



# Determining the benefit of neoadjuvant chemotherapy in reduction of axillary dissection rates in Z0011 trial cohort with high nodal burden

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**Background:** In breast cancer patients fulfilling the Z0011 trial criteria, axillary lymph node dissection (ALND) is reserved for patients with a high nodal burden of  $\geq 3$  metastatic nodes. In this group of patients, to avoid an ALND, neoadjuvant chemotherapy (NACT) could be given instead to achieve nodal pathological complete response (pCR). However, the benefit of NACT in achieving nodal pCR and avoiding ALND in this group of patients is unknown. We aimed to determine the nodal pCR rate in this group of patients who otherwise would have needed an ALND.

**Methods:** cT1-2N0 breast cancer patients, with histologically proven nodal metastasis, who underwent NACT were identified from a prospectively maintained database. The sonographic criteria of  $\geq 3$  abnormal nodes, which has been reported as highly predictive of high nodal burden, was then used to identify the high nodal burden group. Nodal pCR was determined based on the ALND following NACT.

**Results:** Twenty-four patients with high nodal burden were identified. Mean age was 55.2 years. 91.7% had invasive ductal carcinoma and 29.2% had grade III cancer. 54.2% achieved nodal pCR which was associated with ypT ( $P=0.006$ ). Nodal pCR was 75%, 70% and 30% in the triple negative, human epidermal growth factor receptor2 (HER2) positive and ER/PR+HER2- tumors, respectively.

**Conclusions:** In the postulated T1-2 breast cancer patients with high nodal burden, needing an upfront ALND, NACT could result in nodal pCR of 54.2%, with higher pCR in certain subtypes. Hence, to minimize ALND risk, NACT should be offered in this high nodal burden group.

**Keywords:** Neoadjuvant chemotherapy (NACT); Z0011 trial; breast cancer; axillary lymph node dissection (ALND); axillary ultrasound

Submitted Jan 04, 2022. Accepted for publication Mar 29, 2022.

doi: 10.21037/gs-22-7

View this article at: <https://dx.doi.org/10.21037/gs-22-7>

## Introduction

The Z0011 trial has demonstrated no survival difference in the omission of axillary lymph node dissection (ALND) in T1–2 breast cancer patients with <3 lymph nodes involvement. In patients with a high nodal burden of  $\geq 3$  metastatic nodes, an ALND is advocated (1). To avoid an ALND in this group of patients with a high nodal burden, patients could undergo neoadjuvant chemotherapy (NACT) instead. If nodal pathological complete response (pCR) is obtained with NACT, these patients would avoid an ALND, which is associated with multiple complications (2).

NACT could result in nodal pCR in about 40% of patients (3) with a higher rate of nodal pCR observed in patients with certain subtypes such as those positive for human epidermal growth factor receptor2 (HER2). Nevertheless, the benefit of NACT in achieving nodal pCR and consequent reduction of ALND rates in the Z0011 trial patients with high nodal burden has not been previously studied.

It was reported that the number of abnormal nodes on axillary ultrasound could reliably identify the subgroup of patients with high nodal burden in the Z0011 trial cohort (4,5). In particular, in a prior study (5), for patients fulfilling Z0011 trial criteria with a positive percutaneous node biopsy,  $\geq 3$  sonographically abnormal nodes was shown to be highly predictive of high nodal burden status, with an odds ratio of 20.72 and area under the receiver operating characteristic curve of 0.747. 92.9% of patients in that study (5) with  $\geq 3$  sonographically abnormal nodes demonstrated high nodal burden. Applying this sonographic predictive factor to our cohort of T1–2 patients with nodal metastasis who received NACT, we aim to identify the subgroup of patients with high nodal burden who would have otherwise needed an ALND based on Z0011 trial and determine whether NACT, in this group, could result in nodal pCR with avoidance of ALND. We present the following article in accordance with the STROBE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-7/rc>).

## Methods

Newly diagnosed breast cancer patients treated at KK Women's and Children's Hospital, Republic of Singapore from 1st September 2005 to 31st Oct 2017 were retrospectively identified from a prospectively maintained database. We identified the Z0011 trial high nodal burden

subgroup as T1–2 breast cancer patients with no palpable axillary node,  $\geq 3$  abnormal nodes on initial axillary ultrasound and histologically proven nodal metastasis. Among this group of patients, we only included patients who had undergone NACT and an ALND after NACT in order to determine the true nodal status. Patients with occult breast cancer, N3 or distant metastasis, or incomplete data were excluded.

At our institution, in addition to their mammogram and breast ultrasound, most patients would have a dedicated axillary ultrasound with the number of abnormal nodes reported. An abnormal node is defined as having any of these sonographic features: eccentric or uniform cortical thickness  $\geq 3$  mm, displacement, or complete effacement of the fatty hilum. Based on ultrasound, only the most suspicious axillary node would be biopsied.

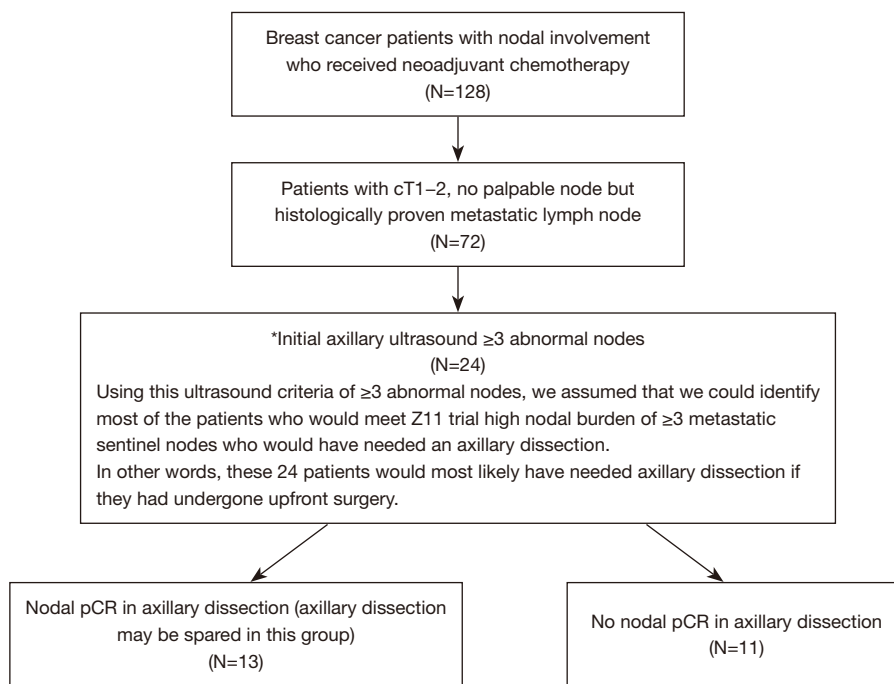
The ultrasounds were performed by trained breast sonographers and the images interpreted by dedicated breast radiologists at a specialized breast centre. The radiologists all had >5 years of experience in breast imaging. The axillary ultrasound would take on average, about 5–10 minutes to complete.

During the study period, patients with nodal metastasis may have been offered an upfront ALND with breast surgery or NACT, depending on the treating clinician's preference. If receiving NACT, the chemotherapy regime was typically anthracycline and taxane-based, with HER2 positive patients also treated with targeted therapy. After completion of NACT, this group of patients would usually undergo ALND and breast surgery. The choice of breast surgery was decided after discussion with each patient.

Demographics, radiological and pathological features of this group of patients were collected. Isolated tumor cells in ALND after NACT were considered as positive nodal involvement. The nodal pCR based on ALND, was used to determine the benefit of NACT in the reduction of ALND rates in this group of high nodal burden patients.

## Statistical analysis

A Fisher exact test was used to compare demographic, radiologic and pathologic variables between patients with ypN0 and ypN+, with  $P < 0.05$  defined as statistically significant. Multivariable logistic regression incorporating a backward elimination selection algorithm was used to identify independent predictors of nodal pCR with  $P$  defined at  $< 0.05$ . SAS V9.4 statistical software (Cary, NC, USA) was used for the analysis.



**Figure 1** Flowchart of the patients in the study. \*, based on this criterion in a published study (5), 92.9% of Z11 trial high nodal burden patients were identified. pCR, pathological complete response.

### Ethical statement

All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by SingHealth Centralised Institutional Review Board (CIRB Ref: 2020/2147) and waiver of patients' informed consent was obtained.

### Results

Of the 128 breast cancer patients with nodal involvement who received NACT, 72 patients had cT1-2 tumor with no palpable axillary node but histologically proven metastatic lymph node (Figure 1). Of these 72 patients, 1, 47 and 24 patients had 0, 1-2 and  $\geq 3$  abnormal nodes on initial ultrasound respectively. The patients with 1-2 abnormal nodes on initial ultrasound had nodal pCR of 38.3%. For the 1 patient with no abnormal lymph node sonographically, she had a positive sentinel lymph node biopsy after her NACT. ALND revealed only that sentinel lymph node to be positive.

A total of 24 patients were included in the analysis. The mean age was 55.2 years (range, 31-70 years). 87.5% and

12.5% underwent mastectomy and lumpectomy respectively (Table 1). 91.7% and 29.2% had invasive ductal carcinoma and grade III cancer. 54.2% and 41.7% had positivity for estrogen receptor (ER) and HER2 respectively. Progesterone receptor (PR) positivity was 33.3%. The mean tumor size based on ultrasound was 31.5 mm (range, 6-50 mm). 13 patients (54.2%) achieved nodal pCR. 10 patients (41.7%) achieved tumor pCR.

Seven (29.2%) patients did not complete the entire course of chemotherapy mainly due to the side effects from chemotherapy.

Based on tumor subtype, there were 10 patients (41.7%) with ER/PR positivity and HER2 negativity and 4 patients (16.7%) who was triple negative. There were 10 patients (41.7%) with HER2 positivity. Among the ER/PR+ HER2- tumors, 30% achieved nodal pCR. In the triple negative (TN) and HER2 positive group, the nodal pCR rate was 75% and 70% respectively.

Univariate analysis revealed age as a continuous variable ( $P=0.024$ ) and ypT ( $P=0.006$ ) to be statistically significant factors for nodal pCR (Table 2). Multivariable analysis incorporating backward elimination only showed ypT ( $P=0.006$ ) to be statistically significant for nodal pCR.

**Table 1** Patient characteristics

Characteristics	N (%) (n=24)
Age (years)	
<50	7 (29.2)
≥50	17 (70.8)
Surgery	
Mastectomy	21 (87.5)
Wide local excision	3 (12.5)
Completed chemotherapy	
Yes	17 (70.8)
No	7 (29.2)
Sonographic tumor size (mm)	
0–20	6 (25.0)
21–50	18 (75.0)
Histology	
Invasive ductal carcinoma	22 (91.7)
Invasive lobular carcinoma/others	2 (8.3)
Tumor grade	
I, II	13 (54.2)
III	7 (29.2)
Missing	4 (16.6)
ER	
Positive	13 (54.2)
Negative	11 (45.8)
PR	
Positive	8 (33.3)
Negative	16 (66.7)
HER2	
Positive	10 (41.7)
Negative	14 (58.3)
ypT (mm)	
0–20	17 (70.8)
21–50	6 (25.0)
>50	1 (4.2)
Nodal pCR	
Yes	13 (54.2)
No	11 (45.8)

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response.

**Table 2** Characteristics between patients with ypN0 and ypN+

Variable	Patients with ypN0 (n=13), n (%)	Patients with ypN+ (n=11), n (%)	P value
Age (years)			0.0778
<50	6 (46.2)	1 (9.1)	
≥50	7 (53.8)	10 (90.9)	
Surgery			0.2228
Mastectomy	10 (76.9)	11 (100)	
Wide local excision	3 (23.1)	0 (0)	
Completed chemotherapy			0.1819
Yes	11 (84.6)	6 (54.5)	
No	2 (15.4)	5 (45.5)	
Radiological			0.4780
Sonographic tumor size (mm)			
0–20	4 (30.8)	2 (18.2)	
21–50	9 (69.2)	9 (81.8)	
Pathologic features on core biopsy			1.0000
Histology			
Invasive ductal carcinoma	12 (92.3)	10 (90.9)	
Invasive lobular carcinoma/others	1 (7.7)	1 (9.1)	
Tumor grade			0.3498
I, II	5 (38.5)	8 (72.7)	
III	5 (38.5)	2 (18.2)	
Missing	3 (23.0)	1 (9.1)	
ER			0.1228
Positive	5 (38.5)	8 (72.7)	
Negative	8 (61.5)	3 (27.3)	
PR			0.0825
Positive	2 (15.4)	6 (54.5)	
Negative	11 (84.6)	5 (45.5)	
HER2			0.2397
Positive	7 (53.8)	3 (27.3)	
Negative	6 (46.2)	8 (72.7)	

**Table 2** (continued)

Table 2 (continued)

Variable	Patients with ypN0 (n=13), n (%)	Patients with ypN+ (n=11), n (%)	P value
ypT (mm)			0.0311
0–20	12 (92.3)	5 (45.5)	
21–50	1 (7.7)	5 (45.5)	
>50	0 (0)	1 (9.1)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

## Discussion

Using the ultrasound criteria of  $\geq 3$  abnormal nodes to identify the Z0011 trial patients with high nodal burden, 54.2% of these patients could achieve nodal pCR post NACT, hence avoiding an ALND. The nodal pCR rate varied with molecular subtype and was highest for the TN subtype. To the best of our knowledge, this is the first study attempting to determine the reduction rate of ALND by NACT in the Z0011 trial postulated high nodal burden patients who otherwise would have required an upfront ALND.

Though AMAROS trial (6) had shown that early breast cancer patients with positive sentinel nodes could be treated safely with radiotherapy instead of ALND, the study included very few patients of high nodal burden of  $\geq 3$  metastatic sentinel lymph nodes, hence the current axilla treatment for this group of patients with high nodal burden remained an ALND.

However, ALND is associated with multiple complications. On the other hand, NACT had shown encouraging rates of nodal pCR. Targeted axillary dissection, which involved the removal of the clipped node and sentinel nodes, could be performed after NACT to identify the patients with nodal pCR, hence sparing these patients an ALND. Various ways of localizing the clipped node, which was the initially metastatic node, have been described. These methods included hookwire localization, radioactive seed, the wireless non-radioactive methods such as Savi Scout, Magseed, radiofrequency localizer etc. (7). Each localizing method is associated with its own advantages and pitfalls and had aided in the identification of patients with nodal pCR after NACT, hence sparing them an ALND. To date, however, it is unknown if NACT could reduce the need for ALND in these Z0011 trial high

nodal burden patients who would otherwise have needed an ALND, which was the aim of this study.

Although our study population was defined on the assumption that  $\geq 3$  sonographically abnormal nodes is highly predictive of the high nodal burden group in the Z0011 trial, we were unable to compare the demographics, radiological and pathological features in our cohort with that of the high nodal burden patients in the Z0011 trial (8) since these features were not reported in the Z0011 trial. However, it has been reported that T1–2 patients who did not fulfil the Z0011 criteria of axillary preservation because of 3 or more metastatic sentinel lymph nodes tended to have higher proportions of T2 and grade III cancers (9) which was similar to our cohort.

NACT could result in nodal pCR, with the pathologic features such as high grade (10), ER negativity and HER2 positivity (11) reported as the most significant factors influencing the nodal pCR rates. In a retrospective study by Pilewskie *et al.* (12), they found that in cT1–2 patients with nodal disease and ER/PR+ HER2– subtype tumors, they had lower ALND rates (15%) if they underwent upfront surgery with breast conservation instead of NACT (34%). There were 2 reasons for this finding. Firstly, this subtype responds poorly to NACT, hence resulting in little nodal pCR. Secondly, if an upfront surgery was performed instead, this group of patients could adopt Z0011 trial criteria of performing an ALND only if there were  $\geq 3$  metastatic nodes, hence allowing axillary preservation in patients with low nodal burden. These two reasons accounted for the lower ALND rates in the upfront surgery group compared to the patients who had undergone NACT.

However, the above study did not distinguish the effect of NACT in the high nodal burden group specifically but determined the effect of NACT in the Z0011 trial cohort collectively. Similarly, in our cohort with ER/PR+ HER2– tumors who underwent NACT, the ALND rate was also reported high at 70%. This high figure is not surprising as our cohort consisted specifically of the supposedly high nodal burden group who would require an upfront ALND. NACT, however, did minimize the risk of ALND in this tumor subtype by 30%.

Conversely, in the same study (12), cT1–2N0 TN or HER2 patients who had NACT had reduced rates of ALND. This was also similar to our cohort with the TN group and the HER2 positive group having the highest nodal pCR rates among the various tumor subtypes.

In our study, ypT was statistically associated with the nodal pCR. This finding was consistent with literature

which reported similar findings (13). Breast tumor pCR have been reported to be highly correlated with nodal pCR (14).

Though patients with percutaneous biopsy proven metastatic nodal disease could have a higher nodal disease compared to those detected on sentinel lymph node biopsy alone (15), 47% of the T1–2 patients with positive percutaneous biopsy would still qualify for Z0011 trial of axillary preservation (16). In particular, our cohort for analysis consisted of cT1–2N0 patients with positive percutaneous nodal biopsy. The sonographic criteria of  $\geq 3$  sonographically abnormal lymph nodes was then applied to define the high nodal burden group who would not qualify for axillary preservation in Z0011 trial. This group of patients underwent NACT instead.

A strength of the paper included documentation of the number of abnormal nodes in the axillary ultrasound reports which was not practiced worldwide. In addition, an ALND was also performed to determine nodal pCR.

Limitations included a small sample size and retrospective nature with possible selection bias of the patients with high risk tumor subtypes for NACT. The high nodal burden group from Z0011 trial was predicated on the number of abnormal axillary nodes on initial axillary ultrasound, which had been reported to be a highly predictive factor. Though this predictive factor does not identify all cases of high nodal burden, in reality, there is no other way in which this ALND reduction rate could be determined. The most certain way to determine the group of patients with high nodal burden would be to perform a sentinel lymph node biopsy and only include those with  $\geq 3$  metastatic sentinel lymph nodes. However, then we would not be able to assess the effect of NACT on the removed lymph nodes to assess nodal pCR rate.

In conclusion, in the postulated subgroup of T1–2 breast cancer patients with high nodal burden who will require an ALND, NACT could result in nodal pCR in 54.2% of these patients. Nodal pCR was also associated with ypT. The nodal pCR benefit was noted most significantly with the TN and HER2+ subtype but could still result in nodal pCR in 30% of ER/PR+ HER2 negative patients. As a result, NACT should be offered in this identified high nodal burden group to minimize ALND risk.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-7/rc>

*Data Sharing Statement:* Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-7/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-7/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by SingHealth Centralised Institutional Review Board (CIRB Ref: 2020/2147) and waiver of patients' informed consent was obtained.

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**Cite this article as:** Yan Z, Wong A, Ng RP, Lee YS, Lim MEA, Leong LCH, Allen J, Lim GH. Determining the benefit of neoadjuvant chemotherapy in reduction of axillary dissection rates in Z0011 trial cohort with high nodal burden. *Gland Surg* 2022;11(5):788-794. doi: 10.21037/gs-22-7