Can axillary surgery be omitted in patients with breast pathologic complete response after neoadjuvant systemic therapy for breast cancer? A real-world retrospective study in China

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Abstract

Purpose

Studies show that axillary surgery can be potentially omitted in certain breast cancer patients who achieve breast pathologic complete response (pCR) after neoadjuvant systemic therapy (NST). However, potential differences between the ypT0 and ypTis subgroups remain to be explored. Furthermore, whether axillary surgery can be omitted in patients with clinically assessed positive axillary lymph nodes (cN+) remains unknown. This study was to evaluate the status of axillary lymph nodes for patients who achieved breast pCR after NST in the real-world study.

Methods

This retrospective cohort study included 258 patients with early or locally advanced breast cancer who underwent breast and axillary surgery after NST. Clinical and pathologic data were compared between patients with breast pCR (ypT0/is) and those without breast pCR.

Results

The rate of breast pCR after NST was 27.1% (70/258). Among the patients with initial cN0, the rate of axillary pCR was similar between the breast pCR and breast non-pCR groups (100% vs. 85.7%, $P=0.1543$). Among those with breast pCR, the rate of axillary pCR was 100% in both the ypT0 and ypTis subgroups. Furthermore, among those with initial cN+, the rate of axillary pCR was higher in the breast pCR group than in the breast non-pCR group (82.7% vs. 22.9%, $P<0.0001$). Among the patients with breast pCR, the rate of axillary pCR was higher in the ypT0 subgroup than in the ypTis subgroup (94.3% vs. 58.8%, $P=0.0034$).

Conclusion

Axillary surgery may potentially be omitted in patients with initial cN0 who achieve breast pCR (ypT0/is), and may also be considered for omission in patients with initial cN+ who achieve ypT0 (not ypTis).

Introduction

Neoadjuvant systemic therapy (NST) is increasingly used in breast cancer treatment, not only for locally advanced disease but also for operable cases. Pathologic complete response (pCR) has been reported to be significantly associated with favorable disease-free and overall survival rates^{1,2}. Therefore, considerable effort has been made to de-escalate therapies for patients with pCR, as redundant therapies induce unnecessary side effects and affect patients' quality of life. In the WSG-ADAPT-TN trial, patients who achieved pCR after nanoparticle albumin-bound paclitaxel-based NST could skip postoperative

anthracycline-containing chemotherapy for chemotherapy de-escalation³. Another aim is to de-escalate or omit surgery in patients with pCR. Results from a feasibility trial by the MD Anderson Cancer Center (MDACC) demonstrated a very high accuracy rate between extensive vacuum-assisted core biopsy/fine-needle aspiration biopsy and lumpectomy of the marked breast tumor bed after NST⁴, suggesting that breast surgery may be omitted in patients with documented breast pCR.

These accumulating data raise the possibility that surgery of axillary lymph nodes might be omitted. Generally, axillary lymph node surgery following NST includes sentinel lymph node biopsy (SNB) and axillary lymph node dissection (ALND). The results of the NSABP B-32 trial have demonstrated that ALND can be de-escalated to SNB after NST in patients with clinically assessed negative axillary lymph nodes (cN0), because SNB is effective and safe for this subpopulation⁵. However, performing SNB following NST in patients with clinically assessed positive axillary lymph nodes (cN+) is controversial. Several large clinical trials have demonstrated that SNB has a relatively high false negative rate in this subpopulation^{6–8}. Therefore, ALND remains the standard surgical approach for patients with initial cN+.

On the other hand, evidence suggest that axillary lymph node status after NST reflects prognosis more accurately than the initial axillary status before NST⁹. Patients with axillary pCR have higher recurrence-free and overall survival rates compared with those with residual axillary disease¹⁰. In fact, about 22–35% of patients with cN+ achieve axillary pCR^{8,11}. Successful distinction of these patients after NST might facilitate the omission of axillary surgeries including ALND and SNB, thereby avoiding postoperative morbidities, such as lymphedema, arm pain, and reduced arm movement, as well as quality of life issues¹².

Several studies have already shown that axillary lymph node status is highly associated with breast pCR^{1,9,13}. The results of a single institution study from the MDACC which enrolled patients with human epidermal growth factor receptor 2 (HER2)-positive and triple-negative (TN) breast cancer revealed that all patients with initial cN0 who achieved the ypT0 status (no residual invasive or *in situ* carcinoma in the breast) also achieved axillary pCR, indicating that omitting axillary surgery might be possible in these patients¹. Subsequently, a similar study reviewing data from the National Cancer Database (NCDB) reported that 98.2% patients with initial cN0 achieved axillary pCR if they achieved the status of no residual invasive carcinoma in the breast (ypT0/is)¹³. Meanwhile, less than 90% of patients with initial cN1 who achieved ypT0/is could achieve axillary pCR in the same study. These results indicate several possibilities. First, both studies focused mainly on HER2-positive and TN breast cancer and more evidence on other molecular subtypes of breast cancer is needed. Second, the definition of breast pCR was different between the two studies, wherein ypT0 and ypT0/is were used in the MDACC and NCDB studies, respectively. Therefore, potential differences between the ypT0 and ypTis subgroups should be clarified. Third, these studies enrolled patients with cN1 disease. In real-world practice, operable Chinese patients usually receive surgery first unless they have more advanced breast cancer such as lymph node metastases (cN+). Therefore, whether axillary surgery can be omitted in patients with cN+ remains an important question.

We therefore conducted a real-world study by the retrospective review of data from a breast cancer center. All molecular subtypes of locally advanced breast cancer with the status of cN0 or cN+ were analyzed to identify subgroups of patients who could potentially avoid axillary surgery after NST.

Patients And Methods

This retrospective cohort study at a single institution included the review of all clinical and pathologic data of patients with early or locally advanced breast cancer ($cT_{1-4}N_{0-3}M_0$) who underwent breast and axillary surgery after NST between January 2015 and July 2019. All patients underwent clinical disease staging with physical examination as well as ultrasonography and/or magnetic resonance imaging of the breast and axilla before NST. Clinically assessed normal axillary lymph nodes were defined as cN0 based on these evaluations. Specifically, all suspicious lymph nodes were evaluated by specimens obtained using fine-needle aspiration or core needle biopsy and those with no tumor cells were classified as cN0; those with tumor cells were classified as cN+. Breast pCR was defined as the absence of invasive carcinoma in the breast, including ypT0 (no residual invasive or *in situ* carcinoma in the breast) and ypTis (*in situ* carcinoma in the breast) as the final pathologic results. Axillary pCR, i.e., ypN0, was defined as the absence of residual carcinoma including macrometastatic and micrometastatic axillary nodal disease, in axillary lymph nodes after NST. All axillary nodes were assessed by standard hematoxylin-eosin staining, and immunohistochemistry was performed if suspicious cells were identified.

Lesions with at least 1% of cells positive for estrogen receptor and/or progesterone receptor were classified as hormone receptor (HR)-positive, and those with 3+ HER2 staining intensity by immunohistochemistry or with *HER2* gene amplification by fluorescence *in situ* hybridization were classified as HER2-positive. Most of the patients received anthracycline- and taxane-based neoadjuvant chemotherapy, and patients with HER2-positive breast cancer also received trastuzumab. All patients underwent standard breast and axillary surgery after NST, and the final surgical approach was left to the surgeon's discretion and the patient's preference based on the advantages and disadvantages of each type of surgery.

For statistical analyses, descriptive variables were presented as means $\pm$ standard deviation. Pathologic axillary status was calculated for patients with and without breast pCR and compared using relative risk ratios (RRs) with 95% confidence intervals (CIs). Categorical variables were compared using the two-side chi-squared test. A $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed by SPSS (version 20.0).

Results

A total of 258 consecutive female patients with breast cancer who received NST followed by surgery were included in the present study. The mean age at diagnosis was 50 (range, 20–75) years, 53.9% (139/258) of the patients were under 50 years of age, and 53.1% (137/258) of the patients were premenopausal. Before NST, 70.2% (181/258) and 18.2% (47/258) of the patients had cT2 and cT3 breast cancer,

respectively, and 79.5% (205/258) of the patients had cN+. Furthermore, the rates of patients with HR-positive/HER2-negative, HR-positive/HER2-positive, HR-negative/HER2-positive, and TN breast cancer were 40.3% (104/258), 16.3% (42/258), 20.9% (54/258), and 22.5% (58/258), respectively. Regarding surgical approaches, most patients (91.9%, 237/258) chose mastectomy and ALND was performed in 88% (227/258) of the patients. Breast pCR was achieved in 27.1% (70/258) of the patients, including those with ypT0 (18.2%, 47/258) and ypTis (8.9%, (23/258). Most patients (60.1%, 155/258) achieved pathologic partial response. In addition, axillary pCR was achieved in 48.8% (126/258) of the patients (Table 1).

Table 1
General and clinical characteristics of all enrolled patients

Characteristics (n = 258)	n (%)
Age at diagnosis, years, mean (range)	50 (20–75)
Age at diagnosis, years	
≤ 50	139 (53.9)
> 50	119 (46.1)
Menopausal status at diagnosis	
Premenopausal	137 (53.1)
Postmenopausal	121 (46.9)
Clinical assessment of tumor size before NST	
cT1	14 (5.4)
cT2	181 (70.2)
cT3	47 (18.2)
cT4	16 (6.2)
Clinical assessment of axillary node stage before NST	
cN0	53 (20.5)
cN+	205 (79.5)
Molecular subtype of breast cancer	
HR-positive/HER2-negative	104 (40.3)
HR-positive/HER2-positive	42 (16.3)
HR-negative/HER2-positive	54 (20.9)
TN	58 (22.5)
Type of breast surgery	
Mastectomy	237 (91.9)

Abbreviations:

NST, neoadjuvant systemic therapy; cT, clinically assessed tumor grade before NST; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple-negative; pCR, pathologic complete response; ypT0, no residual invasive or *in situ* carcinoma in the breast; ypTis, *in situ* carcinoma in the breast; pPR, pathologic partial response; pSD, pathologic stable disease; pPD, pathologic progressive disease; ypN, pathologic axillary lymph node stage after NST

Characteristics (n = 258)	n (%)
Breast-conserving surgery	21 (8.1)
Type of axillary surgery	
Axillary lymph node dissection	227 (88.0)
Sentinel node biopsy	31 (12.0)
Breast pathology	
pCR (ypT0)	47 (18.2)
pCR (ypTis)	23 (8.9)
pPR	155 (60.1)
pSD	30 (11.6)
pPD	3 (1.2)
Axillary lymph node pathology	
ypN0	126 (48.8)
ypN1	63 (24.4)
ypN2	46 (17.8)
ypN3	23 (8.9)
Abbreviations:	
NST, neoadjuvant systemic therapy; cT, clinically assessed tumor grade before NST; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple-negative; pCR, pathologic complete response; ypT0, no residual invasive or <i>in situ</i> carcinoma in the breast; ypTis, <i>in situ</i> carcinoma in the breast; pPR, pathologic partial response; pSD, pathologic stable disease; pPD, pathologic progressive disease; ypN, pathologic axillary lymph node stage after NST	

There were no differences in age at diagnosis, menopausal status, tumor size, and axillary node status before NST between the breast pCR group, defined as patients with ypT0/is status, and the breast non-pCR group. The patients with HR-positive/HER2-negative breast cancer was less likely to achieve breast pCR (ypT0/is) than those with other molecular subtypes ($P < 0.001$) (Table 2).

Table 2
Comparisons between patients with breast pCR (ypT0/is) and non-pCR (non-ypT0/is)

Characteristics	ypT0/is n (%)	non-ypT0/is n (%)	P value
Age at diagnosis, years			
≤ 50 (n = 139)	36 (25.9)	103 (74.1)	0.6746
> 50 (n = 119)	34 (28.6)	85 (71.4)	
Menopausal status at diagnosis			
Premenopausal (n = 137)	36 (26.3)	101 (73.7)	0.7800
Postmenopausal (n = 121)	34 (28.1)	87 (71.9)	
Clinical assessment of tumor size before NST			
cT1 (n = 14)	5 (35.7)	9 (64.3)	0.8966
cT2 (n = 181)	48 (26.5)	133 (73.5)	
cT3 (n = 47)	13 (27.7)	34 (72.3)	
cT4 (n = 16)	4 (25.0)	12 (75.0)	
Clinical assessment of axillary node stage before NST			
cN0 (n = 53)	18 (34.0)	35 (66.0)	0.2271
cN+ (n = 205)	52 (25.4)	153 (74.6)	
Molecular subtype of breast cancer			
HR-positive/HER2-negative (n = 104)	8 (7.7)	96 (92.3)	< 0.001*
HR-positive/HER2-positive (n = 42)	15 (35.7)	27 (64.3)	
HR-negative/HER2-positive (n = 54)	27 (50.0)	27 (50.0)	
TN (n = 58)	20 (34.5)	38 (65.5)	
Abbreviations: breast pCR (ypT0/is), no residual invasive carcinoma in the breast; breast non-pCR (non-ypT0/is), presence of residual invasive carcinoma in the breast; NST, neoadjuvant systemic therapy; cT, clinically assessed tumor grade before NST; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, HR-negative and HER2-negative			
* P< 0.05			

In the group of patients with initial cN0, the postoperative pathological examination of axillary lymph nodes showed that the rate of axillary pCR was similar between the breast pCR (100%, 18/18) and breast non-pCR (85.7%, 30/35, $P = 0.1543$) subgroups. Among those with breast pCR, the rates of axillary pCR

were 100% for both the ypT0 and ypTis subgroups. Similar findings were found by the comparison of different molecular subtypes (Table 3).

Table 3

Postoperative pathology of axillary lymph nodes in patients with initial cN0 who achieved breast pCR (ypT0/is) and non-pCR (non-ypT0/is)

cN0 patients	Pathologically positive axillary lymph nodes				
	n (%)				
	0	1	2	≥ 3	Total
Total					
ypT0	12(100)	0	0	0	12(100)
ypTis	6(100)	0	0	0	6(100)
ypT0/is	18 (100)	0	0	0	18 (100)
non-ypT0/is	30 (85.7)	2 (5.7)	1 (2.9)	2 (5.7)	35 (100)
HR-positive/HER2-negative					
ypT0	1(100)	0	0	0	1(100)
ypTis	2(100)	0	0	0	2(100)
ypT0/is	3 (100)	0	0	0	3 (100)
non-ypT0/is	15 (75)	2 (10)	1 (5)	2 (10)	20 (100)
HR-positive/HER2-positive					
ypT0	0	0	0	0	0
ypTis	1(100)	0	0	0	1(100)
ypT0/is	1 (100)	0	0	0	1 (100)
non-ypT0/is	3 (100)	0	0	0	3 (100)
HR-negative/HER2-positive					
ypT0	4 (100)	0	0	0	4 (100)
ypTis	3 (100)	0	0	0	3 (100)
ypT0/is	7 (100)	0	0	0	7 (100)
non-ypT0/is	4 (100)	0	0	0	4 (100)
TN					

Abbreviations: breast pCR (ypT0/is), no residual invasive carcinoma in the breast; breast non-pCR (non-ypT0/is), presence of residual invasive carcinoma in the breast; ypT0, no residual invasive or in situ carcinoma in the breast; ypTis, *in situ* carcinoma in the breast; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, HR-negative and HER2-negative.

cN0 patients	Pathologically positive axillary lymph nodes				
	n (%)				
	0	1	2	≥ 3	Total
ypT0	7 (100)	0	0	0	7(100)
ypTis	0	0	0	0	0
ypT0/is	7 (100)	0	0	0	7 (100)
non-ypT0/is	8 (100)	0	0	0	8 (100)
Abbreviations: breast pCR (ypT0/is), no residual invasive carcinoma in the breast; breast non-pCR (non-ypT0/is), presence of residual invasive carcinoma in the breast; ypT0, no residual invasive or in situ carcinoma in the breast; ypTis, <i>in situ</i> carcinoma in the breast; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, HR-negative and HER2-negative.					

The postoperative pathological examination of axillary lymph nodes in patients with initial cN + revealed that the rate of axillary pCR was higher in the breast pCR subgroup compared with the breast non-pCR group (82.7% [43/52] vs. 22.9% [35/153], $P < 0.0001$, RR 2.520, 95%CI 2.634–4.961). In the TN breast cancer subgroup, the rate of axillary pCR was 92.3% (12/13). Among the patients with breast pCR, the rate of axillary pCR in the ypT0 subgroup (94.3%, 33/35) was higher than that in the ypTis subgroup (58.8%, 10/17, $P = 0.0034$, RR 1.603, 95%CI 1.068–2.406) (Table 4).

Table 4

Postoperative pathology of axillary lymph nodes in patients with initial cN + who achieved breast pCR (ypT0/is) and non-pCR (non-ypT0/is)

cN + patients	Pathologically positive axillary lymph nodes				
	No. (%)				
	0	1	2	≥ 3	Total
Total					
ypT0	33 (94.3)	0	1 (2.9)	1 (2.9)	35 (100)
ypTis	10 (58.8)	3 (17.6)	1 (5.9)	3 (17.6)	17 (100)
ypT0/is	43 (82.7)	3 (5.8)	2 (3.8)	4 (7.7)	52 (100)
non-ypT0/is	35 (22.9)	23 (15.0)	17 (11.1)	78 (51)	153 (100)
HR-positive/HER2-negative					
ypT0	3 (75)	0	1 (25)	0	4 (100)
ypTis	1 (100)	0	0	0	1 (100)
ypT0/is	4 (80)	0	1 (20)	0	5 (100)
non-ypT0/is	9 (11.8)	13 (17.1)	9 (11.8)	45 (59.2)	76 (100)
HR-positive/HER2-positive					
ypT0	6 (100)	0	0	0	6 (100)
ypTis	4 (50)	2 (25)	1 (12.5)	1 (12.5)	8 (100)
ypT0/is	10 (71.4)	2 (14.3)	1 (7.1)	1 (7.1)	14 (100)
non-ypT0/is	6 (25)	5 (20.8)	1(4.2)	12 (50)	24 (100)
HR-negative/HER2-positive					
ypT0	13 (92.9)	0	0	1 (7.1)	14 (100)
ypTis	4 (66.7)	1 (16.7)	0	1 (16.7)	6 (100)
ypT0/is	17(85)	1 (5)	0	2 (10)	20 (100)
non-ypT0/is	10 (43.5)	2 (8.7)	4 (17.4)	7 (30.4)	23 (100)
TN					

Abbreviations: breast pCR (ypT0/is), no residual invasive carcinoma in the breast; breast non-pCR (non-ypT0/is), presence of residual invasive carcinoma in the breast; ypT0, no residual invasive or *in situ* carcinoma in the breast; ypTis, *in situ* carcinoma in the breast; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, HR-negative and HER2-negative

cN + patients	Pathologically positive axillary lymph nodes				
	No. (%)				
	0	1	2	≥ 3	Total
ypT0	11 (100)	0	0	0	11 (100)
ypTis	1 (50)	0	0	1 (50)	2 (100)
ypT0/is	12 (92.3)	0	0	1 (7.7)	13 (100)
non-ypT0/is	10 (33.3)	3 (10)	3 (10)	14 (46.7)	30 (100)
Abbreviations: breast pCR (ypT0/is), no residual invasive carcinoma in the breast; breast non-pCR (non-ypT0/is), presence of residual invasive carcinoma in the breast; ypT0, no residual invasive or <i>in situ</i> carcinoma in the breast; ypTis, <i>in situ</i> carcinoma in the breast; cN, clinically assessed axillary lymph node stage before NST; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, HR-negative and HER2-negative					

Discussion

Since the prognosis is good for both patients with ypT0 ypN0 and those with ypTis ypN0 breast cancer¹⁴, breast pCR in the present study was defined as the absence of residual invasive carcinoma in the breast, including ypT0 and ypTis. Our analyses revealed that the rate of patients with ypT0/is ypN0 after NST was 23.6%, which was not high. There are several possibilities to explain this finding. First, the present study included all molecular subtypes of breast cancer and 40.3% of the patients had HR-positive/HER2-negative breast cancer, who were less likely to achieve breast pCR (7.7%) compared to those with other molecular subtypes ($P < 0.01$), especially compared to patients with HER2-positive (43.8%) or TN (34.5%) breast cancer. This finding is in agreement with other reports^{15,16}. In addition, HER2-positive patients received trastuzumab only as targeted therapy in the present study, because pertuzumab was not approved for NST in China until 2020. Third, the tumor burden was greater in the current study cohort. The median tumor diameter was 50 mm, 24.4% of the patients were in stage cT3–4, and the rate of cN + was 79.5%. These data reflect the real-world situation in China. Specifically, relatively more patients with advanced breast cancer have been selected to receive NST in recent years; however, those with operable breast cancer usually receive surgery first, even those patients with HER2-positive or TN breast cancer.

Due to the greater tumor burden, the rates of breast pCR were not high in the present study (18.2% and 8.9% in the ypT0 and ypTis subgroups, respectively). On the other hand, a greater tumor burden was also associated with a higher rate of tumor metastasis to axillary lymph nodes and only 20.5% of the enrolled patients had cN0. After NST, however, the rate of axillary pCR increased to 48.8%, indicating that NST could effectively reduce the stage of axillary lymph nodes and that nearly half of these patients may be able to avoid axillary surgery. Furthermore, determination of more accurate indicators can potentially facilitate the identification of patients who may avoid axillary surgery including ALND and SNB. Based on our analyses, the rate of patients achieving axillary pCR was higher in the breast pCR group than in the breast non-pCR group (87.1% vs 34.6%, $P < 0.01$), indicating that those who achieved breast pCR were

more likely to achieve axillary pCR. This finding suggests that breast pCR might be a good indicator to determine patients who might be able to avoid axillary surgery, which requires for exploration in future studies.

In the present study, 18 of the 53 patients with initial cN0 achieved breast pCR after NST; all 18 patients (100%) achieved axillary pCR simultaneously. In comparison, only 30 of the 35 patients with breast non-pCR (85.7%) achieved axillary pCR. Although there was no statistical difference between the breast pCR and breast non-pCR groups, the high axillary pCR rate in the breast pCR group (100%) provides evidence to support that axillary surgery may be omitted in patients with initial cN0 who achieve breast pCR. The study from the MDACC¹ have also confirmed that axillary surgery might be omitted in patients with initial cN0 who achieve ypT0. However, only patients with HER2-positive and TN breast cancer were enrolled and those with the ypTis status were not included in that study. In real-world settings, HR-positive/HER2-negative breast cancer comprises the largest subtype despite the low rate of pCR. Therefore, it is also especially important to explore whether axillary surgery can be omitted in patients with this breast cancer subtype. In the current study cohort, 104 (40.3%) of the 258 enrolled patients were HR-positive/HER2-negative, 23 of these 104 patients had cN0 breast cancer, and 3 patients who achieved breast pCR also achieved axillary pCR, with a success rate of 100%. This finding may indicate that axillary surgery can also be potentially omitted in patients with HR-positive/HER2-negative breast cancer and initial cN0 who achieve ypT0/is status, however, due to the small amount, this needs to be supported by larger data subsequently. This result is consistent with the analysis from other studies^{13,17}, which also provides support that axillary surgery might be omitted in patients with initial cN0 breast cancer of any molecular subtype who achieve the ypT0/is status.

On the other hand, 153 of the 205 patients with initial cN+ achieved breast non-pCR after NST and only 35 of these patients (22.9%) achieved axillary pCR. In comparison, the rate of axillary pCR was higher in patients who achieved breast pCR (43/52, 82.7%) ($P < 0.01$). However, since the rate of axillary pCR is less than 90%, axillary surgery omission is not safe in patients with initial cN+ who achieve breast pCR. In addition, the subgroup analysis showed that only patients with TN breast cancer (12/13, 92.3%) might potentially be considered for axillary surgery omission. This finding is also consistent with the report from the MDACC¹ which demonstrated that the omission of axillary surgery might be safe for patients with TN breast cancer (32/35, 91.4%). However, the subgroup analysis in the NCDB study¹³ led to a different result, wherein the omission of axillary surgery was not safe for all molecular subtypes including TN breast cancer. This discrepancy may be due to differences in the characteristics of patients enrolled in different studies. Therefore, prospective multicenter clinical trials are necessary to obtain more accurate results.

Furthermore, we analyzed patients with initial cN+ breast cancer by categorizing into the ypT0 and ypTis subgroups. Our analyses demonstrated that the axillary pCR rate was higher in the ypT0 subgroup than in the ypTis subgroup (94.3% vs 58.8%, $P < 0.01$). Meanwhile, the high rate value ($> 90\%$) was consistent across all molecular subgroups except for the HR-positive/HER2-negative subgroup, in which only four

patients achieved ypT0, indicating that axillary surgery may also be potentially omitted if ypT0, rather than ypTis, is achieved in patients with initial cN + HER2-positive or TN breast cancer.

The limitations of the present study include a small-sized cohort in a real-world study, which was conducted at a single breast cancer center. Additionally, due to the retrospective study design, the patients with cN + breast cancer could not be analyzed further to distinguish those with cN1 disease from those with cN2 or cN3 disease. However, based on the postoperative pathology, nearly 1/3 of the patients were in ypN2–3, implying that many of the patients had advanced axillary tumor burden. Therefore, prospective multicenter clinical trials will be necessary to obtain more reliable evidence.

Conclusion

In the present study including patients with advanced breast cancer receiving NST in a real-world setting in line with the clinical reality in China, our analyses suggested that axillary surgery might be potentially omitted in patients with initial cN0 breast cancer who achieve breast pCR (ypT0/is) regardless of the molecular subtype and clinical tumor size. Additionally, axillary surgery might also be potentially omitted in patients with initial cN + breast cancer who achieve ypT0 (not ypTis), excluding those with HR-positive/HER2-negative breast cancer.

Declarations

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Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Xiaoming Zha, Jue Wang designed this study and conducted quality control on it. Rui Chen, Yan Li, Xiaoqing Shi participated in the analysis of data and drafted the manuscript. Shuo Li, Qiannan Zhu, Lu Xu, Yinggang Xu, Weiwei Zhang and Xiaofeng Huang were responsible for data collection. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and those of the Helsinki Declaration. This work was approved by the ethics and research committee of the First Affiliated Hospital of Nanjing Medical University (2020-SR-081), and informed consent was obtained from all participants.

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