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Strict versus Liberal Use of Sentinel Node Biopsy in Breast Cancer Surgery: Any Clinical Outcome Differences? A 20-Year Clinical Experience

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Keywords
Breast cancer · Sentinel node biopsy · Axillary recurrence · Survival

Abstract

Introduction: As applied to early breast cancer (BC) patients, sentinel node biopsy (SNB) has undergone major changes over the years, especially concerning the widening of indication criteria or skipping systematic axillary lymph node dissection (ALND) after a positive SN. We aimed to ascertain whether a strict versus a more liberal use of SNB resulted in different clinical outcomes in our clinical experience. ***Methods:*** We studied consecutive BC patients undergoing SNB between January 1, 2000, and March 31, 2020. There were 1,587 patients and 1,634 SNB procedures. Cases were divided into two study groups: the "strict" SNB group (unifocal tumors up to 35 mm in which ALND was always performed for a positive SN, amounting to 1,183 SNBs), and the "liberal" SNB group (extended tumor size up to selected T3 cases, as well as multifocal or bilateral disease, and patients with previous contralateral BC, not always followed by ALND after a positive SN, amounting to 451 SNBs). Patients were closely followed up to the end of the study. ***Results:*** Clinico-pathological variables were strikingly different between study groups, with the liberal group showing a higher risk profile. Cox regression analysis for disease recurrence did not show significant differences in axillary, lymph node, or locoregional recurrence rates or distant relapse. There were no differences in survival between groups. ***Conclusion:*** It seems reasonable to adopt the liberal SNB approach, as the goal of surgical management in early BC patients must be attaining optimal locoregional disease control, no matter the differences in distant metastatic spread rates across different BC risk profiles.

Background

Sentinel node biopsy (SNB) is the first-choice axillary staging procedure in early-stage breast cancer (BC) patients with a clinically negative axilla [1–3]. SNB has undergone relevant changes during the first two decades of its implementation, especially concerning criteria used for SNB indication or the sparing of systematic axillary

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lymph node dissection (ALND) after a positive SN [4, 5]. As for indication criteria, SNB evolved from a strict tumor size upper limit of 2 cm to encompass all T1-T2 patients. A similar trend was also seen from solitary to multicentric tumors, unilateral to bilateral BC, or even using SNB in the neoadjuvant setting, among other changes [6].

As for compulsory ALND after a positive SNB, the striking pathology finding that most of the axillary tumor burden relates to the SN itself led to the ACOSOG Z0011 [7] proposal of avoiding axillary dissection in patients with up to two positive SNs [4]. However, sparing completion of ALND may still be controversial because, as a confounding factor, enhanced axillary radiation therapy is used as a backup armamentarium, with similar morbidity [4, 5, 7, 8]. As an alternative, predictive models of residual axillary disease [9–11] such as the Tenon score were proposed to avoid AD [12], as in our practice. However, the Z011 approach has finally gained full acceptance, even though we must be aware that residual axillary disease may still be left unremoved in some BC patients.

Of note, such evolving criteria for SNB practice have run in parallel with significant changes in the clinical presentation of BC itself. These have resulted in an ever-improving patient prognosis associated with diagnosis at an earlier stage of the condition [13–15]. Therefore, the strict indication criteria and the exhaustive management of the axilla might not be as critical now as they were during the first stages of SNB, more than 20 years ago. We believe that most clinical centers dealing with BC have adopted such changes in SNB practice over the years. With all this in mind, we set out to investigate whether a strict versus a more liberal use of SNB resulted in different clinical outcomes, as measured by axillary recurrence, distant metastases, or survival in a cohort of BC patients that received SNB and were followed-up for a considerable time lapse.

Methods

Patient Inclusion/Exclusion

From our Breast Unit Database, we selected female patients with invasive BC receiving an SNB between January 1, 2000, and March 31, 2020. We excluded patients with ductal carcinoma in situ and patients from the SNB validation period. We also excluded patients accrued for some clinical trials associated with compulsory ALND, and for that matter, any patient receiving ALND after a negative SNB due to tumor factors such as size or multifocality until a more liberal policy was considered. Written informed consent was obtained for all invasive procedures and surgery, as well as for inclusion of patient data in the database. The present study was approved by our Research Ethics Committee on January 20, 2022, with the number P/22-012.

Our database includes the usual baseline and follow-up variables, such as age, surgical pathology results, systemic and radiation adjuvant therapy regimes, local recurrence, distant recurrence, and death, among many others. Our database has been seamlessly kept updated daily to the present. Initially, SNB was performed only in BC patients with solitary tumors up to 35 mm in size with clinically and US scan-negative axillary nodes. Further SNB indications were progressively introduced later on, prompting the following definitions.

Definitions

The "strict" SNB group included patients with a single invasive tumor of up to 35 mm and a clinically negative axilla. ALND was performed after a positive SN.

The "liberal" SNB group included patients with widened indications resulting from our evolving clinical routine, such as some locally advanced (T3) tumors, multifocal or bilateral disease, patients with previous contralateral BC, and pre- or post-neoadjuvant chemotherapy SNB procedures or repeat SNB for tumor recurrence.

Evolving SNB Practice and Study Groups

Initially, we implemented the SNB as a substitute for ALND in early BC patients with a single invasive tumor of up to 35 mm and a clinically negative axilla. The technique for SNB has been described elsewhere [9] and is based on the intra-peritumoral injection of 99m-technetium nanocolloids, preoperative lymphoscintigraphy, and intraoperative detection of the SN using a gamma probe.

From 2003 on, we have been using preoperative axillary US scans as a screening procedure for SNB. From January 2014 on, indications for SNB were extended to include all patients with T2 invasive tumors and multifocal tumors. Also, in early 2014, we applied a modified Tenon score for patients with positive SNs to forgo ALND [8]. Because of an excess of negative ALNDs, from June 2014 on, we incrementally applied the Z0011 approach for patients with one positive SN.

Accordingly, we devised two study groups as previously stated. The first was the "strict" SNB group. Initially, strict patients with SN micrometastases were also subjected to ALND, until 2010, when the results of our clinical trial on skipping ALND in SN with micrometastases were published [16]. The second group was the "liberal" SNB group. Not every patient with macrometastatic-positive SNs in this group was subjected to ALND because we often applied the Tenon score or the Z0011 criteria.

Adjuvant Therapy

Patients were treated according to the "state-of-the-art" clinical protocol of our Breast Unit Database, based on both national and international guidelines. Chemotherapy regimens based on anthracyclines and taxanes, or hormone therapy regimens with tamoxifen or aromatase inhibitors were most commonly used. From 2003 on, trastuzumab was given to Her2+ patients. Adjuvant radiation therapy was based on CT bidimensional planning until 2008 when tridimensional planning was implemented.

Statistical Analysis

We used qualitative or discrete variables expressed as their number and percentage. For univariate analysis, variable comparisons were achieved using the χ^2 test or Fisher's exact test. Statistical significance was set at a p value of <0.05, with a two-tail approach. Rates of axillary and locoregional recurrence were calculated over the SNB procedures, whereas rates of metastases and mortality were calculated over the patient numbers. Taking strict and liberal indications for SNB together, the Cox regression was used for disease recurrence analysis. The Kaplan-Meier test

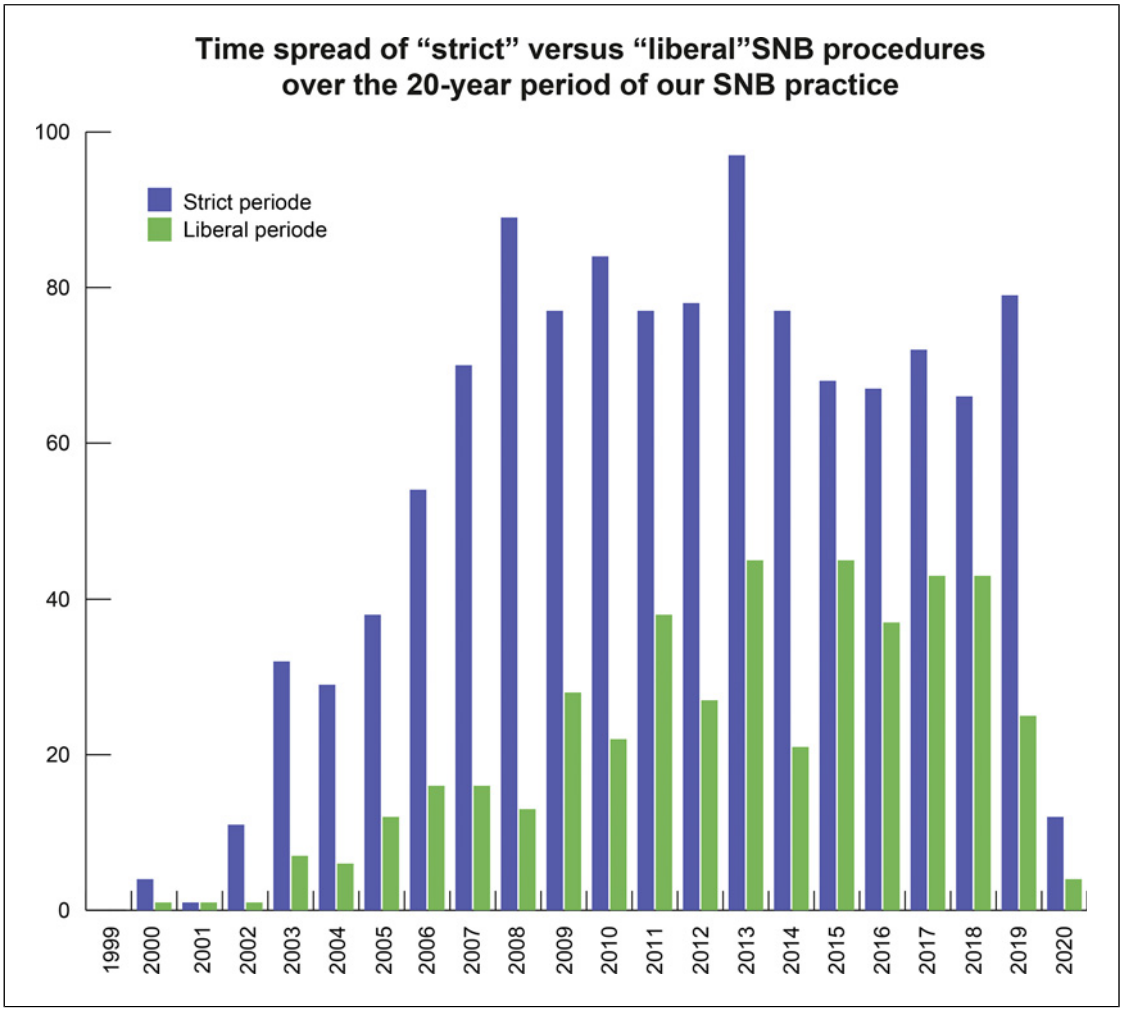

Fig. 1. Time spread of "strict" versus "liberal" SNB procedures over the 20-year period of our SNB practice.

and the log-rank test were used for survival analysis. All statistical analyses were performed using IBM SPSS 25.0.3. statistical package (Armonk, NY, USA).

Results

Over the 20-year period, 2,574 patients were treated for invasive BC, 1,586 of whom received SNB (61.7%). Because some patients presented with synchronous (58) or metachronous (48) bilateral tumors (not all of them receiving SNB), the total number of SNB cases was 1,634. Of these, 1.183 belong to the strict SNB group (72.4%) and 451 to the liberal SNB group (27.6%). Patients in the strict SNB group were followed up for a mean of 86 ± 56 months (SD) (range 2–253 months), while liberal SNB patients were followed up for a mean time of 80.7 ± 67.9 months (SD) (range 2–245 months).

Figure 1 displays the timeline of changes in the clinical management of patients undergoing SNB in our practice. It can be seen that those changes started in 2009 and peaked during the 2013–2015 period. During the 2015–2019 period, the liberal group of patients accounted for more than 50%. Before 2003, no patients with Her2+ tumors received trastuzumab. Triple therapy with trastuzumab + pertuzumab + taxanes was introduced for all candidate patients, irrespective of their group.

Table 1 shows comparative features of both study groups. All considered variables were significantly different among groups. Patients in the liberal group showed increased rates of T2-T3 tumors, Ki67 over 20%, stages II and III, non-luminal A phenotypes, lobular and mixed tumor histologies, age under 50, and diagnosis outside the mass-screening program. Patients in the strict group showed higher rates of lymphovascular invasion, although significance was lost when missing cases were discarded, and histologic grade III, Patients in the liberal group showed higher rates of both macro and micrometastases, as well as higher axillary tumor burden. There were no differences concerning extracapsular extension. Patients in the strict group significantly received more

Table 1. Baseline characteristics of patients and breast tumors according to the study groups: univariate analysis

	Strict SNB-1,183, *N* (%)	Liberal SNB-451, *N* (%)	*p* value
Age			**0.000**
<50	252 (21.3)	146 (32.4)	
50–69	707 (59.8)	219 (48.5)	
≥70	224 (18.9)	86 (19.1)	
T type			**0.000**
Ductal Ca	1,112 (94)	379 (84)	
Lobular Ca	61 (5.2)	59 (13.1)	
Mixt type	10 (0.8)	13 (2.9)	
T size			**0.000**
T1	911 (77)	284 (63)	
T2	272 (23)	147 (32.6)	
T3	0	20 (4.4)	
Lymphovascular invasion			**0.009**
No	864 (73)	320 (71)	**0.513**
Yes	293 (24.8)	108 (23.9)	
Missing	26 (2.2)	23 (5.1)	
BC diagnosis			**0.000**
Clinical care	625 (52.8)	305 (67.6)	
Population mass screening	558 (47.2)	146 (32.4)	
Histological grade			**0.004**
1	375 (31.7)	110 (24.4)	**0.011**
2	537 (45.4)	234 (51.9)	
3	255 (21.6)	94 (20.8)	
Missing	16 (1.3)	13 (2.9)	
Ki67			**0.008**
<20	330 (27.9)	118 (26.2)	
≥20	378 (32)	191 (42.4)	
Missing	475 (40.1)	142 (31.4)	
Surgical procedure			**0.000**
Conservative	1,072 (90.6)	291 (64.5)	
Mastectomy	111 (9.4)	160 (35.5)	
Stage			**0.000**
I	741 (62.6)	224 (49.6)	
IIA	340 (28.8)	132 (29.3)	
IIB	75 (6.3)	69 (15.3)	
III(A + B + C)	27 (2.3)	26 (5.8)	
Phenotype			**0.030**
Luminal A	517 (43.7)	170 (37.7)	
Luminal B her2-	424 (35.8)	160 (35.5)	
Luminal B her2+	96 (8.1)	49 (10.9)	
Her2 pure	33 (2.8)	16 (3.5)	
Triple negative	112 (9.5)	53 (11.7)	
Missing	1 (0.1)	3 (0.7)	

adjuvant radiation therapy, probably as a result of fewer mastectomy procedures. As could be expected from their clinical features, patients in the liberal group significantly received more adjuvant chemotherapy. However, the overall combined adjuvant therapy was not significantly different (Table 2).

To recap, looking at Tables 1 and 2 it can be inferred that patients in the liberal SNB group tended to be younger and less prone to be diagnosed at the mass-screening program than were strict SNB patients. They also tended to show higher tumor size and tumor grade and were more often bilateral and of lobular histologic type, have more macrometastatic SNs, with higher axillary tumor burden and higher disease stage. Also, they were more prone to receiving mastectomy and ALND. Finally, although both groups were similarly treated with adjuvant therapy overall, liberal SNB patients did receive a lower rate of adjuvant radiation therapy and a higher rate of adjuvant chemotherapy.

Table 3 shows specific indications for SNB in the liberal group. Multifocality was the most common of them. Also, in Table 3, event rates of disease recurrence and distant metastases can be seen. Cox regression (not

Table 2. Surgical pathology, adjuvant therapy, and specific mortality characteristics according to the study group. Univariate analysis

	Strict SNB-1183, *N* (%)	Liberal SNB-451, *N* (%)	*p* value
Ax LN dissection			**0.004**
No	986 (83.3)	349 (77.4)	
Yes	197 (16.7)	102 (22.6)	
SN pathology			**0.000**
Negative SN	902 (76.2)	293 (65)	
Micrometastasis	182 (15.4)	109 (24.2)	
Macrometastasis	99 (8.4)	49 (10.8)	
SNB tumor burden			**0.000**
0 positive SN	902 (76.2)	293 (65)	
1 positive SN	231 (19.5)	126 (27.9)	
2 positive SN	39 (3.3)	27 (6)	
≥3 positive SN	11 (1)	5 (1.1)	
LN tumor burden after axillary dissection			**0.000**
0 positive LN	902 (76.2)	293 (65)	
1 positive LN	199 (16.8)	109 (24.1)	
2 positive LN	41 (3.5)	22 (4.9)	
≥3 positive LN	41 (3.5)	27 (6)	
Extracapsular extension			**0.189**
No ECE	1,129 (95.4)	425 (94.2)	
ECE	54 (4.6)	26 (5.8)	
Adjuvant radiation therapy			**0.000**
Not	85 (7.2)	123 (27.3)	
Yes	1,098 (92.8)	328 (72.7)	
Adjuvant chemotherapy*			**0.000**
Not	645 (54.5)	153 (38)	
Yes	538 (45.5)	250 (62)	
Hormone therapy*			**0.449**
Not	148 (12.5)	52 (12.9)	
Yes	1,035 (87.5)	351 (87.1)	
Adjuvant therapy*			**0.185**
Not	38 (3.2)	8 (2)	
Yes	1,145 (96.8)	395 (98)	
Specific mortality*			**0.480**
Alive	1,150 (97.2)	391(97)	
Dead from BC	33 (2.8)	12 (3)	

*Per patient calculation.

Table 3. Locoregional recurrence and metastases rates according to SNB clinical use

	Total SNB, *N* (%)*	Axillary recurrence, *N* (%)	Lymp-node recurrence, *N* (%)	Lymphnode metastases, *N* (%)	Overall metastases, *N* (%)
Strict SNB use	1,183 (72.4)	17 (0.1)	39 (2.4)	27 (1.6)	68 (4.2)
Liberal SNB use					
Synchronous bilateral tumors	96 (5.9)	0	0	0	5 (0.3)
Previous contralateral BC	58 (3.5)	0	3 (0.2)	3 (0.2)	6 (0.4)
Multifocal tumors	205 (12.5)	2 (0.1)	4 (0.3)	3 (0.2)	7 (0.4)
Multicentric tumors	77 (4.7)	1 (0.1)	1 (0.1)	0	3 (0.2)
Tumor size over 35 mm	71 (4.3)	2 (0.1)	4 (0.3)	2 (0.1)	5 (0.3)
Pre-chemo SNB	24 (1.5)	0	0	0	0
Post-chemo SNB	27 (1.6)	1 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Repeat SNB	3 (0.2)	0	0	0	0

*The percentage of indications exceeds 100% because two or more of them were present in several cases.

Table 4. Disease events at follow-up according to the study group, together with Cox regression analysis

	Strict SNB 1183, *N* (%)	Liberal SNB 451, *N* (%)	Cox regression				
			B	*p* value	hazard ratio	95% CI for hazard ratio	
						lower	upper
Axillary recurrence	15/(1.3)	4 (0.9)	−1.231	0.107	0.292	0.065	1.307
Locoregional LN recurrence	18/(1.5)	7 (1.6)	1.216	0.057	3.373	0.965	11.788
Total recurrence	50/(4.2)	22 (4.9)	0.209	0.445	1.232	0.721	2.106
Overall metastases	49/(4.1)	24 (6)	1.063	<0.000	2.896	1.750	4.791
Lymph-node metastases	21/(1.8)	8 (2)	−0.477	0.271	0.621	0.266	1.450
Survival	1,150 (97.2)	391/403 (97)	−0.444	0.131	0.131	0.361	1.141

included in Table 3) did not reveal significant differences when considering rates of disease recurrence according to SNB-specific indications: *p* values from 0.604 to 0.961 for axillary recurrence, *p* values from 0.360 to 0.986, for lymph-node recurrence, and *p* values from 0.271 to 0.984 for metastases. Although the two groups had very different profiles, no significant differences were observed in the rates of axillary recurrence (1.3% vs. 0.9%), which were indeed very low, nor in the rates of lymph-nodal metastases (1.8% vs. 2%), overall recurrence (4.2% vs. 4.9%), overall survival, overall distant metastases (4.1% vs. 6%) or BC (2.8% vs. 3%).

Again, Cox regression analysis did not reveal any significant association of study group and event rates, except for overall metastases rates that were significantly higher in the liberal group. Hazard ratio values and corresponding 95% CI are shown in Table 4. Indeed, all patients had cN0M0 early BC. Furthermore, neither Kaplan-Meyer nor log-rank analysis showed significant differences between groups in terms of axillary recurrence, lymph node recurrence, lymph node metastases, and distant metastases (Fig. 2a–d).

Discussion

In general, an ever-increasing "liberal" policy for SNB practice has been accepted over the years and this has translated into several consensus statements and guidelines. The SNB might still be considered a matter of debate for specific subgroups of BC patients. In our experience, the first additional indication for SNB was in patients with multifocal/multicentric tumors, for which we used separate lymphatic tracer injections. The practical results were similar to those of patients with a single breast tumor, as reported by others [17, 18]. Compared to other reports (17–20), our timeline of SNB changes was somewhat sluggish, although nonetheless remarkable from early on (Fig. 1). Adjuvant therapy evolved according to well-established tumor features, irrespective of the SNB practice. Also, both gene expression testing and new chemotherapy regimes were implemented independently from the surgical procedures.

Our practice paralleled literature reports involving SNB in patients with T3 tumors and clinically negative axilla [19, 20], also showing similar results to those patients with T1-T2 tumors. Data are scant regarding repeat SNB after a previous SN procedure, but in our analysis, we believe it did not have a great bearing for group comparison, a fact that has also been reported in another study with 46 months of follow-up [21]. Others, however, seem more reluctant to repeat SNB given the lower SN detection rates, especially after a complete ALND [22, 23]. We think that SNB in the neoadjuvant setting has proved to be accurate and safe in patients with clinically negative axilla, as already pointed out [6, 24].

In our clinical practice, the more liberal use of SNB did not translate into worse clinical outcomes on retrospective analysis of a cohort of BC patients that were closely followed. Indications for SNB did widen and ALND was often skipped in our "liberal" SNB patients, and although they probably presented with slightly more advanced or higher-risk disease, locoregional control, in terms of axillary recurrence, lymph-node recurrence, lymph-node metastases, was the same as for patients in the strict SNB group, who had undergone a tighter indication scheme and fully comprehensive management of the axilla after a positive SN. Neither did the survival rate show a worsening trend in the liberal patient group compared with the strict patient group. There were significant differences in distant metastatic spread between groups ($p < 0.001$). Indeed, our study groups were remarkably divergent, and many clinical and pathological characteristics pointed to a higher-risk disease profile in the liberal group, which could bring about an increased rate of distant spread. On the other hand, the lack of significant differences in survival could be the result of limited sample size or just too short a follow-up interval as well. It is unclear whether the occurrence of late metastatic spread, especially of visceral metastases, plays a

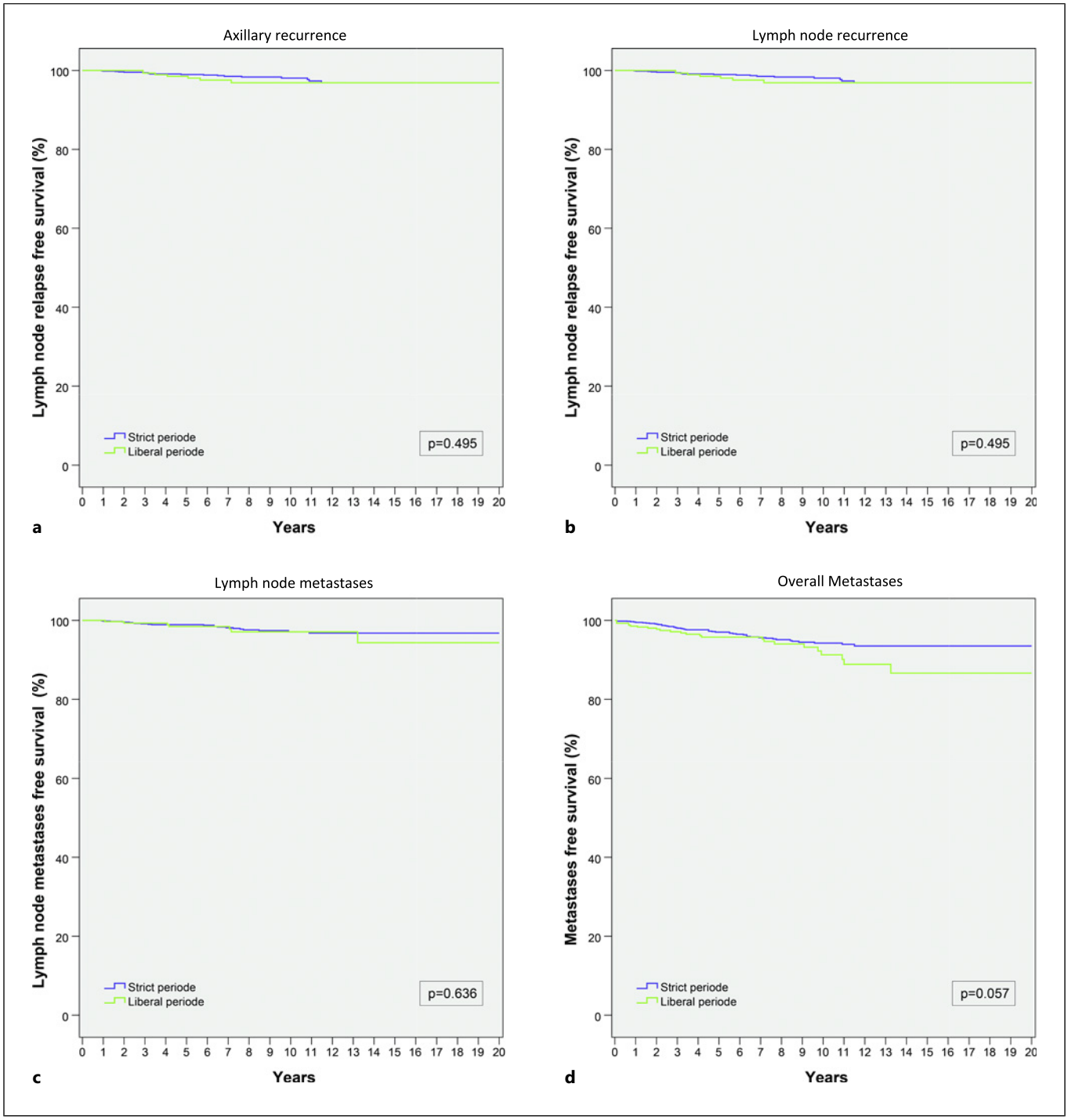

Fig. 2. a Axillary lymph node relapse. **b** Lymph node relapse. **c** Lymph node metastases. **d** Overall metastases.

role in the longer term, considering that we are dealing with low-risk patients, as defined by their referral for SNB.

In the light of our retrospective analysis, adoption of the "liberal SNB approach" seems fully justified, because a very important goal for the surgical management in early BC patients is attaining an optimal locoregional disease control, regardless of the unavoidable differences in distant metastatic spread rates across different risk profiles in node-negative patients. Our investigation is limited by its own retrospective nature, and any extrapolation to the wider early BC population must be cautious. More studies are therefore needed to confirm our results. Other non-randomized studies suggest that indication for SLNB could be further extended to patients for whom the standard treatment usually includes

complete axillary dissection, such as in locally advanced and widespread multicentric tumors [25]. There are, however, still more controversial indications for SLNB being suggested, such as in node-positive patients who respond to neoadjuvant chemotherapy [26]. Meanwhile, on pure practical grounds, adoption of the liberal use of SNB, as defined in our study, seems an acceptable choice.

Conclusion

SLNB has now well-established "extended" indications in early BC and remains the choice procedure with minimal morbidity, high accuracy, and clinical prognostic significance. Recent advances in multimodality therapy and axillary imaging further highlight the potential for de-escalating axillary surgery and SLNB surely has a pivotal role in such a context.

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Statement of Ethics

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital Universitari Mutua de Terrassa Review Board (Date January 20, 2022, N P/22-012). All patients gave their written consent shortly before breast surgery so that their anonymized individual data, including those from clinical follow-up, could be used for scientific purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no relevant financial or nonfinancial interests to disclose.

Author Contributions

Israel Barco, Marc Garcia-Font, Antonio García-Fdez, and Carolina Chabrera contributed to the study conception and design. Elena Vallejo, MCarmen Vidal, Sonia González, Clarisa González, Claudia Beatriz Mitru, Oriol Porta, and Antonio García-Fdez contributed to the material preparation and data collection. Manel Fraile and Antonio García-Fdez contributed to data analysis. The first draft of the manuscript was written by (Israel Barco, Antonio García-Fdez, and Manel Fraile). Manel Fraile was responsible for editing the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

Data from our study patients are not available in the public domain; however, they can be accessed under request to Doctor Antonio García-Fdez, who is responsible for the database of the Breast Unit at the Hospital Universitari Mútua de Terrassa (drgarciafdez@hotmail.com).

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