Received: 15 November 2018 | Revised: 6 April 2019 | Accepted: 9 April 2019

DOI: 10.1111/tbj.13479

ORIGINAL ARTICLE

The Breast Journal WILEY

Axillary dissection in patients with preoperative positive nodal cytology: Genuine need or overtreatment?

Viola Liberale MD[1] | Roberta Rosso MD[1] | Riccardo Arisio MD[2] | Marta D'Alonzo MD[1] | Andrea Villasco MD[1] | Luca Fuso MD[1] | Corrado De Sanctis MD[3] | Paola Modaffari MD[1] | Nicoletta Biglia MD, PhD[1]

[1]Obstetrics and Gynaecology Unit, Department of Surgical Sciences, School of Medicine, Umberto I Hospital, University of Turin, Turin, Italy

[2]Department of Surgical Pathology, School of Medicine, AOU Città della Salute e della Scienza of Turin, University of Turin, Turin, Italy

[3]Breast Unit, Department of Gynecology and Obstetrics, School of Medicine, AOU Città della Salute e della Scienza of Turin, University of Turin, Turin, Italy

Correspondence
Nicoletta Biglia, Obstetrics and Gynaecology Unit, Umberto I Hospital, A.O. Ordine Mauriziano, Largo Turati 62, 10128 Turin, Italy.
Email: nicoletta.biglia@unito.it

Abstract

Recent studies demonstrated the possibility to avoid axillary dissection (ALND) in selected patients with one or two metastatic nodes. Otherwise, patients with positive nodal ultrasound-guided fine-needle aspiration cytology (US-FNAC) currently undergo ALDN. The aim of this study is to quantify the nodal burden in patients with positive US-FNAC treated with ALND and to evaluate if clinical or pathological characteristics associated with low nodal involvement can be identified. This is a multicentric retrospective study involving 297 patients who underwent ALND because of a positive preoperative US-FNAC. A total of 157 patients showed bulky axillary lymph nodes at diagnosis, and 70% of them had three or more metastatic nodes. One hundred and forty patients had a clinically negative axilla and in 50% of them, 4 or more metastatic nodes were found with axillary dissection. Overall, the median number of metastatic nodes was 5. Favorable pathological characteristics of tumors were found in patients with only one or two metastatic nodes: smaller primary tumor, a lower proportion of grade 3, invasive lobular carcinomas and a higher proportion of low-Ki67 tumors. In the group of patients with clinically negative axilla and potentially meeting ACOSOG Z0011 criteria, 22 (31%) showed less than three metastatic axillary nodes. A preoperative positive axillary FNAC is associated with a metastatic nodal burden significantly higher than in patients with positive sentinel lymph node biopsy (SLNB). Nevertheless, about 30% of patients with cN0 axilla, positive axillary FNAC performed because of suspicious nodes on imaging, T1-2 primary tumor and breast-conserving surgery showed less than three metastatic axillary nodes, thus meeting ACOSOG Z0011 trial's criteria and therefore would be eligible for skipping ALND according to current guidelines.

KEYWORDS

axillary lymph node dissection, invasive breast cancer, positive sentinel node, sentinel lymph node biopsy, ultrasound FNA

1 | INTRODUCTION

The surgical management of the axilla still plays a crucial role in the treatment of breast cancer patients and axillary lymph nodes status remains an important prognostic indicator, as well as tumor size, histological type and grade, lymphovascular invasion, proliferative activity, hormone receptor status, Her-2/neu status, and age of the patient.[1,2]

For almost a century, axillary lymph node dissection (ALND) has been the standard technique in the axillary staging and treatment, but during the last years, axillary surgery has undergone significant changes toward an increasingly conservative approach, based on the introduction of the sentinel lymph node biopsy (SLNB) in the 1990s. This technique has quickly become the gold standard for the assessment of the axilla in early breast cancer patients with clinically and ultrasound negative axillary lymph nodes, thus limiting ALND to patients with metastatic sentinel nodes.[3-5] Around 40%-70% of sentinel node-positive patients undergoing ALND have no metastases in the removed nodes.[6,7]

Between 2011 and 2013, two studies have significantly changed the management of the axilla: the ACOSOG Z0011 trial and the IBCSG 23-01 trial.[8,9] The ACOSOG Z0011 trial demonstrated that ALND can be omitted without affecting both overall survival and disease-free survival, in selected patients with early breast cancer (cT1-T2), clinically and ultrasound negative axilla (cN0) and one or two micro- or macro-metastatic sentinel nodes, receiving breast-conserving surgery followed by total breast irradiation. Two years later, the IBCSG 23-01 trial confirmed these findings in patients with the same clinical T and N characteristics and one or two micro-metastatic sentinel nodes, undergoing either breast-conserving surgery followed by total breast irradiation or mastectomy not followed by radiotherapy. Unfortunately, the mastectomy group only accounted for 9% of the cohort; therefore, to date, the omission of ALND in the patients undergoing mastectomy can't be accepted as a standard procedure.

On the other hand, patients with a positive fine-needle aspiration cytology (FNAC) on axillary nodes, directly undergo ALND. This procedure is still the gold standard, both in case of multiple bulky nodes and in case of just one suspicious node detected by imaging only.[10,11] This raises the question of why some patients with up to two metastatic sentinel nodes can be spared ALND, while women with a positive axillary FNAC currently undergo this invasive procedure, even if cancer cells are detected in a single node just suspicious on imaging and not palpable?

The purpose of this study is to quantify the nodal burden in patients with positive FNAC treated with ALND. We also looked for any clinical and pathological characteristics potentially associated with low nodal involvement, to possibly identify a subgroup of patients with a low risk of high nodal burden.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This is a retrospective multicentric study on 391 patients with primary invasive breast cancer treated with primary axillary dissection because of a positive preoperative FNAC of axillary nodes between January 1st, 2006 and December 31st, 2016 at the University Department of Obstetrics and Gynecology of Mauriziano "Umberto I" Hospital and "Sant'Anna" Gynecologic Hospital in Torino.

Patients of any age treated either with mastectomy or conservative breast surgery are included, provided they had no concomitant malignancy, previous diagnosis of breast cancer or neoadjuvant chemotherapy. Moreover, only those patients who underwent complete ALND, defined as excision of Berg level I, II, III were considered eligible.[12,13]

Ninety-four patients were eventually excluded: 42 because of neoadjuvant chemotherapy; 25 because of incomplete data about FNAC; 21 because they had a diagnosis of breast cancer in the past; five because of first-level ALND only; and one because of an axillary metastasis from primary ovarian carcinoma. Therefore, 297 patients were selected for the study.

Of each patient the following variables have been considered: age and menopausal status at the time of surgery, type of surgery (mastectomy or breast-conserving surgery), characteristics of primary tumor (size, histotype, grading [according to Nottingham combined histological grading system], Ki67 expression, Her-2/neu, and hormone receptor status), clinical condition of the axilla (palpable or not palpable nodes), imaging method which detected the suspicious lymph nodes, ultrasound size of the axillary node on which FNAC was performed, number of excised, and metastatic axillary nodes.

2.2 | Fine needle aspiration cytology

All patients in the study underwent an axillary ultrasound, carried out by a dedicated breast radiologist. Criteria for defining a lymph node as suspicious included: overall size >1 cm, round shape, the absence of fatty hilum, and increased concentric or focal cortical thickness ≥3 mm.[14,15] Where nodes with these characteristics were identified, FNAC was performed with a 21- or 22-gauge needle. If more than one abnormal lymph node was detected, the largest or the one with the worst characteristic was analyzed. The slides were stained using Papanicolaou, hematoxylin and eosin and Giemsa stains for cytological analysis. The FNAC was considered positive when categorized as C5 (malignant).[16]

2.3 | Statistical analysis

Data were analyzed using SPSS software, version 20.0 for Windows (IBM Corp).

Results are reported as frequencies, mean, median and ranges. Qualitative variables are compared with the Chi-square and Fisher's exact test; variance analysis is used to compare quantitative variables. The normality of the variables was tested with the Kolmogorov-Smirnov test. For non-normally distributed variables, a non-parametric analysis was performed using the Mann-Whitney test. A two-tailed *P*-value ≤ .05 was considered statistically significant.

3 | RESULTS

The sample included 297 patients. Median age was 60 years (range 27-83 years) and 209 patients (70.4%) were postmenopausal at the time of surgery. Breast-conserving surgery was performed in 142

TABLE 1 Clinical and pathological characteristics of the tumor in the two groups of patients

	Nonpalpable lymph nodes (N0)	Palpable lymph nodes (N1?)	*P*-value
Total = 297 patients	140 (47.1%)	157 (52.9%)	
Age (y)			
Mean	60.23 SD 13.361	58.52 SD 14.120	Ns
Median	63 (range 27-82)	(range 28-83)	
Menopausal status			
Postmenopausal	102 (72.9%)	114 (72.6%)	Ns
Premenopausal	38 (27.1%)	43 (27.4%)	
Surgery			
Mastectomy	73 (52.1%)	82 (52.2%)	Ns
Breast-conserving	67 (47.9%)	75 (47.8%)	
Primary tumor			
Nonpalpable	27 (19.3%)	11 (7.0%)	.002
Palpable	113 (80.7%)	146 (93.0%)	
Size of the primitive tumor (mm)			
Mean	28.10 SD 12.712	31.57 SD 18.44	.05
Median	25 (range 9-80)	25 (range 7-110)	
pT			
pT1	36 (25.7%)	36 (22.9%)	Ns
pT2	92 (65.7%)	93 (59.2%)	
pT3-pT4	12 (8.6%)	28 (17.8%)	
Histotype			
Invasive ductal	121 (86.4%)	130 (82.8%)	Ns
Invasive lobular	11 (7.9%)	14 (8.9%)	
Other	8 (5.7%)	13 (8.3%)	
Grading			
G1	1 (0.7%)	4 (2.5%)	.09
G2	44 (31.4%)	34 (21.7%)	
G3	95 (67.9%)	119 (75.8%)	
Hormone receptors			
Positive	115 (82.1)	128 (81.5%)	Ns
Negative	25 (17.9%)	29 (18.5%)	
HER2			
Negative	108 (77.1%)	116 (73.9%)	Ns
Positive	32 (22.9%)	41 (26.1%)	
Ki67			
<20%	25 (17.9%)	18 (11.5%)	.01
≥20%	99 (70.7%)	121 (77.0%)	
Missing	16 (11.4%)	18 (11.5%)	
Molecular profile			
Luminal A	19 (13.6%)	14 (8.9%)	Ns
Luminal B HER2–	67 (47.9%)	68 (43.3%)	
Luminal B HER2+	16 (11.4%)	31 (19.7%)	
HER2+	16 (11.4%)	10 (6.4%)	
Triple negative/basal-like	9 (6.4%)	20 (12.7%)	
Missing	13 (9.3%)	14 (8.9%)	
Excised lymph nodes			
Mean	17.55 SD 6.626	17. 53 SD 6.00	Ns
Median	16 (range 8-48)	16 (range 8-39)	
Number of metastatic lymph nodes			
Mean	6.1 SD 5.947	8 SD 7.248	.019
Median	4 (range 1-40)	5 (range 1-34)	
Number of metastatic lymph nodes			
1	27 (19.3%)	25 (15.9%)	Ns
2	19 (13.6%)	18 (11.5%)	
3	15 (10.7%)	13 (8.3%)	
≥4	79 (56.4%)	101 (64.3%)	
1 or 2	46 (32.9%)	43 (27.4%)	Ns
>2	94 (67.1%)	114 (72.6%)	
Size of FNA node (mm)			
Mean	15.08 SD 4.188	20.8 SD 6.56	<.001
Median	15 (range 7-27)	20 (range 7-40)	

patients (47.5%), while 155 patients (52.5%) underwent a mastectomy. Palpable axillary lymph nodes were found in 157 patients (52.9%), while 140 (47.1%) had clinically negative axilla and suspicious nodes on imaging, then confirmed as metastatic by FNAC. Clinical, and pathological characteristics of the tumor in the two groups are listed in Table 1. Overall, the median number of excised axillary nodes was 16 (range 8-48), the median number of metastatic nodes was 5 (range 1-40) and the median size of the node on which FNAC was performed was 18 mm (range 7-40 mm).

The comparison between the group of patients in which the suspicious axillary nodes were clinically detected and the group in which they were only found by imaging showed no difference in age and menopausal status, type of breast surgery, median size and histological type of primary tumor (25 mm), hormone receptor status, HER-2/neu amplification, Ki67 expression, and molecular classification of the tumor.

In both groups, the primary tumor was palpable in most of the patients (93.0% in patients with clinically positive nodes vs 80.7% in patients with clinically negative axilla; $P = .002$). Although pT2 were the most represented tumors in both groups, patients with

palpable axillary nodes were more likely to be pT3 and pT4 compared with those presenting with clinically negative axilla (8.6% vs 17.8%; $P = .066$). The median number of excised axillary nodes was 16 in both groups, while the median number of metastatic nodes was nonsignificantly higher in patients with clinically positive axilla: (5, range 1-40 vs 4, range 1-34; $P = .519$). The median size of the axillary node on which FNAC was performed was 20 mm (range 7-40 mm) in the group of patients with palpable axillary nodes and 15 mm (range 7-27 mm) in the group of patients with negative axilla ($P < .001$; Table 1).

Less than three metastatic nodes were found in about 30% of patients, with no difference between patients with palpable lymph nodes (27.4%) and those with clinically negative axilla (32.9%). Moreover, also in case of a clinically negative axilla, 56% of patients had more than four metastatic lymph nodes.

Patients with one or two metastatic nodes compared with patients with three or more metastatic nodes had significantly smaller primitive tumors (median size 25 mm, range 8-80 mm vs 27 mm, range 7-110 mm; $P < .001$), less frequent lobular histotype (2.2% vs 11.1%; $P = .035$), less frequent grade 3 tumors (65.2% vs 75.0%; $P = .022$) and a higher proportion of low-Ki67 tumors (23.6% vs 10.6%; $P = .010$). No statistically significant differences were observed regarding the remaining characteristics of patients and tumors analyzed (Table 2).

With the purpose of identifying a subgroup of patients fitting with ACOSOG Z0011 trial's criteria we analyzed the group of 140 patients with clinically negative axilla and positive FNAC performed because of suspicious lymph nodes on imaging. One hundred and thirty patients had T1-T2 tumor and 72 of them received breast-conserving surgery. In 22 of these patients (31% of cases), less than three axillary nodes were found.

4 | DISCUSSION

Recent guidelines suggest that in selected patients with one to two metastatic sentinel lymph nodes (SLNs) ALND can be avoided; on the other side, women with a positive axillary FNAC on a single lymph node, still need the axillary clearance.[2,17]

This may look like a paradox, as stated by N. C. Verheuvel in a recent paper: "the better the radiologist (or imaging procedure) can identify axillary metastases, the worse the surgical consequences for the patient."[18,19]

This study was performed to better understand how often this holds true in every day's practice.

In our series of 297 women with a diagnosis of invasive breast cancer and preoperative axillary lymph nodes involvement, 157 (52.9%) had bulky palpable nodes and 140 (47.1%) had suspicious nodes on imaging; all of them had positive preoperative FNAC and underwent ALND according to the current guidelines.

More than half of the patients (52%) underwent a mastectomy as the primary surgical approach. In the literature, this procedure is performed, as primary surgery in 27%-34% of unselected breast cancer patients.[20,21] In our Institutions, primary mastectomy accounts for 29% of the cases. The higher proportion of mastectomies in positive preoperative FNAC patients may reflect the worse primary tumors characteristics. In this series, we found large tumors (median size 25 mm; stage ≥ pT2 75.8%), with unfavorable prognostic factors, such as a high tumor grade (G3 72%), high proliferative activity (Ki67 > 20% 74.1%), and frequent Her-2/neu amplification (Her + 24.6%).

Similar figures are reported in recent papers comparing women with preoperative positive FNAC to those with positive SLNB, both undergoing ALND. Boland et al found that the FNAC-positive patients, compared to the positive SLNB group, are more likely to undergo mastectomy (53.8% vs 35.5%, $P < .001$). In the FNAC-positive group more aggressive tumor characteristics were found: a higher median tumor grade (3 vs 2; $P < .001$) and a higher frequency of Her-2/neu amplification (25% vs 12.6%; $P < .001$).[19] Verheuvel et al published similar results with a higher proportion of mastectomies in FNAC-positive patients than in SLNB-positive group (64.7% vs 31.3%, $P < .001$), because of larger tumors (≥ 20 mm 83% vs 41.8%, $P < .001$), with worse prognostic factors: high tumor grade (G3 27% vs 18%, $P < .001$) and Her-2/neu amplification (18.7% vs 8%, $P < .006$). [18]

The median number of excised axillary lymph nodes in our series is 16 (range 8-48); only twelve patients had less than 10 lymph nodes removed, mainly because of age-related hypomobility of the shoulder, limiting axillary access.

The median number of metastatic lymph nodes is 5, higher than the number reported in patients with clinically negative axilla undergoing SLNB.

In the study of Boland,[19] the number of metastatic lymph nodes was 3 in FNAC-positive patients vs 1 in SLNB-positive patients; in the studies of Verheuvel[18] and Van Wely[22] were, respectively, 4 and 1. In the paper of Bortolini,[23] more than 50% of the 239 FNAC-positive patients had pN2a/pN3a disease, compared with only 18% of SLNB-positive patients. In the Van Wely's series, more than 50% of FNAC-positive patients had three metastatic lymph nodes compared to 23.7% in positive SLNB patients ($P < .0001$). Cools-Lartigue et al compared the tumor characteristics between the same groups finding no significant differences in the number of metastatic lymph nodes possibly because of the small sample size.[24]

Our study suggests that positive axillary FNAC identifies a subgroup of patients with an extensive axillary disease, with a median number of 5 metastatic lymph nodes.

However, in our series of 72 patients with nonpalpable axillary nodes, positive FNAC, T1-2 primary tumor and breast-conserving surgery, 22 (31%) showed less than three metastatic axillary nodes, therefore fitting with ACOSOG Z0011 criteria and would have avoided axillary dissection.[8] Other studies have found similar results.[19,22]

Unfortunately, we could not find any clinical or pathological feature potentially able to preoperatively identify this subgroup of patients who might avoid ALND (Table 3).

TABLE 2 Characteristics of patients with one or two metastatic nodes compared with patients with three or more metastatic nodes

	1-2 metastatic lymph nodes	>2 metastatic lymph nodes	*P*-value
Total = 297 patients	89 (30.0%)	208 (70.0%)	
Age (y)			
Mean	59.79 SD 13.854	59.13 SD 13.763	Ns
Median	60 (range 28-82)	60.5 (range 27-83)	
Menopausal status			
Postmenopausal	67 (75.3%)	142 (68.3%)	Ns
Premenopausal	22 (24.7%)	66 (31.7%)	
Surgery			
Mastectomy	50 (56.2%)	105 (50.5%)	Ns
Breast-conserving	39 (43.8%)	103 (49.5%)	
Primary tumor			
Nonpalpable	15 (16.9%)	23 (11.1%)	Ns
Palpable	74 (83.1%)	185 (88.9%)	
Size of the primitive tumor (mm)			
Mean	25.07 SD 11.029	32.02 SD 17.086	<.001
Median	25 (range 8-80)	27 (range 7-110)	
pT			
pT1	29 (32.6%)	43 (20.7%)	.001
pT2	58 (65.2%)	127 (61.1%)	
pT3	2 (2.2%)	26 (12.5%)	
pT4	0 (0.0%)	12 (5.8%)	
Histotype			
Invasive ductal	79 (88.8%)	172 (82.7%)	.035
Invasive lobular	2 (2.2%)	23 (11.1%)	
Other	8 (9.0%)	13 (4.4%)	
Grading			
G1	4 (4.5%)	1 (0.5%)	.022
G2	27 (30.3%)	51 (24.5%)	
G3	58 (65.2%)	156 (75.0%)	
Hormone receptors			
Positive	72 (80.9%)	171 (82.2%)	Ns
Negative	17 (19.1%)	37 (17.8%)	
HER2			
Negative	72 (80.9%)	152 (73.1%)	Ns
Positive	17 (19.1%)	56 (26.9%)	
Ki67			
<20%	21 (23.6%)	22 (10.6%)	.01
≥20%	61 (68.5%)	159 (76.3%)	
Missing	7 (7.9%)	27 (13.0%)	
Molecular profile			
Luminal A	15 (16.9%)	18 (8.7%)	Ns
Luminal B HER2−	40 (44.9%)	95 (45.7%)	
Luminal B HER2+	13 (14.6%)	34 (16.3%)	
HER2+	4 (4.5%)	22 (10.6%)	
Triple negative/basal-like	11 (12.4%)	18 (8.7%)	
Missing	6 (6.7%)	21 (10.1%)	
Axillary lymph nodes			
Palpable lymph nodes	43 (48.3%)	114 (54.8%)	Ns
Nonpalpable lymph nodes	46 (51.7%)	94 (45.2%)	
Size of FNA lymph node (mm)			
Mean	17.55 SD 6.693	18.34 SD 6.057	Ns
Median	15 (range 7-40)	18 (range 7-40)	

(Continues)

TABLE 1 (Continued)

Fine-needle aspiration cytology-positive patients can be divided into two groups: those with clinically detected nodes and those with suspicious nodes on imaging only. No statistically significant difference is found between the two groups regarding age, menopausal status, type of breast surgery, the median size of primary tumor, histotype, grade, biological variables, and molecular classification of the tumor. The median number of metastatic nodes was not statistically different as well (respectively, 5, range 1-40 vs 4, range 1-34; $P = .519$) and in both groups, only about one out of three patients has less than three metastatic lymph nodes. Three or more metastatic nodes were found in 70% of patients, but in about 60% the metastatic lymph nodes were 4 or more. These results are consistent with Verheuvel's study, in which 63% of patients showed more than two metastatic axillary lymph nodes and with Boland's analysis in which over 60% of patients had three or more positive lymph nodes.[18,20]

Assuming the tumor burden as the independent variable, a comparison was made between the clinical and pathological characteristic of the primary tumor in patients with one to two and three or more metastatic lymph nodes. In women with one or two metastatic axillary lymph nodes, we found on the average, smaller tumors, a smaller proportion of invasive lobular carcinoma, a higher frequency of G1, G2, and low-Ki67 tumors. Unfortunately, all these differences are not statistically significant and do not help in preoperatively identifying patients with positive FNAC who could be spared the ALND.

A promising strategy to avoid ALND in clinically node-positive (cN+) patients could be the use of neoadjuvant chemotherapy (NACT) that, in selected patients, allows an axillary downstaging. Studies report good rates of nodal pathologic complete response (pCR). The rate of pCR depends on tumor subtype, ranging from 40% to 60% overall, and approaching 70%-80% among patients with triple-negative and HER2-amplified tumors.[25] Current NCCN guidelines[17] endorse the use of post-NACT SLNB for axillary staging in patients with cN + disease

TABLE 3 Characteristics of patients fitting with ACOSOG Z0011 trial's criteria and eligible for breast-conserving surgery compared with patients fitting with ACOSOG Z0011 trial's criteria but not eligible for breast-conserving surgery and patients with nonpalpable axillary nodes at diagnosis but not meeting other ACOSOG Z0011 trial's criteria

	cN0 axilla, T1-T2 primitive tumor, breast-conserving surgery, and 1-2 metastatic nodes (Group A)	cN0 axilla, T1-T2 primitive tumor, breast-conserving surgery, and > 2 metastatic nodes (Group B)	cN0 axilla,>T2 primary tumor, and/or non-breast-conserving surgery (Group C)	*P*-value (group A vs group B)
Total = 140 patients	22 (15.7%)	50 (35.7%)	68 (48.6%)	
Age (y)				
Mean	59.91 SD 13.169	62.51 SD 11.597	58.71 SD 14.443	Ns
Median	64 (range 35-77)	64 (range 27-82)	56 (range 35-82)	
Menopausal status				
Postmenopausal	16 (72.7%)	41 (82%)	45 (66.2%)	Ns
Premenopausal	6 (27.2%)	9 (18%)	23 (33.8%)	
Primary tumor				
Nonpalpable	5 (22.7%)	8 (16%)	14 (20.6%)	Ns
Palpable	17 (77.3%)	42 (84%)	54 (79.4%)	
Size of primary tumor (mm)				
Mean	23.27 SD 8.316	23.92 SD 7.128	32.61 SD 15.217	Ns
Median	22.5 (range 10-48)	25 (range 9-37)	30 (range 12-80)	
pT				
pT1	8 (36.4%)	13 (26%)	15 (22.1%)	Ns
pT2	14 (63.6%)	37 (74%)	41 (60.3%)	
pT3-4	0 (0%)	0 (0%)	12 (17.6%)	
Histotype				
Invasive ductal	17 (77.3%)	43 (86%)	59 (86.8%)	Ns
Invasive lobular	1 (4.5%)	5 (10%)	5 (7.4%)	
Other	4 (18.2%)	2 (4%)	4 (5.8%)	
Grading				
G1	0 (0%)	0 (0%)	1 (1.5%)	Ns
G2	9 (40.9%)	15 (30%)	20 (29.4%)	
G3	13 (59.1%)	35 (70%)	47 (69.1%)	
Hormone receptors				
Positive	18 (81.8%)	40 (80%)	56 (82.4%)	Ns
Negative	4 (18.2%)	10 (20%)	12 (17.6%)	
HER2				
Negative	18 (81.1%)	40 (80%)	50 (73.5%)	Ns
Positive	4 (18.2%)	10 (20%)	18 (26.5%)	
Ki67				
<20%	3 (13.6%)	5 (9.8%)	17 (25%)	Ns
≥20%	16 (72.7%)	37 (72.5%)	47 (69.1%)	
Missing	3 (13.6%)	8 (17.7%)	4 (5.9%)	
Molecular profile				
Luminal A	3 (13.6%)	4 (7.8%)	13 (19.1%)	Ns
Luminal B HER2−	12 (54.5%)	25 (49%)	30 (44.1%)	
Luminal B HER2+	2 (9.1%)	3 (5.9%)	10 (14.7%)	
HER2+	2 (9.1%)	7 (13.7%)	7 (10.3%)	
Triple negative/basal-like	2 (9.1%)	3 (5.9%)	4 (5.9%)	

(Continues)

TABLE 3 (Continued)

	cN0 axilla, T1-T2 primitive tumor, breast-conserving surgery, and 1-2 metastatic nodes (Group A)	cN0 axilla, T1-T2 primitive tumor, breast-conserving surgery, and > 2 metastatic nodes (Group B)	cN0 axilla,>T2 primary tumor, and/or non-breast-conserving surgery (Group C)	*P*-value (group A vs group B)
Missing	3 (13.6%)	8 (17.7%)	4 (5.9%)	
Excised lymph nodes				
Mean	14 SD 4.515	17.06 SD 5.843	19.06 SD 7.266	Ns
Median	14 (range 8-22)	16 (range 8-40)	17 (range 9-48)	
Size of FNA node (mm)				
Mean	14.68 SD 5.075	15.04 SD 4.228	15.09 SD 3.932	Ns
Median	12.5 (range 8-25)	15 (range 9-27)	15 (range 7-25)	

who convert to clinically node-negative following systemic therapy. Technical modifications, including the use of dual tracer and retrieval of at least three SLNs, resulted in clinically acceptable false-negative and identification rates. ALND is required in case of positive SLNs after NACT; in a recent study almost 50% of patients with cN1 disease who converted to cN0 following NACT were spared ALND.[26]

5 | CONCLUSIONS

A positive axillary FNAC is associated with a metastatic nodal burden significantly higher than in patients with positive SLNB. Nevertheless, according to our study, about one to three of patients with cN0 axilla, positive axillary FNAC performed because of suspicious nodes on imaging, T1-2 primary tumor and breast-conserving surgery showed less than three metastatic axillary nodes, thus meeting ACOSOG Z0011 trial's criteria and therefore would be eligible for skipping ALND according to current guidelines. Unfortunately, no diagnostic or predictive tools are available to sort out the patients that could benefit from the preoperative diagnosis of a small axillary nodal burden and be spared the invasive procedure of ALND. However, in light of our findings, clinical approach to the subgroup of cN0 women fitting with previously mentioned criteria and eligible for breast-conserving surgery should be reconsidered. In these patients, SLNB could be an option to avoid about 30% unnecessary ALND.

A further change in clinical practice could come from the consideration that a fair number of cN + patients could benefit from NACT because of the downstaging that can be achieved also in the axillary nodes and avoid axillary dissection in case of a negative post-NACT sentinel node.

CONFLICT OF INTEREST

The authors declare that they have no actual or potential conflict of interest.

ORCID

Viola Liberale https://orcid.org/0000-0002-9056-8235
Marta D'Alonzo https://orcid.org/0000-0001-9153-8399
Andrea Villasco https://orcid.org/0000-0002-9841-7722
Paola Modaffari https://orcid.org/0000-0001-5300-4185
Nicoletta Biglia https://orcid.org/0000-0003-1009-5309

REFERENCES

1. Quan ML, McCready D. The evolution of lymph node assessment in breast cancer. *J Surg Oncol*. 2009;99:194-198.
2. Gnant M, Harbeck N, Thomssen C. St. Gallen/Vienna 2017: a brief summary of the consensus discussion about escalation and de-escalation of primary breast cancer treatment. *BreastCare*. 2017;2017(12):102-107.
3. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer. A multicenter validation study. *N Engl J Med*. 1998;339:941-946.
4. Giuliano AE, Haigh PI, Brennan MB, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *J Clin Oncol*. 2000;18:2553-2559.
5. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med*. 2003;349:546-553.
6. Gur AS, Unal B, Ozbek U, et al. Validation of breast cancer nomograms for predicting the non-sentinel lymph node metastases after a positive sentinel lymph node biopsy in a multi-center study for the Turkish federation of breast disease associations protocol MF08-01 investigators. *Eur J Surg Oncol*. 2010;36:30-35.
7. Meattini I, Saieva C, Bertocci S, et al. Predictive factors for additional non-sentinel lymph node involvement in breast cancer patients with one positive sentinel node. *Tumori J*. 2015;101:78-83.
8. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305:569-575.
9. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;2045:297-305.
10. O'Leary DP, O'Brien O, Relihan N, et al. Rapid on-site evaluation of axillary fine-needle aspiration cytology in breast cancer. *Br J Surg*. 2012;99:807-812.
11. Sauer T, Karesen R. The value of preoperative ultrasound guided fine-needle aspiration cytology of radiologically suspicious axillary lymph nodes in breast cancer. *Cytojournal*. 2014;11:26.

12. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26:v8-v30.
13. Linee guida AIOM. Neoplasie della mammella. 2016.
14. Elmore LC, Appleton CM, Zhou G, Margenthaler JA. Axillary ultrasound in patients with clinically node-negative breast cancer: which features are predictive of disease? *J Surg Res*. 2013;184:234-240.
15. Dialani V, James DF, Slanetz PJ. A practical approach to imaging the axilla. *Insight Imaging*. 2015;6:217-229.
16. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. *Ann Oncol*. 2008;19:614-622.
17. Gradishar W, Anderson B, Balassanian R, et al. NCCN guidelines insights. breast cancer, version 1.2017. Featured updates to the NCCN guidelines. *JNCCN*. 2017;15:433-451.
18. Verheuvel NC, van den Hoven I, Ooms H, Voogd AC, Roumen R. the role of ultrasound-guided lymph node biopsy in axillary staging of invasive breast cancer in the post-ACOSOG Z0011 Trial Era. *Ann Surg Oncol*. 2015;409-415.
19. Boland MR, Ni Cearbhaill R, Fitzpatrick K, et al. A positive node on ultrasound-guided fine needle aspiration predicts higher nodal burden than a positive sentinel lymph node biopsy in breast carcinoma. *World J Surg*. 2016;40:2157-2162.
20. Garcia-Etienne CA, Tomatis M, Heil J, et al. Mastectomy trends for early-stage breast cancer: a report from the EUSOMA multi-institutional european database. *Eur J Cancer*. 2012;13:1947-1956.
21. Kummerow KL, Du L, Penson DF, Shyr YU, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. *Jama Surg*. 2015;150:9-16.
22. van Wely BJ, de Wilt J, Schout P, et al. Ultrasound-guided fine-needle aspiration of suspicious nodes in breast cancer patients; selecting patients with extensive nodal involvement. *Breast Cancer Res Treat*. 2013;140:113-118.
23. Bortolini M, Genta F, Biacchiardi CP, Zanon E, Camanni M, Deltetto F. Axillary dissection in breast cancer patients with metastatic sentinel node: to do or not to do? *Suggestions from our series. ISRN Oncol*. 2011;2011:527904.
24. Cools-Lartigue J, Sinclair A, Trabulsi N, et al. Preoperative axillary ultrasound and fine-needle aspiration biopsy in the diagnosis of axillary metastases in patients with breast cancer: predictors of accuracy and future implications. *Ann Surg Oncol*. 2013;20(3):819-827.
25. Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. *JAMA Oncol*. 2017;3(4):549-555.
26. Mamtani A, Barrio AV, King TA, et al. How often does neoadjuvant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastases? results of a prospective study. *Ann Surg Oncol*. 2016;23:3467-3474.

How to cite this article: Liberale V, Rosso R, Arisio R, et al. Axillary dissection in patients with preoperative positive nodal cytology: Genuine need or overtreatment? *Breast J*. 2019;00:1–8. https://doi.org/10.1111/tbj.13479