Breast Cancer Research and Treatment (2023) 197:515–523
https://doi.org/10.1007/s10549-022-06817-8

CLINICAL TRIAL

Axillary ultrasound after neoadjuvant therapy reduces the false-negative rate of sentinel lymph node biopsy in patients with cytologically node-positive breast cancer

Yu Liu[1,2,3] · Ying Wang[4] · Senwen Feng[5] · Zeyan Xu[1,2] · Mengxia Yao[6] · Xiaomei Huang[1,2] · Pinxiong Li[1,2] · Lei Wu[1,2] · Chunling Liu[1,2] · Xin Chen[7] · Changhong Liang[1,2,3] · Zaiyi Liu[1,2]

Received: 15 August 2022 / Accepted: 10 November 2022 / Published online: 13 December 2022

Abstract

Objectives This study aimed to determine whether post-neoadjuvant therapy (NAT) axillary ultrasound (AUS) could reduce the false-negative rate (FNR) of sentinel lymph node biopsy (SLNB). We also performed subgroup analyses to identify the appropriate patient for SLNB.

Methods A total of 220 patients with cytologically proven axillary node-positive breast cancer who underwent both SLNB and axillary lymph node dissection (ALND) after NAT were included. We calculated the FNR of SLNB. In the case of post-NAT AUS results available, AUS was classified as negative or positive. Then the FNR of post-NAT AUS combined with SLNB was evaluated. Subgroup analyses based on the number of sentinel lymph nodes removed, molecular subtypes, and the clinical N stage were also performed.

Results The overall axillary lymph node pathological complete response rate was 45.5% (100/220). The FNR of SLNB alone was 15.8% (95%CI: 9.2 to 22.5%). Post-NAT AUS results were available for 181 patients. When combined negative post-NAT AUS results and SLNB, the FNR was reduced to 7.5% (95%CI: 2.4 to 12.7%). Subgroup analyses of the FNR for SLNB alone and negative post-NAT AUS combined with SLNB were shown as follows: in cases patients with less than three sentinel lymph nodes (SLNs) and at least three SLNs removed, the FNR was decreased from 24.5 to 13.2%, and 9.0 to 5.0%, respectively. The FNR was decreased from 20.8 to 10.5% in HR+/HER2+subgroup, 21.4 to 16.7% in HR−/HER2+subgroup, 15.9 to 7.0% in HR+/HER2− subgroup, and 0% in HR−/HER2− subgroup, respectively. For cN1 patients, the FNR was decreased from 18.1 to 12.1% while 17.1 to 3.6% for cN2 patients and 0% for cN3 patients.

Conclusion Using negative post-NAT AUS may help to decrease the FNR and improve patient selection for SLNB.

Keywords Node-positive breast cancer · Axillary ultrasound · Neoadjuvant therapy · Sentinel lymph node

Introduction

Neoadjuvant therapy (NAT) is the standard of care for patients with clinically axillary lymph node-positive breast cancer [1]. For patients with ALN pCR after NAT, omission of ALND can reduce morbidity and complications, such as lymphedema, numbness, axillary web syndrome, and upper-extremity range of motion [2]. Sentinel lymph node biopsy (SLNB) is an alternative surgical method for staging the axilla after NAT in patients with clinically node-positive breast cancer [3]. However, several large prospective trials have shown that the overall false-negative rates (FNR) of SLNB were 12.6% (in the Z1071 trial) to 14.2% (in the SENTINA trial) [4–6], which exceeds the clinically accepted cutoff of 10% [7, 8]. Thus, the appropriate use of SLNB in the NAT setting remains controversial [9, 10].

With the evolution of ALN management, medical imaging in the NAT setting has become of great significance. According to American College of Radiology, or ACR, Appropriateness Criteria, the most accurate imaging modality in the evaluation of residual ALN disease after NAT is

Yu Liu, Ying Wang, and Senwen Feng have contributed equally to this work.

✉ Changhong Liang
liangchanghong@gdph.org.cn

✉ Zaiyi Liu
zyliu@163.com

Extended author information available on the last page of the article

ultrasound [11]. The morphologic ultrasound features of ALN showing cortical thickness of more than 3 mm, loss of fatty hilum, oval shape, or peripheral nonhilar blood flow were associated with residual ALN disease [12–14]. Unfortunately, axillary ultrasound alone cannot accurately predict ALN pCR preoperatively, with a false-negative rate (FNR) of up to 29% [15–17]. Promisingly, previous studies reported that combining negative post-NAT AUS findings with SLNB could decrease the FNR, from 12.6 to 9.8% in the Z1071 trial [18] and 8.4 to 2.7% in the SN FNAC trial [19]. However, the rather wide 95%CI in the SN FNAC trial and an FNR close to 10% in the Z1071 trial could not determine whether negative post-NAT AUS decreased the FNR of SLNB, which deserves further study. Furthermore, these studies did not perform subgroup analysis by the number of sentinel lymph nodes (SLNs) removed, molecular subtypes, and clinical N stage. These parameters could be associated with the FNR for SLNB [20–22].

This study aimed to further determine whether negative post-NAT AUS could reduce the FNR for SLNB. We also performed subgroup analysis to identify the appropriate patient for AUS combined with SLNB.

Methods

Study design and patients

This study was approved by the ethics committee of Guangdong Provincial People's Hospital. Informed consent was waived due to the retrospective nature of the study. After a review of the electronic medical record, patients with biopsy-proven lymph node-positive breast cancer who received NAT followed by SLNB and then ALND between July 2014 and July 2021 were initially included. Exclusion criteria were as follows: (1) patients missing clinical information ($n=5$); (2) SLNB failure (failure to identify sentinel lymph node, $n=3$); (3) patients with prior breast cancer ($n=2$); (4) patients treated in other institutions ($n=7$) (Fig. 1). The NAT regimens were based on the current National Comprehensive Cancer Network guideline [23].

Axillary ultrasound examination

After NAT and within 1 month before surgery, some of the patients underwent an AUS examination. The AUS evaluation was performed by one of the two sonographers (YL and MX. Y with 5 and 10 years of experience, respectively) by using a 5-18MHZ linear array transducer. The morphologic ultrasound features of ALN showing cortical thickness of more than 3 mm, loss of fatty hilum, oval shape, or peripheral nonhilar blood flow were defined as positive [12–14]. ALN was classified as negative if the sonographer did not see any ALN on AUS or judged the ALN was normal in morphologic appearance after NAT.

Pathological evaluation

The status of ALN pCR was determined by surgical pathology within 1 month after NAT, which was defined as a complete absence of micrometastases and macrometastases in ALN. Isolate tumor cells were considered as ALN pCR (ypN0) [24]. Immunohistochemistry (IHC) was used if nodes were negative on hematoxylin and eosin stains.

The status of estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 was determined by IHC. Patients with a Ki-67 proliferation index less 30% were classified as low proliferation, and high proliferation otherwise [25]. The

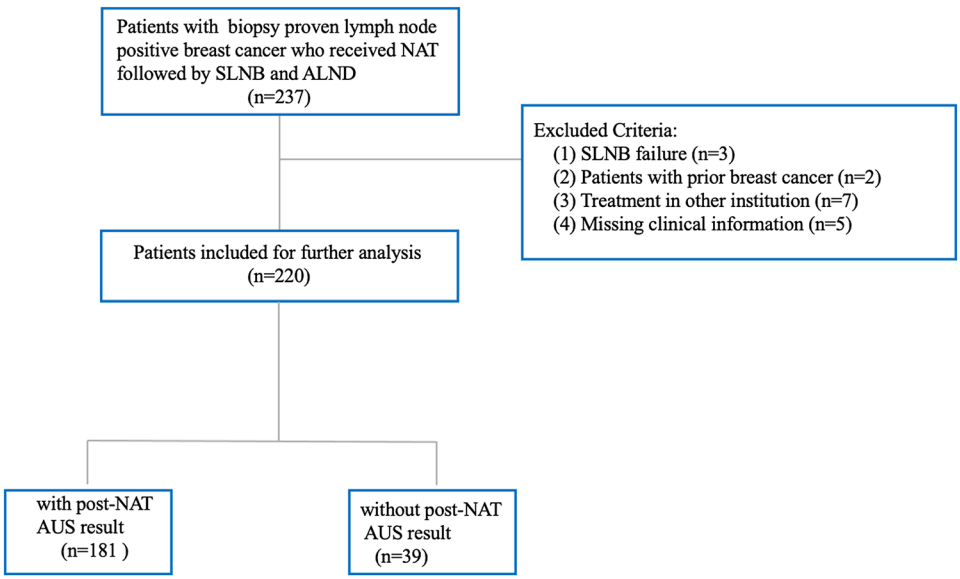

Fig. 1 The flowchart of the study. *SLNB* sentinel lymph node biopsy; *ALND* axillary lymph node dissection; *NAT* Neoadjuvant therapy; *AUS* axillary ultrasound

status of ER and PR was regarded as positive if the tumor showed at least 1% of positive cells on nuclear staining [26]. HER2-positive was defined as IHC 3+ or IHC 2+ and amplified by fluorescence in situ hybridization (FISH). HER2-negative was defined as IHC 0 or IHC 1+ or IHC 2+ and FISH-negative [27]. The molecular subtypes were classified as HR-positive/HER2-positive, HR-negative/HER2-positive, HR-positive/HER2-negative, and HR-negative/HER2-negative.

Statistical analysis

Demographic and clinicopathological variables between groups were compared using *t* test or Wilcoxon rank sum test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. For the post-NAT AUS alone, a false-negative event was defined as patients with negative nodes in the post-NAT AUS who had a residual disease in either SLNB or ALND, or both. For SLNB alone, a false-negative event was defined as patients with negative sentinel nodes who had a residual disease in ALND. For the combined post-NAT AUS with SLNB, a false-negative event was defined as patients with negative nodes in the post-NAT AUS and SLNB who had a residual disease in ALND. The FNR was calculated as the number of false-negative events divided by the total number of patients with residual disease (in either SLNB or ALND, or both). 95% confidence interval (CI) was calculated using exact (Clopper-Pearson) confidence limits for binominal proportion. Fisher's exact test was used to compare the FNRs between groups. All *P* values were two-sided tests, and a *P* value less than 0.05 was considered significant. The data were analyzed with SPSS version 23.0 (SPSS, Chicago, IL, US) and R software version 3.5.0 (Vienna, Austria).

Results

Patients

After exclusion criteria were applied, a total of 220 patients were finally enrolled in this study (Fig. 1). The overall ALN pCR rate was 45.5% (100/220). ALN pCR rates according to molecular subtypes were in 61.2% (38/62) HR-positive/HER2-positive group, 66.7% (28/42) in HR-negative/HER2-positive group, 51.9% (14/27) in HR-negative/HER2-negative group, and 29.0% (20/69) in HR-positive/HER2-negative group.

Three patients (1.4%) received an anthracycline-based regimen without a taxane, 104 patients (47.2%) received a taxane/anthracycline-based combination, 102 patients (46.4%) received a taxane-based regimen without an anthracycline, and 11 patients (5.0%) received a no taxane/no anthracycline-based regimen. Of the 104 human epidermal growth factor receptor 2 (Her2)-positive patients, 52 patients (50.0%) received trastuzumab, 43 patients (41.3%) received trastuzumab and Pertuzumab, and 9 patients (8.7%) did not receive anti-HER2 regimen because of financial burden.

FNR of SLNB in the entire cohort

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of SLNB after NAT were 84.2, 100, 100, 84.0, and 91.4%, respectively. Overall, the FNR for SLNB alone was 15.8% (95%CI 9.2 to 22.5%). Among 102 patients with less than three SLNs removed, the FNR was 24.5% (95%CI 12.6 to 36.5%). While the FNR decreased to 9.0% (6/67, 95%CI 1.9 to 16.0%) in patients with at least three SLNs removed ($P = 0.02$, Supplementary Figure S1).

Comparison of clinicopathological variables

Only the number of sentinel lymph nodes (SLNs) removed, and tumor histology showed significant differences between patients with and without post-NAT AUS results (($P < 0.05$, Table 1). In addition, there was a higher proportion of cN2, PR-positive, HER2-negative, and HR-positive/HER2-negative in the positive post-NAT AUS group ($P < 0.05$, Table 2).

Post-NAT AUS results and pathologic ALN status

Post-NAT AUS results were significantly associated with pathologic ALN status ($P < 0.001$) (Supplementary Figure S2). Patients with positive AUS findings were more likely to have a greater number of positive SLNs and ALNs than those with negative AUS findings (range: 0–10 *vs.* 0–5 and 0–24 *vs.* 0–16, respectively, $P < 0.001$). The sensitivity, specificity, PPV, NPV, and accuracy of post-NAT AUS were 63.3, 84.3, 82.7, 66.0, and 72.9%, respectively. The FNR of AUS was 36.7% (36/98, 95%CI 27.0 to 46.4%) (Supplementary Figure S2).

FNR of SLNB when combined with negative post-NAT AUS results

In this study, using negative post-NAT AUS results to select patients for SLNB, the FNR was 7.5% (95%CI 2.4 to 12.7%). The sensitivity, specificity, PPV, NPV, and accuracy of post-NAT AUS combined with SLNB were 91.8, 84.3, 87.4, 89.7, and 88.4%, respectively. 13 patients with ALN pCR were subjected to an unnecessary ALND. 8 patients with negative SLNB had residual ALN disease who would have been undertreated had they undergone SLNB alone. The majority of patients ($n = 160$) underwent appropriate axillary surgery (Fig. 2).

Table 1 Comparison of clinicopathological characteristic between patients with post-NAT AUS available and patients with post-NAT AUS not available.

Characteristics	Post-NAT AUS not available ($N=39$)	Post-NAT AUSavailable ($N=181$)	P
Age	47.44 ± 10.88	49.62 ± 9.99	0.467
Age group(year)			0.086
≦40	12 (30.8%)	30 (16.6%)	
40–50	11 (28.2%)	48 (26.5%)	
≧50	16(41.0%)	103(56.9%)	
Menopausal status			0.106
Pre-menopause	26 (66.7%)	95 (52.5%)	
Post-menopause	13 (33.3%)	86 (47.5%)	
Clinical T stage			0.070
T1	8 (20.5%)	16 (8.8%)	
T2	22 (56.4%)	126 (69.6%)	
T3	8 (20.5%)	25 (13.8%)	
T4	1 (2.6%)	14 (7.7%)	
Clinical N stage			0.666
N1	25 (64.1%)	129 (71.3%)	
N2	10 (25.6%)	36 (19.9%)	
N3	4 (10.3%)	16 (8.8%)	
Tumor histology			0.031
IDC	35 (89.7%)	175 (96.7%)	
ILC	0 (0%)	3 (1.7%)	
other	4 (10.3%)	3(1.7%)	
ER			0.359
Negative	11 (28.2%)	65(35.9%)	
Positive	28 (71.8%)	116 (64.1%)	
PR			0.217
Negative	14 (35.9%)	86 (47.5%)	
Positive	25 (64.1%)	95 (52.5%)	
Ki-67			0.287
Low	11 (28.2%)	37 (20.4%)	
High	28 (71.8%)	144 (79.6%)	
HER2			0.208
Negative	17 (43.6%)	99 (54.7%)	
Positive	22 (56.4%)	82 (45.3%)	
Molecular subtype			0.413
HR + /HER2 +	15(38.5%)	47(26.0%)	
HR−/HER2 +	7(17.9%)	35 (19.3%)	
HR−/HER2−	3(7.7%)	24 (13.3%)	
HR + /HER2−	14 (35.9%)	75 (41.4%)	
Type of surgery			0.583
Conserving surgery	3 (7.7%)	21 (11.6%)	
Mastectomy	36 (92.3%)	160 (88.4%)	
The number of SLNs removed	2.44 ± 1.77	3. 67 ± 2.78	< 0.001
The number of ALNs removed	15.21 ± 6.57	13.29 ± 6.76	0.931

AUS: axillary ultrasound; *NAT* neoadjuvant chemotherapy; *HER2* human epidermal growth factor receptor 2; *HR* hormone receptor; *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma; *SLN* sentinel lymph node; *ALN* axillary lymph node.

Subgroup analysis results are shown in Table 3. Although no statistical significance was observed, the FNR was lower for negative post-AUS combined with SLNB when compared with SLNB alone ($P > 0.05$, Table 3).

Table 2 Comparison of clinicopathological characteristic between patients with negative AUS and patients with positive AUS

Characteristics	AUS negative ($N=106$)	AUS positive ($N=75$)	P
Age	48.80 ± 9.23	50.79 ± 10.94	0.085
Age group(year)			0.396
≦40	16 (15.1%)	14 (18.7%)	
40–50	32 (30.2%)	16 (21.3%)	
≧50	58 (54.7%)	45 (60.0%)	
Menopausal status			0.475
Pre-menopause	58 (54.7%)	37 (49.3%)	
Post-menopause	48 (45.3%)	38 (50.7%)	
Clinical T stage			0.463
T1	12 (11.3%)	4 (5.3%)	
T2	70 (66.0%)	56 (74.7%)	
T3	16 (15.1%)	9(12.0%)	
T4	8 (7.5%)	6 (8.0%)	
Clinical N stage			0.001
N1	87 (82.1%)	42 (56.0%)	
N2	12 (11.3%)	24 (32.0%)	
N3	7 (6.6%)	9 (12.0%)	
Tumor histology			0.816
IDC	103 (97.2%)	72 (96.0%)	
ILC	1 (0.9%)	2 (2.7%)	
Other	2 (1.9%)	1 (1.3%)	
ER			0.121
Negative	43 (40.6%)	22 (29.3%)	
Positive	63 (59.4%)	53(70.7%)	
PR			0.004
Negative	60 (56.6%)	26 (34.7%)	
Positive	46(43.4%)	49(65.3%)	
Ki-67			0.901
Low	22 (20.8%)	15(20.0%)	
High	84 (79.2%)	60(80.0%)	
HER2			0.007
Negative	49 (46.2%)	50 (66.7%)	
Positive	57(53.8%)	25 (33.3%)	
Molecular subtype			0.004
HR + /HER2 +	33(31.1%)	14(18.6%)	
HR−/HER2 +	24(22.7%)	11(14.7%)	
HR−/ HER2−	16(15.1%)	8 (10.7%)	
HR + /HER2−	33 (31.1%)	42 (56.0%)	
Type of surgery			0.541
Conserving surgery	11 (10.4%)	10 (13.3%)	
Mastectomy	95 (89.6%)	65 (86.7%)	
The number of SLNs removed	3.55 ± 2.60	4.05 ± 3.00	0.130
The number of ALNs removed	12.65 ± 6.68	14.19 ± 6.81	0.697

AUS axillary ultrasound; *HER2* human epidermal growth factor receptor 2; *HR* hormone receptor; *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma; *SLN* sentinel lymph node

Discussion

In this study, we observed that the strategy of combined negative post-NAT AUS and SLNB resulted in an FNR of 7.5%. Subgroup analysis showed that the FNR exceeded the clinically accepted threshold of 10% only in patients with less than three nodes removed, HER2-positive, and cN1 breast cancer. The study demonstrated that negative

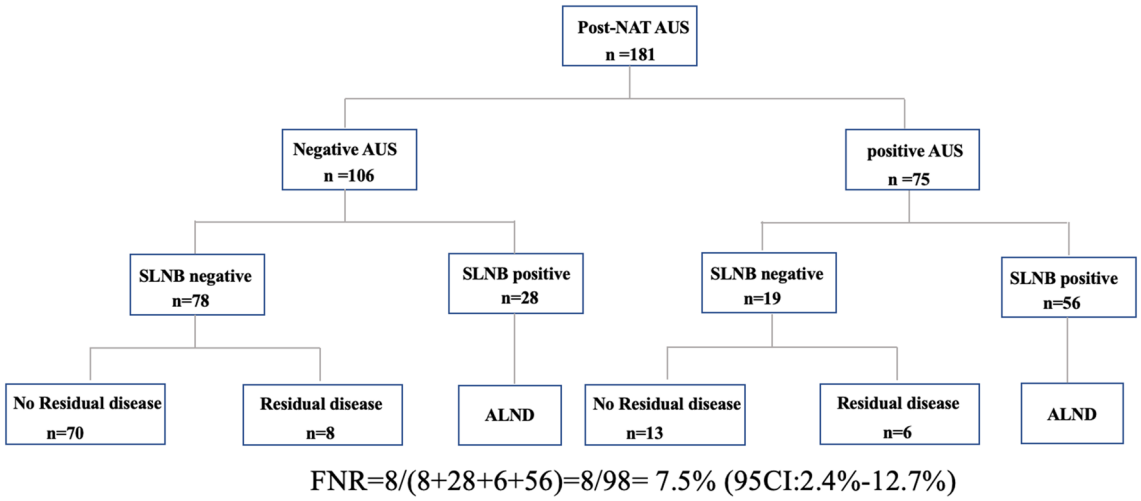

Fig. 2 The false-negative rate when selection of patients for SLNB based on post-NAT AUS results.*NAT* neoadjuvant therapy; *AUS* axillary ultrasound; *ALND* axillary lymph node dissection; *SLNB* sentinel lymph node biopsy

Table 3 Subgroups analysis of the FNR when AUS was combined with SLNB

Subgroup analysis	Post-NAT AUS combined with SLNB				SLNB alone			
	False-negative events	Residual disease identified in SLNB or ALND	FNR (%)	95%CI	False-negative events	Residual disease identified in SLNB or ALND	FNR (%)	95%CI
The number of SLNs removed								
< 3 SLN removed	5	38	13.2	1.9, 24.4	13	53	24.5	12.6, 36.5
≧3 SLN removed	3	60	5.0	1.0, 13.9	6	67	9.0	1.9, 16.0
Molecular subtypes								
HR+/HER2+	2	19	10.5	1.3, 33.1	5	24	20.8	7.1, 42.2
HR−/HER2+	2	12	16.7	2.1,48.4	3	14	21.4	4.6,50.7
HR−/HER2−	0	10	0	–	0	13	0	–
HR+/HER2−	4	57	7.0	2.0, 13.9	11	69	15.9	7.1, 24.8
Clinical N stage								
Clinical N1	7	58	12.1	5.0, 23.3	13	72	18.1	10.0, 28.9
Clinical N2	1	28	3.6	0.9.18.3	6	35	17.1	6.6,33.6
Clinical N3	0	12	0	–	0	13	0	–

FNR false-negative rate; *AUS* axillary ultrasound; *SLNB* Sentinel lymph node biopsy; *SLN* Sentinel lymph node; *HER2* human epidermal growth factor receptor 2; *HR* hormone receptor

post-NAT AUS combined with SLNB could improve the ability to accurately restage the axilla.

The most essential finding of the present study was that combining negative post-NAT AUS and SLNB could decrease FNR, which is in agreement with previous studies [18, 19]. However, our work differs from their studies in two ways. First, this is a real-world example of the application of post-NAT AUS to guide SLNB outside a clinical trial. Second, the subgroup analysis of the study may be useful to guide individual treatment. Notably, the confidence intervals in this study are also wide due to a small sample size; but the study is still valuable because ALND for all pre-NAT node-positive patients has largely been abandoned, so it is difficult to replicate these data. Perhaps a meta-analysis is needed at this point. When applying negative post-NAT AUS and SLNB to the patients in our study, 13 patients with ALN pCR were subjected to ALND (false positive events, potentially overtreatment). In addition, 8 patients with negative SLNB had residual ALN disease (false-negative events, potentially undertreatment). The majority of patients ($n = 160$) underwent appropriate axillary surgery. We also attempt to analyze the results of performing ALND

according to SLNB results for patients with positive post-NAT AUS to avoid potential overtreatment. Six patients with negative SLNB had residual ALN disease (false-negative events, potentially undertreatment), and the false-negative rate for AUS combined with SLNB was 14.3(14/98, evidence from Fig. 2). According to previous studies, SLNB alone after NAC is associated with low recurrence for patients with ALN pCR. However, SLNB alone still has an inferior prognosis for patients with residual axillary disease after NAC [28–31]. Thus, we only propose using negative post-NAT AUS to select patients for SLNB.

We also found that the FNR for negative post-NAT AUS combined with SLNB exceeded the threshold 10% in patients with less than three nodes removed. Previous studies reported a lower FNR when more SLNs were removed, similar with the trends with ours [4, 5]. As the accuracy of any sampling test to a large extent depends on the amount of material sampling, these results were not surprising. Thus, post-NAT AUS has the potential to guide surgeons in accurately staging the axilla by removing at least three SLNs. In addition, the FNRs were different across molecular types, which might be because of the different responses to NAT in different subtypes [32]. Further, in both HR-negative/HER2-positive and HR-positive/HER2-positive subgroups, the FNR also exceeded 10%. The reason may be because HER2-positive subgroup showed a stronger response to NAT than other molecular subtypes. Tumors that respond more strongly may undergo greater changes in the lymphatic drainage pattern [33]. Hence, there is a potential for clinicians to select SLNB alone more confidently in HER2-negative breast cancer with negative post-NAT AUS. Our results also showed that the FNR for negative post-NAT AUS combined with SLNB was highest in the cN1, followed by cN2 and cN3 subgroup. There are several reasons for this. Firstly, the higher ALN burden was more easily detected on AUS [15]. Secondly, the small sample size in the cN2 and cN3 subgroups (36 patients and 16 patients, respectively) is also undoubtedly a factor.

Our results were consistent with the previous studies [4–6], in which the FNR for SLNB alone was higher than the predetermined acceptable FNR. Therefore, improved methods for patient selection are needed to guide the use of SLNB. Previous studies reported that targeted axillary dissection and SLNB, dual tracer SLNB, using lymph node examination by immunohistochemistry can decrease the FNR [34, 35], which did not perform in our study. However, we provided a cost-effective and simple method for selecting patients for pursuing SLNB and obtained satisfied results that combined negative post-NAT AUS and SLNB could reduce the FNR and improve patient section for SLNB.

Our study had several limitations. Firstly, this is a retrospective design, causing an inevitable risk of selection bias and confounding. Secondly, we did not use special techniques (such as clipping nodes with I^{125} radioactive seed and wires) [35] in this study.

Conclusion

Using negative AUS may help to decrease the FNR and improve patient selection for SLNB. Further, post-NAT AUS has the potential to guide surgeons in accurately staging the axilla by removing at least three SLNs or in HER2-negative patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-022-06817-8.

Author contributions YL, YW, SF: conceptualization; YL, SF, ZX, XH, MY: methodology; YL, XH, ZX, CL: verification of data; CL, ZL, YW: investigation; MY, CL, XC,PL: visualization; MY, LW, CL: supervision; YL, SF: writing—original draft; CL, ZL, YW, ZX, XH: writing—review & editing.

Funding This work was funded by the Key-Area Research and Development Program of Guangdong Province (No.2021B0101420006); National Natural Science Foundation of China (No.82071892, 82271941,82272088, 82171920); Guangdong Provincial Key Laboratory of Artificial Intelligence in Medical Image Analysis and Application (No.2022B1212010011); the National Science Foundation for Young Scientists of China (No.82102019, 82001986); Project Funded by China Postdoctoral Science Foundation (No.2020M682643, 2021M700897); High-level Hospital Construction Project (DFJH201805, DFJHBF202105).

Data availability Due to the privacy of patients, the data related to patients cannot be available for public access but can be obtained from the corresponding author (liangchanghong@gdph.org.cn) on reasonable request approved by the institutional review board of all enrolled centers.

Declarations

Conflict of interest All authors declare no competing interests.

References

1. Samiei S, Simons JM, Engelen SME, Beets-Tan RGH, Classe JM, Smidt ML, Group E (2021) Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: a systematic review and meta-analysis. JAMA Surg 156(6):e210891
2. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Giuliano AE et al (2007) Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American college of surgeons oncology group trial Z0011. J Clin Oncol 25(24):3657–3663
3. Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, Bear HD, Caldwell CB, Walker AP, Mikkelson WM et al (2005) Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National surgical adjuvant breast and bowel project protocol B-27. J Clin Oncol 23(12):2694–2702

4. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, Lebeau A, Liedtke C, von Minckwitz G, Nekljudova V et al (2013) Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 14(7):609–618
5. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Leitch AM, Kuerer HM, Bowling M, Flippo-Morton TS et al (2013) Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 310(14):1455–1461
6. Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, Meterissian S, Arnaout A, Brackstone M, McCready DR et al (2015) Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 33(3):258–264
7. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, Bedrosian I, Hobbs BP, DeSnyder SM, Hwang RF et al (2016) Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol 34(10):1072–1078
8. Harvey SC, Wolff AC (2015) Does a picture make a difference? Ultrasound guidance in the management of the axilla after neoadjuvant chemotherapy. J Clin Oncol 33(30):3367–3369
9. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE (2017) Sentinel lymph node biopsy for patients with early-stage breast cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol 35(5):561–564
10. Sun X, Wang XE, Zhang ZP, Shi ZQ, Cong BB, Wang YS, Shao ZM (2020) Neoadjuvant therapy and sentinel lymph node biopsy in HER2-positive breast cancer patients: results from the PEONY trial. Breast Cancer Res Treat 180(2):423–428
11. Expert Panel on Breast I, Slanetz PJ, Moy L, Baron P, diFlorio RM, Green ED, Heller SL, Holbrook AI, Lee SJ, Lewin AA et al (2017) ACR appropriateness criteria((R)) monitoring response to neoadjuvant systemic therapy for breast cancer. J Am Coll Radiol 14(11S):S462–S475
12. Kim R, Chang JM, Lee HB, Lee SH, Kim SY, Kim ES, Cho N, Moon WK (2019) Predicting axillary response to neoadjuvant chemotherapy: breast MRI and US in patients with node-positive breast cancer. Radiology 293(1):49–57
13. Eun NL, Son EJ, Gweon HM, Kim JA, Youk JH (2020) Prediction of axillary response by monitoring with ultrasound and MRI during and after neoadjuvant chemotherapy in breast cancer patients. Eur Radiol 30(3):1460–1469
14. Chung HL, Le-Petross HT, Leung JWT (2021) Imaging updates to breast cancer lymph node management. Radiographics 41(5):1283–1299
15. Schwentner L, Helms G, Nekljudova V, Ataseven B, Bauerfeind I, Ditsch N, Fehm T, Fleige B, Hauschild M, Heil J et al (2017) Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy—results from the multi-center SENTINA trial. Breast 31:202–207
16. Peppe A, Wilson R, Pope R, Downey K, Rusby J (2017) The use of ultrasound in the clinical re-staging of the axilla after neoadjuvant chemotherapy (NACT). Breast 35:104–108
17. Samiei S, de Mooij CM, Lobbes MBI, Keymeulen K, van Nijnatten TJA, Smidt ML (2021) Diagnostic performance of noninvasive imaging for assessment of axillary response after neoadjuvant systemic therapy in clinically node-positive breast cancer: a systematic review and meta-analysis. Ann Surg 273(4):694–700
18. Boughey JC, Ballman KV, Hunt KK, McCall LM, Mittendorf EA, Ahrendt GM, Wilke LG, Le-Petross HT (2015) Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: results from the American college of surgeons oncology group Z1071 trial (alliance). J Clin Oncol 33(30):3386–3393
19. Morency D, Dumitra S, Parvez E, Martel K, Basik M, Robidoux A, Poirier B, Holloway CMB, Gaboury L, Sideris L et al (2019) Axillary lymph node ultrasound following neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: results from the SN FNAC study. Ann Surg Oncol 26(13):4337–4345
20. Cao S, Liu X, Cui J, Liu X, Zhong J, Yang Z, Sun D, Wei W (2021) Feasibility and reliability of sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer patients with positive axillary nodes at initial diagnosis: an up-to-date meta-analysis of 3578 patients. Breast 59:256–269
21. Myers SP, Ahrendt GM, Lee JS, Steiman JG, Soran A, Johnson RR, McAuliffe PF, Diego EJ (2021) Association of tumor molecular subtype and stage with breast and axillary pathologic complete response after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol 28(13):8636–8642
22. Gimbergues P, Abrial C, Durando X, Le Bouedec G, Cachin F, Penault-Llorca F, Mouret-Reynier MA, Kwiatkowski F, Maublant J, Tchirkov A et al (2008) Sentinel lymph node biopsy after neoadjuvant chemotherapy is accurate in breast cancer patients with a clinically negative axillary nodal status at presentation. Ann Surg Oncol 15(5):1316–1321
23. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, Blair SL, Burstein HJ, Dang C, Elias AD et al (2021) NCCN guidelines(R) insights: breast cancer, version 42021. J Natl Compr Canc Netw 19(5):484–493
24. Samiei S, van Nijnatten TJA, de Munck L, Keymeulen K, Simons JM, Kooreman LFS, Siesling S, Lobbes MBI, Smidt ML (2020) Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. Ann Surg 271(3):574–580
25. Nielsen TO, Leung SCY, Rimm DL, Dodson A, Acs B, Badve S, Denkert C, Ellis MJ, Fineberg S, Flowers M et al (2021) Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in breast cancer working group. J Natl Cancer Inst 113(7):808–819
26. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M et al (2010) American society of clinical oncology/college of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28(16):2784–2795
27. Loibl S, Gianni L (2017) HER2-positive breast cancer. Lancet 389(10087):2415–2429
28. Piltin MA, Hoskin TL, Day CN, Davis J Jr, Boughey JC (2020) Oncologic outcomes of sentinel lymph node surgery after neoadjuvant chemotherapy for node-positive breast cancer. Ann Surg Oncol 27(12):4795–4801
29. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, Vicini E, Morigi C, Corso G, Intra M, Canegallo F, Ratini S, Leonardi MC et al (2021) Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. Eur J Surg Oncol 47(4):804–812
30. Barrio AV, Montagna G, Mamtani A, Sevilimedu V, Edelweiss M, Capko D, Cody HS 3rd, El-Tamer M, Gemignani ML, Heerdt A et al (2021) Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-a rare event. JAMA Oncol 7(12):1851–1855
31. Wong SM, Basik M, Florianova L, Margolese R, Dumitra S, Muanza T, Carbonneau A, Ferrario C, Boileau JF (2021) Oncologic safety of sentinel lymph node biopsy alone after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol 28(5):2621–2629
32. Gerber B, Schneeweiss A, Mobus V, Golatta M, Tesch H, Krug D, Hanusch C, Denkert C, Lubbe K, Heil J et al (2022) Pathological response in the breast and axillary lymph nodes after neoadjuvant

systemic treatment in patients with initially node-positive breast cancer correlates with disease free survival: an exploratory analysis of the geparocto trial. Cancers (Basel) 14:3
33. Kim WH, Kim HJ, Park CS, Lee J, Park HY, Jung JH, Kim WW, Chae YS, Lee SJ, Kim SH (2020) Axillary nodal burden assessed with pretreatment breast MRI Is associated with failed sentinel lymph node identification after neoadjuvant chemotherapy for breast cancer. Radiology 295(2):275–282
34. Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Feliberti EC, Hunt KK (2016) Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0–T4, N1–N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (alliance). Ann Surg 263(4):802–807
35. Murthy V, Young J, Tokumaru Y, Quinn M, Edge SB, Takabe K (2021) Options to determine pathological response of axillary lymph node metastasis after neoadjuvant chemotherapy in advanced breast cancer. Cancers (Basel) 13:16

Authors and Affiliations

Yu Liu[1,2,3] · Ying Wang[4] · Senwen Feng[5] · Zeyan Xu[1,2] · Mengxia Yao[6] · Xiaomei Huang[1,2] · Pinxiong Li[1,2] · Lei Wu[1,2] · Chunling Liu[1,2] · Xin Chen[7] · Changhong Liang[1,2,3] · Zaiyi Liu[1,2]

Yu Liu
yuyua0808@163.com

Ying Wang
liuivy527@163.com

Senwen Feng
fsw9295@163.com

Zeyan Xu
zeyx0708@163.com

Mengxia Yao
yaomengxia1635@163.com

Xiaomei Huang
xmhuang1992@163.com

Pinxiong Li
lipinxiong403@swmu.edu.cn

Lei Wu
wl858998458@163.com

Chunling Liu
liuchunlling79@163.com

Xin Chen
wolfchenxin@163.com

1 Department of Radiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, 106 Zhongshan Er Road, Guangzhou 510080, China

2 Guangdong Provincial Key Laboratory of Artificial Intelligence in Medical Image Analysis and Application, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China

3 The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China

4 Department of Medical Ultrasonics, The First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang West Road, Guangzhou 510120, China

5 Department of General Surgery, Guangdong Second Traditional Chinese Medicine Hospital, Guangzhou 510095, China

6 Department of Ultrasound, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, 106 Zhongshan Er Road, Guangzhou 510080, China

7 Department of Radiology, School of Medicine, Guangzhou First People's Hospital, South China University of Technology, 1 Panfu Road, Guangzhou 510180, China