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ORIGINAL ARTICLE – BREAST ONCOLOGY

Axillary Lymph Node Ultrasound Following Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: Results from the SN FNAC Study

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ABSTRACT

Background. The sentinel node biopsy following neoadjuvant chemotherapy (SN FNAC) study has shown that in node-positive (N+) breast cancer, sentinel node biopsy (SNB) can be performed following neoadjuvant chemotherapy (NAC), with a low false negative rate (FNR = 8.4%). A secondary endpoint of the SN FNAC study was to determine whether axillary ultrasound (AxUS) could predict axillary pathological complete response (ypN0) and increase the accuracy of SNB.

Methods. The SN FNAC trial is a study of patients with biopsy-proven N+ breast cancer who underwent SNB followed by completion node dissection. All patients had AxUS following NAC and the axillary nodes were classified as either positive (AxUS+) or negative (AxUS−). AxUS was compared with the final axillary pathology results.

Results. There was no statistical difference in the baseline characteristics of patients with AxUS+ versus those with AxUS−. Overall, 82.5% (47/57) of AxUS+ patients had residual positive lymph nodes (ypN+) at surgery and 53.8% (42/78) of AxUS− patients had ypN+. Post NAC AxUS sensitivity was 52.8%, specificity 78.3%, and negative predictive value 46.2%. AxUS FNR was 47.2%, versus 8.4% for SNB. If post-NAC AxUS− was used to select patients for SNB, FNR would decrease from 8.4 to 2.7%. However, using post-NAC AxUS in addition to SNB as an indication for ALND would have led to unnecessary ALND in 7.8% of all patients.

Conclusion. AxUS is not appropriate as a standalone staging procedure, and SNB itself is sufficient to assess the axilla post NAC in patients who present with N+ breast cancer.

Management of the axilla in breast cancer has changed drastically in the past few decades. Axillary lymph node dissection (ALND) was initially used to stage the axilla in all breast cancer surgery cases; however, ALND has many known associated risks, such as lymphedema, limited arm movement, and nerve injury.[1] After publication of the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B32 trial, sentinel node biopsy (SNB) has become the standard of care for clinically node-negative T1–T3 breast cancer.[2–4] SNB following neoadjuvant chemotherapy (NAC) in clinically node-negative patients was proved feasible and accurate, with a false negative rate (FNR) of $< 10\%$.[5] Three prospective studies have evaluated whether SNB can accurately stage the axilla of patients with biopsy proven node-positive (N+) axilla after NAC: sentinel node biopsy following neoadjuvant chemotherapy (SN FNAC),[6] American College of Surgeons Oncology Group (ACOSOG)

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Z1071,[7] and Sentinel Lymph Node Biopsy in Patients with Breast Cancer Before and After Neoadjuvant Chemotherapy (SENTINA).[8]

In the SN FNAC study, patients with biopsy-proven N+ breast cancer who received NAC had their axilla evaluated prospectively by clinical examination, ultrasound, and SNB before undergoing completion node dissection (CND). The FNR of SNB was 8.4%, meeting the pre-specified primary endpoint of $< 10\%$. The SN FNAC, ACOSOG Z1071 and SENTINA trials have shown that using dual tracer, retrieving two sentinel nodes or more, using immunohistochemistry (IHC), and considering nodes with isolated tumor cells post NAC [ypN0(i+)] as N+ could lower the FNR.

Axillary ultrasound (AxUS) and lymph node biopsy have been shown to be effective when used together to predict axillary lymph node involvement in patients with breast cancer.[9] It has been found that the ultrasound features most associated with malignancy are an increase in cortical thickness and the absence of a hyperechoic hilum.[10,11] Current literature is unclear on the role of AxUS as a predictor of axillary status following NAC.

In ACOSOG Z1071, post-NAC AxUS helped identify patients without suspicious lymph nodes who could undergo SNB with a lower FNR.[7,12] Unfortunately, using AxUS to select patients for SNB in this setting could lead to unnecessary ALND in patients with suspicious nodes on AxUS who had actually achieved axillary pathological complete response (ypN0).

Using the SN FNAC cohort of patients, we evaluated (1) whether post-NAC AxUS can accurately predict for ypN0, and (2) whether AxUS can be used to increase the accuracy of SNB in this setting.

METHODS

SN FNAC Trial

The SN FNAC was a prospective, phase II, multicentric study of patients with biopsy-proven N+ breast cancer who received NAC and who had SNB followed by CND. The primary endpoint was to evaluate the accuracy of SNB in this setting. Ten academic university-affiliated centers in Canada and the US participated in the study. Protocol and consent forms were approved by each centre's Scientific and Research Ethics Committee.

Eligible patients were T0-3, N1-2, M0-X. Exclusion criteria included any prior axillary surgery and neoadjuvant radiotherapy to the breast or the axilla. All patients underwent SNB (radioisotope was mandatory and blue dye optional) followed by CND. IHC was used if nodes were negative on hematoxylin and eosin (H&E) stains and ypN0(i+) were considered as N+.

Axillary Ultrasound (AxUS) Examination

Clinical examination and AxUS at initial diagnosis and following NAC were recorded prospectively. Physicians and radiologists were asked to determine lymph node status (positive or negative). Radiological characteristics of suspicious lymph nodes have been widely described in previous publications (i.e. increased cortical thickness, loss of fatty hilum, increased vascularization and rounded shape).[10,11] No specific criteria were mandated as per protocol to classify nodes as being positive or negative. Radiologists were asked, based on the AxUS results, to determine if they believed the lymph node would end up being positive or negative on final pathology.

Statistical Analysis

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated by comparing the results of the post-NAC AxUS with the final nodal pathology. Descriptive statistics were performed, including the Chi square test, to evaluate the effect of AxUS on SNB accuracy.

RESULTS

From March 2009 to December 2012, 153 N+ breast cancer patients were enrolled in the SN FNAC study, and 145 met the eligibility criteria. Results from SN FNAC showed that SNB could be performed following NAC, with an identification rate of 87.6% (127/145 patients) and an FNR of 8.4%. Forty-four of 145 patients (30.3%) had ypN0 disease, thus node dissection could have been avoided for these patients (Fig. 1).

Post-NAC AxUS results were available in 135 patients, 115 of whom underwent AxUS followed by SNB + CND. Accuracy was determined by comparing post-NAC AxUS with final nodal pathology (Fig. 2).

Baseline Patient, Tumor, and Treatment Characteristics

Of the 135 patients with available post-NAC AxUS results, 57 (42.2%) had a positive ultrasound (AxUS+) and 78 (57.8%) had a negative ultrasound (AxUS−) (Fig. 3). Table 1 lists the patient baseline characteristics. There was no statistical difference in clinical and radiologic stage, tumor characteristics, and treatment received between the AxUS+ and AxUS− patients.

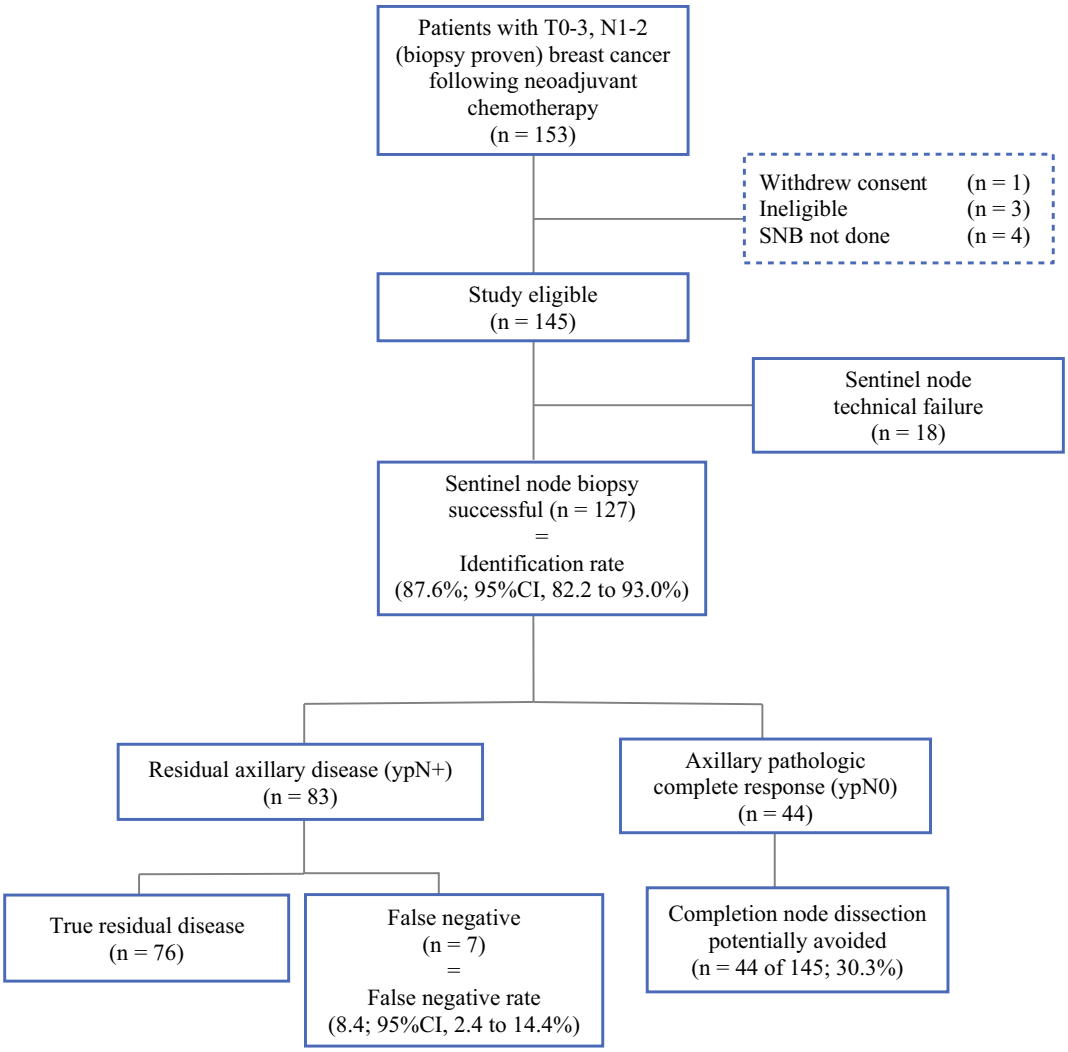

FIG. 1 SN FNAC trial. *SN FNAC* sentinel node biopsy following neoadjuvant chemotherapy, *SNB* sentinel node biopsy, *CI* confidence interval

Axilla Ultrasound and Physical Examination as Predictors of the Axillary Response

Overall, 82.5% (47/57) of patients with AxUS+ had residual axillary lymph node disease (ypN+), while 53.8% (42/78) of patients with AxUS− also had a ypN+ (Table 2).

AxUS following NAC had a sensitivity of 52.8%, specificity of 78.3%, PPV of 82.4%, NPV of 46.2%, and an accuracy of 61.5%. SNB itself had a sensitivity of 91.6%, specificity of 100%, PPV of 100%, NPV of 86.3%, and an accuracy of 94.5% (Table 3).

Overall, 83% (120/144) of patients whose clinical examination data were available did not have palpable disease in the axilla following NAC, but 58.3% (70/120) of these patients had ypN+. Axillary physical examination following NAC had a sensitivity of 22.3%, specificity of 94.0%, PPV of 87.5%, NPV of 39.2%, and an accuracy of 47.2% (Table 3).

Post-Neoadjuvant Chemotherapy AxUS and Lymph Node Status

Patients with AxUS+ did not have a significantly higher number of positive nodes compared with patients with AxUS− (3.74 vs. 1.95; $p = 0.111$). The number of metastatic sentinel lymph nodes (1.20 vs. 0.93; $p = 0.236$) and size of the largest metastatic deposit (9.55 mm vs. 6.27 mm; $p = 0.092$) was similar in both groups; however, more lymph nodes were dissected in patients with a AxUS+ versus patients with a AxUS− (16.07 vs. 13.87; $p = 0.024$). Patients with a AxUS+ had more positive non-sentinel nodes (2.7 vs. 1.1; $p = 0.022$) (Table 4).

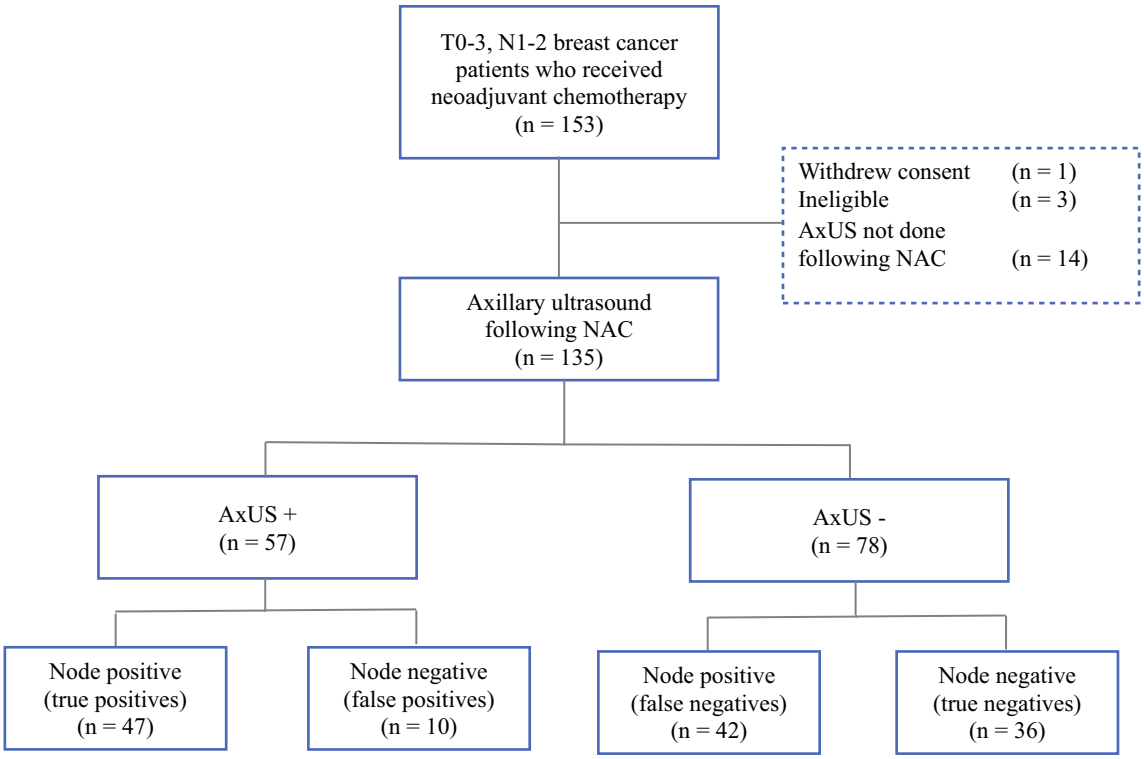

FIG. 2 Axillary ultrasound following neoadjuvant chemotherapy as part of the SN FNAC trial. *SN FNAC* sentinel node biopsy following neoadjuvant chemotherapy, *SNB* sentinel node biopsy, *AxUS* axillary ultrasound, *NAC* neoadjuvant chemotherapy

Use of AxUS to Increase the Accuracy of Sentinel Node Biopsy in Node-Positive Breast Cancer Patients Following Neoadjuvant Therapy

Using AxUS− to select patients for SNB would have decreased the SNB FNR from 8.4 to 2.7% [95% confidence interval (CI) −1.0–8.2]. The NPV would increase from 86.3 to 93.9% (95% CI 85.8–100) (Fig. 3), and the accuracy of AxUS followed by SNB would be 90.4% (95% CI 85.1–95.8). Among all patients who underwent an AxUS followed by SNB + CND, the number of unnecessary CNDs (performing a CND in patients who achieved ypN0) would have been 7.8% (9/115). In the presence of AxUS+, 19.6% of patients (9/46) achieved ypN0 and would have undergone an unnecessary CND (Table 5).

DISCUSSION

Current literature is unclear on the role of AxUS as a predictor of axillary status following NAC.[13,14] The SENTINA trial has shown that neither AxUS nor clinical examination with palpation of the axilla were sufficient to predict lymph node status in this setting, and that surgical staging was required to correctly evaluate the axilla.[15] The ACOSOG Z1071 trial found that AxUS following NAC could help guide axillary surgery and lower the FNR of SNB. They were also able to identify lymph node features (i.e. longer short-axis and long-axis diameter, increased cortical thickness, and absence of fatty hilum) predictive of axillary status post systemic treatment.[16]

Our study showed that AxUS was not as sensitive or specific as SNB in predicting final axillary lymph node status. When comparing axillary physical examination, AxUS and SNB, SNB is significantly more accurate at determining axillary lymph node status. Sensitivity and NPV are of paramount importance in the age of post-neoadjuvant/adjuvant therapy. It is crucial to minimize the risk of missing any residual axillary disease since it would deprive patients from possibly benefiting from improvements in outcome from adjuvant treatment such as capecitabine,[17] especially in triple-negative breast cancer and T-DM1[18] in human epidermal growth factor receptor (HER2)-positive breast cancer.

If AxUS was to replace SNB or ALND as a method to stage the axilla after NAC, it would be associated with an FNR of 47.2%. Using AxUS followed by SNB would decrease the FNR as low as 2.7%, with an NPV of 93.7%. In ACOSOG Z1071, using AxUS− to select patients for SNB would have also decreased the calculated FNR from 12.6 to 9.8%, with an NPV of 83.8%.[12] However, going straight to ALND in the presence of AxUS+ would lead to an increase in the number of unnecessary CNDs in patients

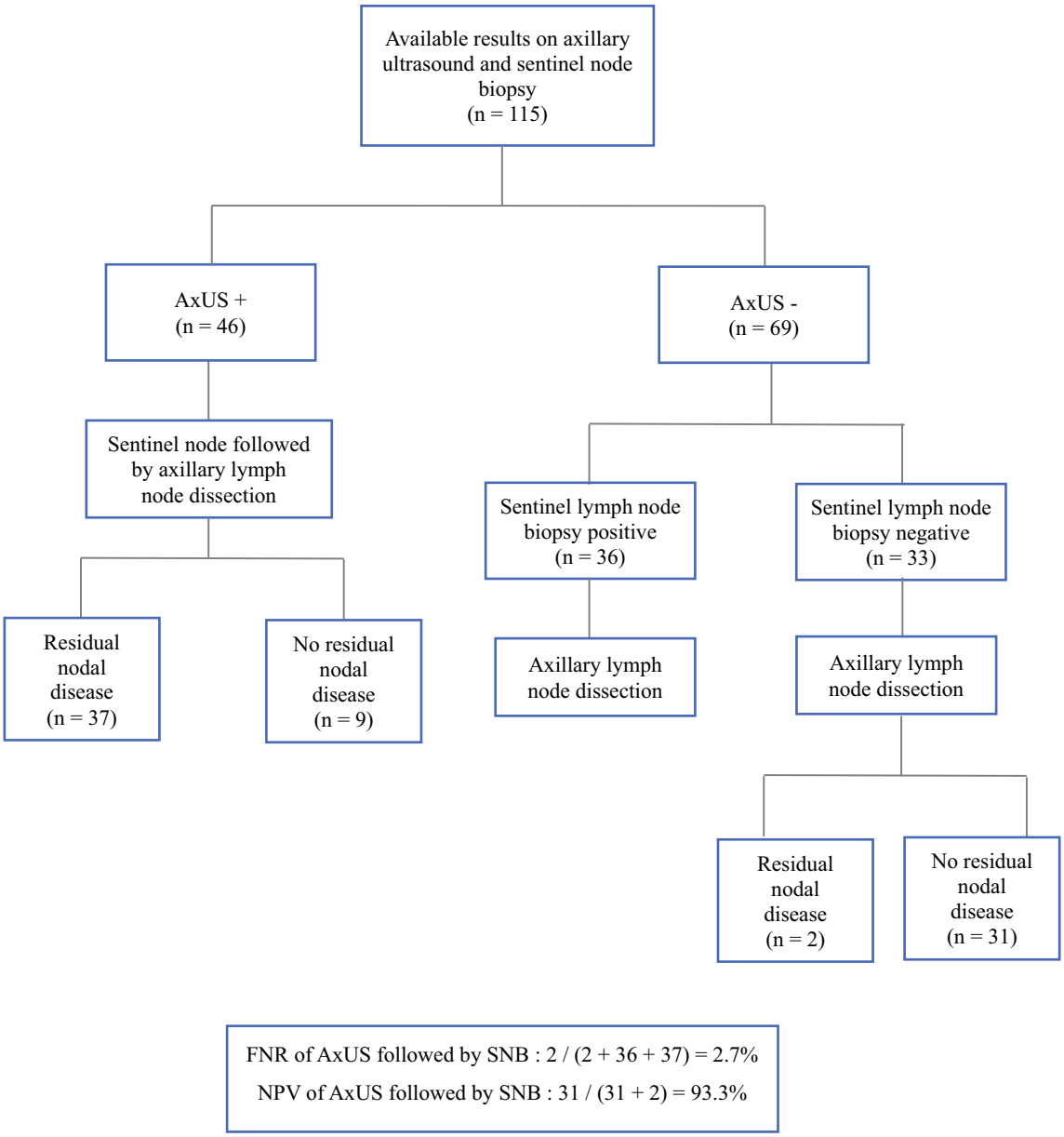

FIG. 3 Axillary ultrasound and sentinel node biopsy following neoadjuvant chemotherapy as part of the SN FNAC trial. *SN FNAC* sentinel node biopsy following neoadjuvant chemotherapy, *AxUS* axillary ultrasound, *FNR* false negative rate, *NPV* negative predictive value

who achieved ypN0—19.6% of patients in the SN FNAC study and 28.3% of patients in the ACOSOG Z1071 trial (Table 5).

In our study, patients with AxUS+ had an increased number of nodes removed compared with patients with a normal ultrasound (13.9 vs. 16.1; $p = 0.024$). This could be explained by the fact that surgeons were more aggressive during the dissection knowing the post-NAC AxUS was suspicious. It could also be because the presence of macroscopic nodal disease is more easily seen on AxUS and would also encourage the surgeon to retrieve more nodes. In addition, patients with a AxUS+ had more positive non-sentinel nodes (2.7 vs. 1.1, $p = 0.022$); however, the majority of these patients also had a positive SNB, which means they would have undergone a CND. Given that we demonstrated no difference in the number of positive nodes removed in the presence of AxUS+ versus AxUS−, and that increasing the number of resected lymph nodes is associated with more surgical complications,[1,19,20] it is possible that the use of AxUS might be associated with an increase in surgical morbidity; however, this has not been evaluated in the current study.

TABLE 1 Comparison of patient and tumor characteristics for patients with either suspicious or normal post-chemotherapy axillary ultrasound

	Post-chemotherapy AxUS+ (n = 57)		Post-chemotherapy AxUS− (n = 78)		
	N	%	*N*	%	
Median age at diagnosis, years	49		50		0.603
Radiological T at diagnosis					0.469
0	0	0	0	0	
1	13	23.2	17	22.7	
2	33	58.9	50	66.7	
3	10	17.9	8	10.7	
Clinical T at diagnosis					0.222
0	3	5.4	0	0	
1	3	5.4	4	5.1	
2	29	50.0	45	57.7	
3	21	39.3	29	37.2	
Clinical N at diagnosis					0.864
0	10	17.9	13	16.7	
1	42	75.0	61	78.2	
2	4	7.1	4	5.1	
3	0	0	0	0	
Pathology on initial biopsy					0.912
Invasive lobular carcinoma	3	5.3	5	6.4	
Invasive ductal carcinoma	53	93.0	71	91.0	
Other	1	1.8	2	2.6	
Grade on initial biopsy					0.448
1	4	7.5	7	9.0	
2	27	50.9	31	39.7	
3	22	41.5	40	51.3	
Tumor markers					0.086
Luminal A and Luminal B HER2−	36	63.2	43	55.1	
Luminal B HER2+	5	8.8	20	25.6	
HER2+	6	10.5	5	6.4	
Triple-negative	10	17.5	10	12.8	
Chemotherapy completed					0.206
Yes	48	84.2	58	74.4	
No	9	15.8	20	25.6	
Type of surgery					0.167
Total mastectomy	24	42.11	42	54.55	
Partial mastectomy	33	57.89	35	45.45	
Technical failure at sentinel node biopsy					0.369
Yes	8	14.0	7	9.0	
No	49	86.0	70	89.7	

AxUS axillary ultrasound, *HER2* human epidermal growth factor receptor 2

In this study, the type of ultrasound machines and probes used were not standardized. Central review of the AxUS images was not performed. Positive or negative AxUS was a binary variable that was recorded prospectively at local sites for research purposes and represents the interpretation of the radiologist reporting the ultrasound. Although this is seen as a limitation of the study, since these results are from a multicentric trial involving many different centers, it does support a broad applicability of the results.

TABLE 2 Association between axillary ultrasound and final axillary lymph node pathology

	Post-NAC AxUS+		Post-NAC AxUS−	
	N	%	*N*	%
Sentinel node biopsy	*n* = 46		*n* = 69	
Positive	33	71.7	36	52.2
Negative	13	28.3	33	47.8
Axillary lymph node dissection	*n* = 57		*n* = 78	
Positive	47	82.5	42	53.8
Negative	10	17.5	36	46.2

NAC neoadjuvant chemotherapy, *AxUS* axillary ultrasound

TABLE 3 Axillary ultrasound and sentinel node biopsy characteristics

	Axillary physical examination		Axillary ultrasound		Sentinel node biopsy	
	%	95% CI	%	95% CI	%	95% CI
Sensitivity	22.3	13.9–30.8	52.8	42.4–63.2	91.6	83.9–96.6
Specificity	94.0	87.4–100	78.3	66.3–90.2	100	92.0–100
PPV	87.5	74.3–100	82.4	72.6–92.3	100	
NPV	39.2	30.4–47.9	46.2	35.1–57.2	86.3	75.6–92.7
Accuracy	47.2	39.1–55.4	61.5	53.3–69.7	94.5	89.0–97.7
FNR	77.6	69.2–85.1	47.2	36.8–58.3	8.4	2.4–14.4
Total (*n*)	144		135		127	

CI confidence interval, *PPV* positive predictive value, *NPV* negative predictive value, *FNR* false negative rate

TABLE 4 Extent of axillary lymph node disease according to axillary ultrasound results

	Post-NAC AxUS+ (*n* = 57)		Post-NAC AxUS− (*n* = 78)		*p* value
	Mean	95% CI	Mean	95% CI	
Total number of lymph nodes removed (mean)	16.07	13.89–18.26	13.87	12.16–15.58	0.024
Total number of positive nodes (mean)	3.74	2.25–5.23	1.95	1.15–2.75	0.111
Number of metastatic SLNs (mean)	1.20	0.86–1.54	0.93	0.64–1.22	0.236
Size of the largest metastatic SLNs (mean, mm)	9.55	5.98–13.13	6.27	4.51–8.034	0.092
Number of non-SLN metastatic lymph nodes (mean)	2.74	1.32–4.16	1.10	0.44–1.76	0.022

NAC neoadjuvant chemotherapy, *AxUS* axillary ultrasound, *SLNs* sentinel lymph nodes

TABLE 5 Accuracy of axillary sentinel node in patients with post-NAC axillary ultrasound

	SN FNAC trial (*n* = 115) (%)	ACOSOG Z1071 trial (*n* = 470) (%)
FNR	2.7	9.8
NPV	93.9	83.8
Unnecessary ALND in all AxUS	7.8	8.3
Unnecessary ALND in AxUS+	19.6	28.3

SN FNAC sentinel node biopsy following neoadjuvant chemotherapy, *ACOSOG* American College of Surgeons Oncology Group, *FNR* false negative rate, *NPV* negative predictive value, *ALND* axillary lymph node dissection, *AxUS* axillary ultrasound

Although our study had a smaller sample size than the ASOCOG Z1071 trial, the results obtained were remarkably similar. Other limitations include the absence of evaluation of the impact of clipping nodes and ensuring their removal on the accuracy of nodal staging and relevance of post-NAC AxUS. We now know that placing a

clip in the biopsy-proven N+ at initial biopsy, and retrieving the clipped node at the time of SNB using targeted node dissection (either with iodine-125 seed or wire localization), decreases the FNR of SNB substantially (FNR = 2.0%).[21] We believe targeted axillary dissection and SNB following NAC would be a preferred method over AxUS to increase the accuracy of post-NAC axillary staging since it is not associated with an increase in unnecessary CND. Direct comparison of these two strategies was not studied as part of the SN FNAC trial.

CONCLUSIONS

We believe that AxUS is not an appropriate stand-alone staging procedure and that SNB itself is sufficient to assess the axilla post NAC in patients who present with N+ breast cancer. AxUS screening post NAC can be used to improve the accuracy of SNB in this setting and might be useful for surgeons who do not feel confident to restage the axilla of these patients using only SNB. However, dissecting the axilla of all patients with AxUS+ comes at the cost of increasing the number of unnecessary node dissections. Preference should be given to novel methods, such as targeted node dissection used in addition to SNB, which can optimize the accuracy of axillary node staging without causing unnecessary morbidity.

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