	66.70	33.30			
Surgical technique	Non guided surgery	5	20.00	60.00	40.00	0.81	0.11-6.04	.609
	Guided surgery	20	80.00	65.00	35.00			
III-stage	IIIB	6	24.00	83.30	16.70	0.28	0.03-2.83	.364
	IIIC	17	68.00	75.00	25.00	2.10	0.32-13.61	.661
	IIID	2	8.00	50.00	50.00	1.88	0.10-34.13	.600
Adjuvant therapy	Anti-PD1 adjuvant therapy	14	56.00	64.30	35.70	0.97	0.19-5.03	.648
	No adjuvant therapy	11	44.00	63.60	36.40			

The 2-year RRFS was 65.70% (95% CI 46.30%-85.10%). Median survival was not reached (Figure 2). The 2-year MSS was 78.10% (95% CI 60.85%-95.35%).

Among patients who developed regional recurrences, 44.44% ($n=4$) were treated with anti-PD1 immunotherapy, 2 due to simultaneous distant or in-transit recurrence and 2 as a neoadjuvant approach; 33.33% ($n=3$) were salvaged through TLND. One patient received radiation therapy, and a final patient did not receive treatment due to widespread disease, which was managed through best supportive care.

Postoperative stage IIIB patients demonstrated a superior 2-year regional recurrence-free survival (83.30%) than those with stages IIIC-IIID (59.60%), although it was not statistically significant (log-rank $P=.238$) (Figure 3). Additionally, a non-statistically significant improvement in 2-year MSS was observed in patients with stage IIIB (100.00%), in comparison to stages IIIC-IIID (71.50%) (log-rank $P=.196$). Additionally, a lack of statistically significant difference in RRFS was observed between patients who received adjuvant immunotherapy after conservative surgery and those who did not (log-rank $P=.963$) (Figure 4).

The short-term surgical complications reported included seroma (32.00%, $n=8$), hematoma (8.00%, $n=2$), and wound infection (4.00%, $n=1$). These complications were graded I-II according to the Clavien-Dindo classification. No cases of clinically apparent lymphedema were observed in the long-term follow-up visits.

Discussion

The present cohort describes the outcomes of a novel conservative surgical approach to patients with melanoma who have lymph node metastasis. This approach involves resection of the metastatic nodes, while leaving macroscopically uninvolved lymph nodes in the regional basin. Although index-node surgery—the resection of a metastatic lymph node after immunotherapy—has been implemented in clinical trials on neoadjuvant therapy, conservative surgery as first-line approach for patients with low-burden metastatic disease has not been previously evaluated in prospective longitudinal studies. In this clinical context, conservative nodal surgery has been demonstrated to preclude over two-thirds of the radical dissections that had been conventionally performed in clinical practice over a two-year period.

This conservative approach is supported by indirect evidence, which has repeatedly shown the lack of clear survival benefit associated with radical lymph node surgery. In this regard, the Multicenter Selective Lymphadenectomy Trial-II and Dermatologic Cooperative Oncology Group clinical trials revealed that complete dissections could be safely avoided in up to 75% of patients with microscopic lymph node metastasis managed by SLNB.[9,10] Consequently, these findings led to a modification in the standard of care in 2017, resulting in the discontinuation of mandatory lymph node dissection in these patients.[11] In comparative terms, SLNB could be regarded as a conservative procedure purely aimed at the selective resection of a potentially micrometastatic lymph node. Moreover, the extent of lymph node dissection has not been associated with improved oncological outcomes. The number of lymph nodes removed has not been correlated with recurrence-free survival, suggesting that the extension of lymph node dissection has no impact on relapse and survival of patients with stage III melanoma.[12] Additionally, studies examining the extent of surgery in various anatomical locations have shown that, for instance, in patients undergoing groin dissection, between 45% and 75% of additional elective iliac-obturator deep node dissections performed were avoidable.[13,14]

More recently, a form of conservative surgery has been used in clinical trials of neoadjuvant immunotherapy, in which a metastatic lymph node—referred to as the *index node*—is identified, monitored, and removed after completion of the neoadjuvant treatment courses.[2,15,16] In patients with a complete response in the index node, no further surgery was offered, a practice that aligns with the principles of oncological efficacy and safety. Similarly, the RRFS observed in this cohort indicates that TLND has been safely avoided in nearly 66% of

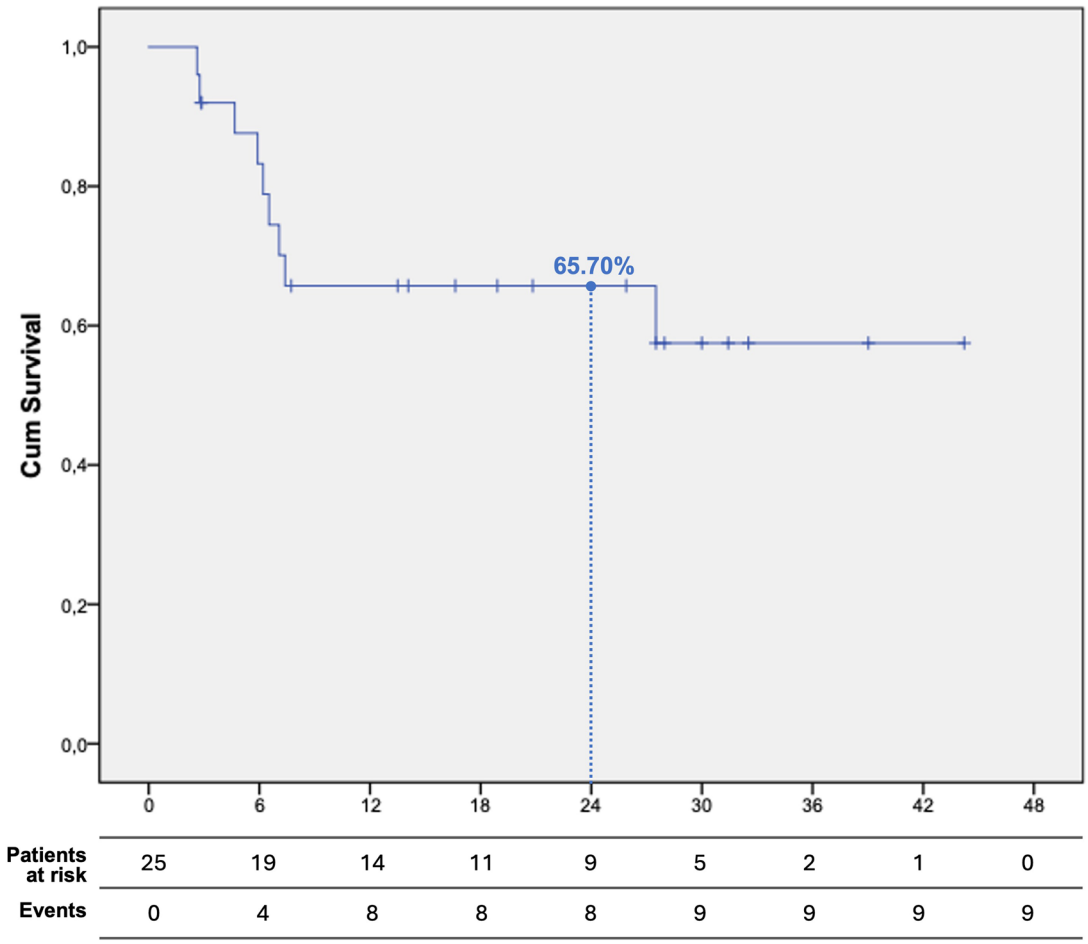

Figure 2. Kaplan-Meier curve for the regional recurrence-free survival of the cohort.

patients, with this rate increasing to 83% in stage-IIIB patients, those with lower tumor burden (N1b, N2b), and intermediate-risk primary tumors (T1b-T3a), although this difference was not statistically significant. At the conclusion of the study period, 6 patients died due to distant metastasis, all classified as IIB/IIC. The recent hypothesis of parallel tumor progression, which posits that distant progression does not require lymph node metastases, could explain why radical lymph node interventions are not expected to improve the patient's overall survival.[4] The question then arises as to whether it is worthwhile to perform radical surgery in those patients at higher risk of distant progression (T3b-T4b), or to opt for a more conservative surgery for regional control.

The current neoadjuvant strategy involves the administration of 2-3 cycles of immunotherapy prior to surgery, after which surgical and adjuvant treatment is completed or not. This approach offers a more precise and personalized therapeutic approach, informed by the observed response to treatment. Phase II and III trials have shown a 20% and 26% absolute increase in recurrence and event-free survival through this approach, with a major pathological response in 59% and complete pathological response in 21% of the patients in the trials of ipilimumab-nivolumab and pembrolizumab, respectively.[2,3] However, toxic events of grade 3 or higher have been reported in up to 30% of patients, and less than 10% of the patients could not be operated on because of disease progression or toxic events before surgery.[2,3] Thus, for those patients with a poorer clinical condition, or for those who decline neoadjuvant treatment, conservative surgery may be a viable option prior to radical lymph node dissection. With respect to age, the patients enrolled in this cohort had a mean age of 65 years, and 40% of the cohort was older than 75 years. In these age groups, the melanoma committee is typically less inclined to offer entry into a clinical trial and more prone to suggest less radical options. Moreover, for elderly patients, in whom a survival benefit is even more challenging to demonstrate, a more conservative approach aimed at keeping regional areas free of disease might be of interest; a scenario, as observed in this cohort, that could be considered suitable for conservative NS.

In terms of safety, the incidence of seroma observed (32%) aligns with prior reports on TLND complications.[9,17] However, in this cohort, the utilization of drainage systems, widely regarded as an effective seroma prevention method, was employed in only 20% of the patients due to the more limited dissection permitted by conservative surgery. The absence of lymphedema in this cohort is noteworthy when contrasted with reported rates of 5-10% following complete lymph node dissection as observed in the MSLT-I trial. This finding supports the reduced morbidity of conservative nodal approaches.[18] In any case, most patients were discharged from the hospital within a median period of 1 day, which is notably shorter than the standard length of stay after TLND.[17] The median hospital stay of one night is indicative of the adoption of a conservative

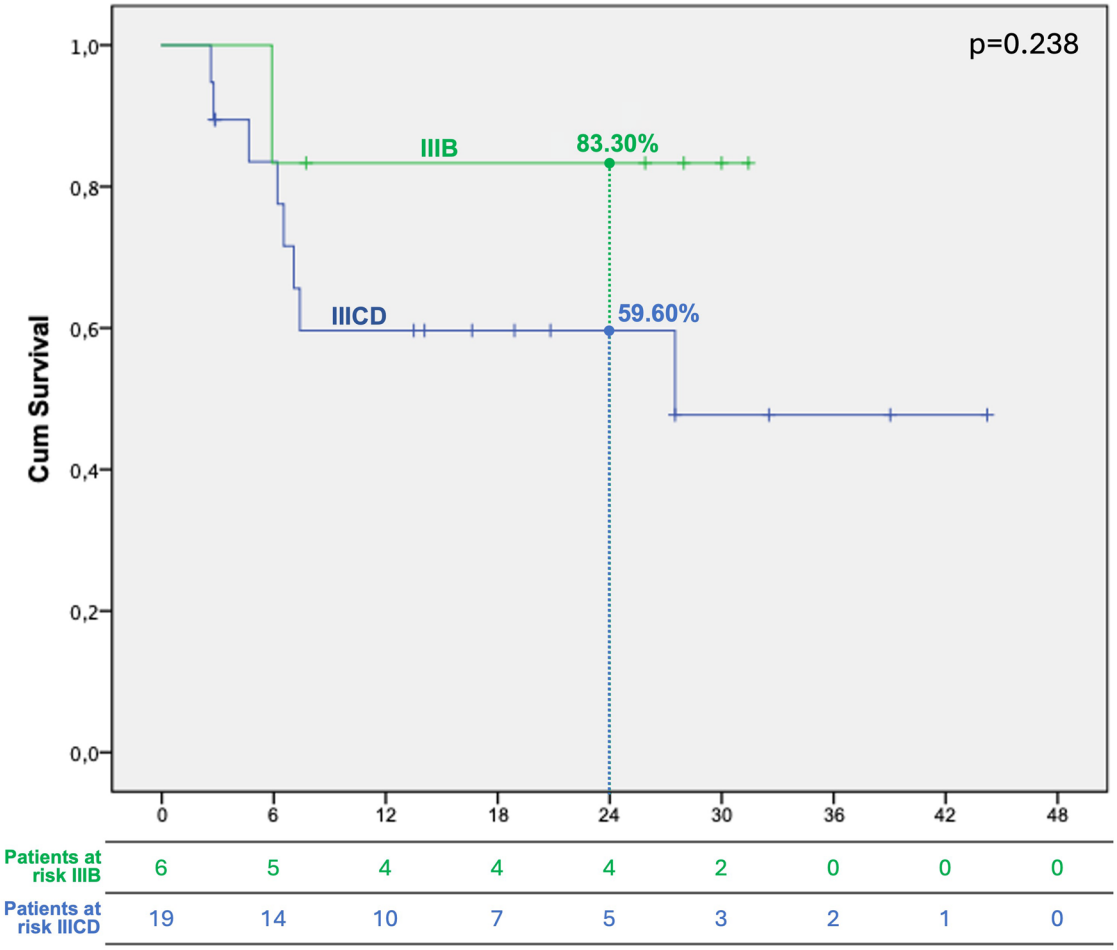

Figure 3. Kaplan-Meier curves for the regional recurrence-free survival in stage IIIB and stage IIIC-D patients (log-rank *P* = .238).

surgical approach and the organizational context of participating centers, which are public referral hospitals within the Spanish National Health System. Overnight observation is often preferred for patients traveling long distances, and hospitalization protocols may differ from those in privately funded systems.

At the time this study was initiated, neoadjuvant therapy had not yet become the standard of care for patients with lymph node metastasis. The advent of this therapeutic approach in clinical practice was precipitated by the publication of the phase II trial of neoadjuvant pembrolizumab in 2023, followed by the neoadjuvant ipilimumab-nivolumab phase III clinical trial in 2024.[2,3] In fact, contribute to the study's value by offering evidence regarding an alternative therapeutic approach, conservative lymph node surgery, for patients who, even today, would not be eligible for neoadjuvant immunotherapy, due to contraindications or to patients′ preferences.

The limitations of this cohort primarily stem from the recruited sample size. The initiation of this cohort overlapped with the onset of the COVID-19 pandemic, delaying the start of recruitment. Additionally, this cohort coincided with neoadjuvant clinical trials. This concurrence not only resulted in considerable competition for recruitment, potentially influencing the selection of patients who did not meet the criteria for clinical trials or who declined due to their clinical situation. Another potential limitation pertains to the survival outcomes examined in this study, particularly the use of RRFS instead of recurrence-free survival. However, considering the more recent hypothesis of tumor progression, nodal surgery is not expected to impact recurrences other than regional recurrence on the nodal basin treated.[4] Consequently, RRFS, as opposed to RFS, which encompasses local, regional, and distance recurrence, was deemed more appropriate to the objectives of this study. Finally, the intervention under study has not been compared with the standard treatment, radical lymph node dissection. Ethical aspects and the need for a significantly larger sample size, as well as competition with other clinical trials, led us to abandon the possibility of undertaking a comparative clinical trial. However, the originality of the approach, unprecedented in the current literature, and its prospective design provide a strong foundation to support further, more extensive studies.

Conclusion

The conservative regional nodal surgery approach has the potential to contribute to the prevention of unnecessary TLNDs, particularly in real-world clinical settings where neoadjuvant immunotherapy may not be feasible as a first-line option. Longer-term, larger, and comparative series would be of interest to achieve broader knowledge about the effectiveness and safety of this conservative approach.

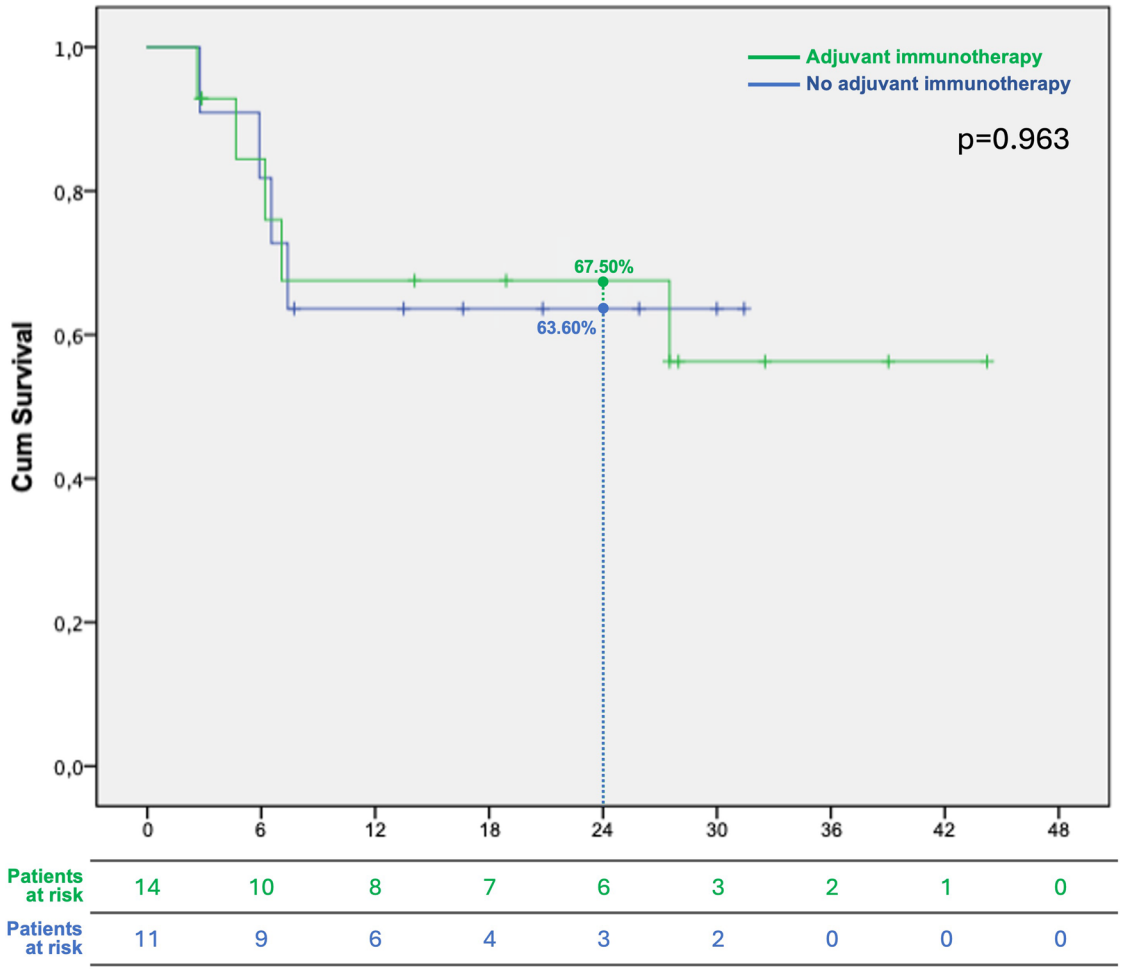

Figure 4. Kaplan-Meier curves for the regional recurrence-free survival in patients receiving and not receiving adjuvant immunotherapy (log-rank *P* = .963).

Acknowledgments

None.

Author contributions

David Moreno-Ramírez (Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing—original draft, review & editing), Almudena Fernández-Orland (Investigation, Review of original draft), Blanca de-Unamuno (Investigation, Review of original draft), Lucía Jiménez-Puñal (Investigation, Review of original draft), Francisco M. Almazán-Fernández (Investigation, Review of original draft), Aram Boada (Investigation, Review of original draft), Juan J. Ríos-Martín (Investigation, Review of original draft), Rafael Botella-Estrada (Funding acquisition, Investigation, Review of original draft), Lara Ferrándiz (Conceptualization, Formal analysis, Project administration, Investigation, Methodology, Resources, Validation, Writing—original draft, review & editing)

Funding

This study has been funded by MCIU-Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Health, through the project "PI20/01217" and "PI20/00790" and co-funded by the European Union.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

Data availability

The data that support the findings of this study are available under authorization from the Local Data Protection Committee.

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