ORIGINAL ARTICLE
Turk J Surg 2023; 39 (2): 136-144

Frequency of axillary nodal complete pathological response of breast cancer patients in neoadjuvant chemotherapy setting: A cross-sectional study

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ABSTRACT

Objective: Pathological complete response (pCR) occurs in about 20-30% of patients undergoing systemic neoadjuvant therapy. This leads to the idea of sparing the patient the morbidity associated with axillary surgery. "Wait and watch" policy for cancers which achieve complete pathological response on neoadjuvant systemic therapy is a well-established practice in various cancers like the esophagus, rectum and larynx. This has led to organ preservation protocols being practiced worldwide for these cancers without affecting the overall survival of the patient. We believe patients undergoing a complete pathological response in the breast may be spared axillary surgery. Axillary surgery leads to morbidity and extra financial burden with no added advantage in survival.

Material and Methods: A total of 326 patients with breast cancer who had received neoadjuvant systemic chemotherapy from 2015 to 2020 were included in our retrospective study. Final histopathology of the breast and axillary surgery was noted to report the frequency of complete pathological response. The frequency of positive nodal disease with respect to stage, grade and type of cancer was measured.

Results: Among 326 patients, our study showed that 53% of patients with complete pathological response in breast also had complete response in the axilla compared to 43% with incomplete pathological response. No significant difference was found for age, menopausal status, initial tumor size when patients with complete pathological response were compared to non or partial responders. The rate of complete pathological response was higher in patients with clinically node negative patients after NACT, hormone negative, HER2 positive and triple negative population.

Conclusion: Our results indicated that 53% of the patients who developed complete pathological response in the breast underwent needless axillary procedure. Axillary surgery can be staged after the breast surgery if residual tumor is present on the histopathological specimen. In case of pCR, omission of axillary surgery can be considered. However, a larger population, multi-centric studies are needed for treatment guidelines.

Keywords: Neoadjuvant chemotherapy, axillary nodal response, breast cancer

INTRODUCTION

Pakistan has reported the highest incidence of breast cancer among Asian countries except Israel. According to a study, the projected incidence of breast cancer will rise to approximately from 23.1% in 2020 to 60.7% in 2025 (1,2). In Pakistan, one in every nine woman is at risk of developing breast cancer (3). The mortality rate in our country is one of the highest in South Asia owing to ignorance, lack of awareness and the dearth of a centralized screening program (3). Our breast cancer patients develop cancer at a comparatively younger age and present more frequently with an advanced stage cancer (4,5). Health prediction models point towards an increasing incidence in breast cancer worldwide including Pakistan (6,7). Breast cancer will be more prevalent in younger women, leading to more distress and affecting more families. Despite higher incidence of the disease, there are fewer facilities available countrywide to perform sentinel node biopsy, and hence, axillary dissection is still a standard procedure to address the axilla regardless of axillary nodal status in neoadjuvant setting resulting in additional morbidity of arm swelling and lymphedema.

Surgical management of the axilla in curable breast cancer has undergone a major paradigm shift in the last few decades. Historically, Halstead mastectomy was the

Cite this article as: Abidi SS, Vohra L, Kerawala AA, Kafeel A, Tahseen MU, Javed S. Frequency of axillary nodal complete pathological response of breast cancer patients in neoadjuvant chemotherapy setting: A cross-sectional study. Turk J Surg 2023; 39 (2): 136-144.

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Received: 14.03.2022
Accepted: 26.04.2023
Available Online Date: 19.06.2023

DOI: 10.47717/turkjsurg.2023.5708

biggest achievement endorsing the concept to address local disease aggressively which resulted in extensive mutilation and morbidity, afterwards in 1902, modified radical mastectomy emerged and was widely accepted endorsing the fact that breast cancer is a systemic disease and hence local treatment should not be aggressive in presence of effective adjuvant chemotherapy though carrying the risk of lymphedema and arm swelling (8-14).

In the late 20s, sentinel node biopsy became the preferred method for staging early breast cancer patients with clinically impalpable lymph nodes in the axilla (15-18). Trials like (NSABP-32, ALMANAC, Sentinella-GIVOM) proved SLNB was safe and effective in determining axillary metastasis and should be used instead of a formal axillary dissection in early breast cancer patients without clinically palpable nodes in the axilla (19-21). The ACOSOG Z0011 trial further established this by showing no benefit of ALND if one or two sentinel nodes were found positive for cancer in breast conservation setting (22). However, the use of sentinel lymph node biopsy after neoadjuvant treatment for breast cancer is not widely established. Higher false negative rate and lower detection rate after systemic therapy, as shown by the SENTINA trial and other studies, can be reduced with dual mapping and identification of at least three SLNs perioperatively.

Pathological complete response (pCR) occurs in about 20-30% of patients undergoing systemic neoadjuvant therapy. This leads to the idea of sparing the patient the morbidity associated with axillary surgery (23). A pCR is defined as no residual invasive disease in the breast and the axillary lymph nodes with rates varying according to the different breast cancer (BC) subtype. Hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative 7-16% hormone receptor-positive and HER2-positive 30-40%, hormone receptor-negative and HER2-positive 50-70%, triple-negative BC (TNBC) 25-33% (24).

"Wait and watch" policy for cancers which achieve complete pathological response on neoadjuvant systemic therapy is a well-established practice in various cancers like the esophagus, rectum and larynx (25). This has led to organ preservation protocols being practiced worldwide for these cancers without affecting the overall survival of the patient (25). We believe that patients undergoing complete pathological response in the breast may be spared an axillary surgery. Axillary surgery leads to morbidity and extra financial burden with no added advantage in survival as the patient is already cancer free after neoadjuvant chemotherapy.

This study will help us determine the subset of patients who can be spared an axillary surgery. In addition to saving the morbidity of an open procedure, this will lead to economic benefit for the patient and the society as a whole.

MATERIAL and METHODS

Between January 1st, 2015 to December 31st, 2020, the data of a total of 326 patients with diagnosed breast cancer and who underwent neoadjuvant chemotherapy followed by surgery was retrospectively included in this study. Tumor stage and immuno-histochemistry were recorded along with the final histopathology report of the breast and the axilla. All patients included in the study were above 18 years of age with diagnosed breast cancer, who underwent neoadjuvant chemotherapy. However, the patients who were operated on outside our hospital or whose histopathology specimen was reported and tested elsewhere and the patients who had incomplete medical records were excluded from the study. Sentinel node biopsy was performed by dual dye technique (radio-isotope and methylene blue dye), at least three sentinel nodes were retrieved in post neo-adjuvant patients. In case three nodes could not be found, the procedure was converted to formal axillary dissection to reduce false negative rate. In addition, if one or more sentinel nodes were positive for micro or macro metastasis, axillary dissection was performed.

The ethical exemption for this study was approved by the ethics review committee. Patients' personal information was deleted at the time of analysis and all responses were de-identified after data entry to maintain anonymization. No techniques were used to impetrate missing data so as to prevent bias in the study. Demographical and tumor related characteristics were calculated as descriptive. Chi-square test was used to compare the groups of achievers and non-achievers of complete pathological response with respect to patient's demographic and cancer related data and the patients who received negative axillary lymph node status over histopathology after axillary lymph node dissection (ALND). A logistic regression model was fitted to identify the predictors associated with complete pathological response and negative axillary lymph node status after ALND for the patients receiving NACT. The data was analyzed through SPSS software version. 22.0.

RESULTS

A total number of 326 accessible patients receiving NACT were included into the study. Mean age of the patients was 50.2 years. The median of abnormal breast lymph nodes prior to chemotherapy was one (SD= 0.897, R= 0-5) while the median of abnormal breast lymph nodes after chemotherapy was zero (SD= 0.792, R= 0-3). Median tumor size was 30 mm (SD= 12.6, R= 1-167). A total of 191 patients (65%) underwent core biopsy of the lymph nodes for metastasis, a median of three sentinel lymph nodes were removed (SD= 3, R= 0-4) among which a median of zero lymph nodes were positive on histopathology. Around half of the patients (53%) had a cancer clinical stage of T2N1, with most patients having grade II CA (73%) in the study.

Among the assayed cases, most patients had ER-/PR-/HER2+ status on histopathology (37.5%). Later, during follow-up, a total of 197 patients (67.5%) underwent axillary lymph node dissection, the positive lymph nodes on biopsy had a median of one (SD= 3.41, R= 0-20). Most patients (56.7%) underwent modified radical mastectomy. Baseline characteristics of the patients and tumors are described in Table 1.

Complete versus incomplete pathological response of the tumor and axillary lymph nodes in response to NACT were analyzed through univariate analysis and summarized in Table 2. A total of 104 patients (67.1%) achieved complete pathological response in the breast after NACT. It was observed that equivalent percentages of the patients with age group <50 and >50 achieved complete pathological response, which was statistically significant (<50 and >50= 30% and 70%; p= .001). Premenopausal women were observed to achieve pCR slightly higher than postmenopausal women (pre MP= 33.6%, post MP= 29.2%; p= 0.58), but the difference was not statically significant. Similarly, patients with clinical stage T0, T1 and T2 achieved pCR more than those with high clinical stage of T3 and T4, yet the difference was not significant (T0, T1, T2 and T3, T4 group= 31.3% and 25%; p= 0.48). The percentage of the patients with grade I, II and III achieving complete response was significantly comparable (grade I, II and III, group= 29% and 35%; p= 0.01). Patients with pre-treatment estrogen negative status achieved high pCR rate than patients with pre-treatment estrogen positive status (estrogen positive group= 17%, estrogen negative group= 43%; p= 0.001).

Potential predictors for complete pathological response were analyzed by fitting into a logistic regression model. Patients of age <50 years had very high odds of achieving pCR after NACT, but the result was insignificant (OR= 2.8; 1.07 CI, p= 0.30). Similarly, pre-menopausal women were very likely to achieve pCR after NACT (OR= 3.92; 1.83 CI, p= 0.18). Patients with grade I and II had fair chances of achieving pCR (OR= 1.4; .35 CI, p= 0.56). The patient group with estrogen negative status prior to treatment had very higher odds of achieving complete pathological response after NACT (OR= 4.5; 6.94 CI, p= 0.01). The details are summarized in Table 3. The patient group having negative lymph nodes post ALND achieved higher percentage of pCR than patients with positive lymph node status post ALND (negative LN and positive LN= 53% and 3%, p= 0.001) as illustrated in Figure 1.

A logistic regression model was fitted for analyzing the potential predictors of negative axillary lymph nodes status achievement after axillary lymph node dissection (ALND) in patients receiving NACT. The details are given in Table 4. The patients with initial tumor size >20 mm prior to NACT had high chances of achieving negative axillary nodal status on histopathology (OR= 1.6; .5, p= 0.48). The patient group with estrogen negative tumor had fair chances of achieving negative axillary response post NACT (OR= 1.3; .34 CI, p= 0.56).

DISCUSSION

After significant achievements in the de-escalation of breast surgery using neoadjuvant chemotherapy, there is growing interest in the de-escalation of axillary surgery. Our study reported that 67.1% of 326 post neoadjuvant patients achieved complete pathological response in the breast, and of these, 53% of the patients also had complete response in the axilla. In a recent study by Sanaz, it has been reported that 97% with breast pCR had a negative lymph node metastasis comparing to 71.6% without pCR (26). In another study at Samsung medical center, it has been evaluated that in a study of 1044 patients, 87% of patients with breast pCR have also achieved axillary pCR with overall 51% patients achieved pCR in total study (27). We reported clinically N0 status after neoadjuvant chemotherapy, and hormone receptor negative/HER2 positive tumors were most likely to achieve pCR in the axilla. Similar rates of pCR have been seen in a recently published study by Lim et al., where ~44% of HER2+ patients and ~37% of triple negative patients achieved pathological complete response (28). Our study also showed a positive relation between the receptor status and breast and axillary pCR with 41% patients with initial ER-status achieving pCR compared to 17.1% patients with ER+ tumors with 4.5 OR, 6.94 CI .01 p-value. For patients with both breast and axilla pCR response, when compared with subtypes according to receptor status, it was observed that in HER2+ patients, 64% and in triple negative group patients, 37.9% achieved pCR. Achieving breast pCR after neoadjuvant treatment has been linked with better survival outcomes (29). However, Kuerer et al. were the first to report relationship between breast and axillary complete response in 1998 which brought attention to possible de-escalation treatment strategies in this patient population (30). Our findings were also in line with the National Cancer Database (NCDB) analysis reporting complete response in 30.821 cT1-2N0-1 breast cancers for HER2-positive (*44%) and triple-negative (*37%) subtypes (31).

In another study, Tadros et al. have demonstrated a strong correlation between breast pCR and axilla pCR in their study. They have noted that breast pCR was higher in triple negative group with 37.5% compared to HER2+ group with 35.7%, and further they have concluded that 527 patients who achieved pCR with NST having HER2+ and triple negative breast cancer were all later found to have axillay pCR in the nodes (32). A similar study showed a strong correlation in achieving breast pCR with NST in patients with ER-, triple negative and ER+ HER2+ patients although they received low PCR rates in ER+ HER2- patients (33).

Table 1. Baseline characteristics of the patients and tumors and axillary node status	
Characteristics	**n (%)**
Age (mean), years	50.2
Menopausal status	
Pre-menopausal	148 (46.7)
Post-menopausal	146 (46.1)
Peri-menopausal	23 (7.3)
Number of abnormal lymph nodes pre-chemo	
No abnormal lymph node	59 (19)
1	156 (50.2)
2	63 (20.3)
3	32 (10.3)
5	1 (0.3)
Number of abnormal lymph nodes post-chemo	
No abnormal lymph node	214 (67.1)
1	45 (20.6)
2	34 (9.0)
3	25 (3.2)
Core biopsy of lymph nodes positive for metastasis	191(65)
Clinical stage	
T1N0	8 (4.8)
T1N1	17 (10.2)
T2N0	21 (12.7)
T2N1	88 (53.0)
T3N0	4 (2.4)
T3N1	20 (12.0)
T4N0	2 (1.2)
T4N1	6 (3.6)
Histology of invasive ductal CA	171 (96.6)
Grade	
I	10 (3.2)
II	228 (73.1)
III	74 (23.7)
Size of invasive focus	
Complete response	88 (31)
<1 cm	79 (27.8)
1-2 cm	47 (16.5)
>2 cm	69 (24.3)
4 cm	1 (0.4)
Receptor status	
ER-/PR-/HER2-	116 (37.5)
ER/PR/HER2+	51 (16.5)
ER/PR+ HER2-	99 (32)
ER/PR- HER2+	38 (12.3)

Table 1. Baseline characteristics of the patients and tumors and axillary node status (continue)	
Number of sentinel lymph nodes retrieved	
No sentinel lymph node retrieved	44 (28)
1	18(11.5)
2	13 (8.3)
>3	42 (26.8)
Number of lymph nodes positive on histopathology	
Complete response pathology	126 (68.1)
1	24 (13.0)
2	10 (5.4)
3	4 (2.2)
>3	19 (10.3)
Axillary lymph node dissection given	197 (67.5)
Nodes recovered in ALND	
None	76 (39)
<3	1 (0.5)
<10	8 (4.1)
<20	70 (35.9)
<30	35 (17.9)
<40	5 (2.6)
Positive lymph node biopsy	112 (90.3)
No. of positive nodes after ALND	
None	60 (48.8)
<3	32 (26.0)
<5	9 (7.3)
<10	16 (13.0)
<20	6 (4.9)
Type of surgery	
Mastectomy + SLNBx + AxLND	160 (56.7)
Mastectomy + SLNB	47 (16.7)
BCS + ALND	44 (15.6)
BCS + SLNB	31 (11.0)

SLNB: Sentinel lymph node biopsy, AxLND: Axillary lymph node dissection, BCS: Breast conserving surgery, ER: Estrogen receptor, PR: Progesterone receptor, SLN: Sentinel lymph node biopsy, BCS: Breast conserving surgery, ALND: Axillary lymph node dissection.

A large randomized prospective trial, ACSOG Z1071, has also reported similar responses to neoadjuvant therapy with regard to tumor biology. Seven hundred and one patients with cT1-T4, N1-N2 disease were recruited. Of triple negative tumors, 47% achieved complete pathological response, amongst these, 80% of patients also achieved complete response in the axilla (34-36).

As of now, surgical treatment remains gold standard for patients who have complete response in the breast. Although multiple trials like RESPONDER, NRG-BR005, MICRA trials are underway to identify group of patients with exceptional response to NAST identified with core needle biopsy of the tumor bed, these patients can avoid breast surgery. However, the current reported false negative rates by these studies are higher than the accepted threshold (37).

Retrospective data with a small cohort is one of the limitations of this study. Nevertheless, our results are in accordance with large randomized trials like ACSOG Z1071 supporting its applicability.

The idea that patients who achieve breast pCR can be spared of surgery leads to an exciting pathway of de-escalation in breast cancer treatment. Thus, identifying the group of patients who are more sensitive to NACT, refinement of techniques to reduce false negative rate of core needle biopsy of the tumor bed to

Table 2. Univariate analysis of patient and tumor characteristics and comparison between complete versus incomplete pathological response of primary tumor and axillary nodes after neoadjuvant chemotherapy

	Complete response		Incomplete response		
Characteristic	**No.**	**%**	**No.**	**%**	**p**
Total patients	104	67.1	51	32.9	
Patient's age (years)					
≤50	47	30.3	108	69.7	
>50	41	31.7	88	68.2	.00
Menopausal status					
Pre-menopausal	51	33.6	101	66.4	
Post-menopausal	37	29.2	94	71.8	.58
Clinical stage					
T0, T1 and T2	42	31.3	92	68.7	
T3 and T4	8	25	24	75	.48
Histopathological finding					
Ductal invasive CA	51	29.8	120	70.2	
Other	0	-	6	100	.11
Grade					
0	0	-	1	100	
I, II	61	29.3	147	70.7	
III, IV	26	35.1	48	64.9	.01
Receptor status					
Estrogen positive	23	17.2	111	82.8	.01
Estrogen negative	62	43.4	81	56.6	.00
HER2+	57	64.0	32	34.9	.01
Triple negative	44	37.9	72	62	.00

Table 3. Logistic regression analysis. Association of patient's demographics, estrogen receptor status and tumor characteristics with complete pathologic response

Characteristics	**OR**	**Wald 95% CI**	**p**
Age <50 years	2.8	1.07	.30
Pre-menopausal	3.92	1.83	.18
Tumor grade I, II	1.4	.35	.56
Estrogen negative	4.5	6.94	.01

OR: Odds ratio.

detect pCR will not only help to minimize breast surgery but also recognize selective patients who are more likely to achieve axillary pCR in association with the breast, and hence, the omission of axillary surgery can also be considered.

Ethics Committee Approval: This study was approved by Aga Khan University Ethics Review Committee (Decision no: 2021-6022-17743, Date: 05.05.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AAK; Design - SSD; Supervision - LV; Fundings - LV; Data Collection and/or Processing - AAK, SSD, AK; Analysis and/or Interpretation - UT; Literature Search - SJ; Writing Manuscript - SSD, AAK; Critical Reviews - LV.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

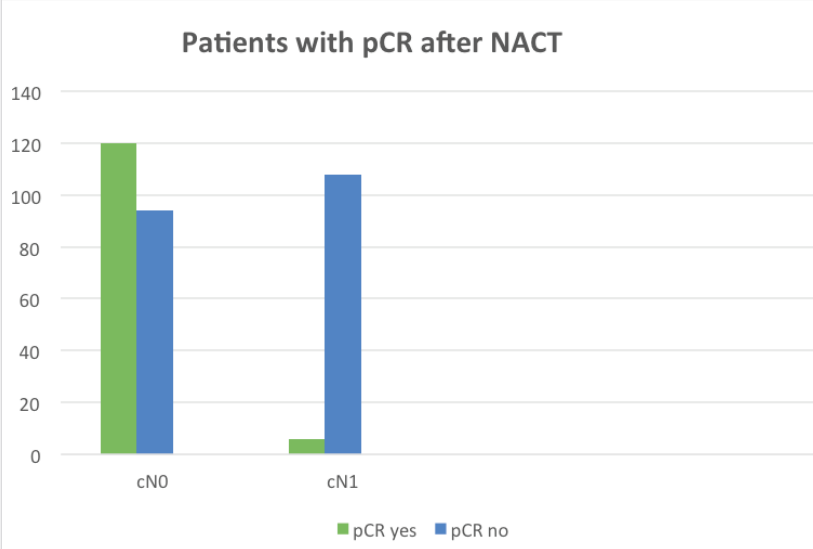

Figure 1. Illustrating the count of the achievers and non-achievers of complete pathological response among patient groups who were clinically node negative versus clinically node positive after NACT.

Table 4. Logistic regression analysis. Association of patient's demographics, estrogen receptor status and tumor characteristics with negative lymph nodes after axillary lymph node dissection

Characteristics	OR	Wald 95% CI	p
Initial tumor size >20 mm	1.6	.5	.48
Estrogen negative receptor status	1.3	.34	.56

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (2): 136-144

Neoadjuvan kemoterapi ortamında meme kanseri hastalarında aksiller nodal tam patolojik yanıtın sıklığı: Kesitsel bir çalışma

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ÖZET

Giriş ve Amaç: Sistemik neoadjuvan tedavi gören hastaların yaklaşık %20-30'unda patolojik tam yanıt (pCR) oluşur. Bu da hastayı aksiller cerrahiyle ilişkili morbiditeden koruma fikrine yol açar. Neoadjuvan sistemik tedaviyle tam patolojik yanıt alınan kanserler için "bekle ve izle" politikası; özofagus, rektum ve larenks gibi çeşitli kanserlerde köklü bir uygulamadır. Hastanın genel sağkalımını etkilemeden bir memede tam bir patolojik yanıt geçiren hastaların aksiller cerrahiden kurtulabileceğine inanıyoruz. Aksiller cerrahi, morbiditeye ve ekstra mali yüke yol açarken sağkalımda herhangi bir ek avantaj sağlamaz.

Gereç ve Yöntem: Retrospektif çalışmamıza 2015-2020 yılları arasında neoadjuvan sistemik kemoterapi alan toplam 326 meme kanserli hasta dahil edildi. Meme ve aksiller cerrahinin nihai histopatolojisinin, tam patolojik yanıtın sıklığını bildirdiği kaydedildi. Evre, derece ve kanser tipine göre pozitif nodal hastalık sıklığı ölçüldü.

Bulgular: Çalışmamız, üç yüz yirmi altı hasta arasında, memede tam patolojik yanıt olan %53 hastanın aksillada da tam yanıta sahip olduğunu, buna karşılık eksik patolojik yanıt olan %43 hastada olduğunu gösterdi. Tam patolojik yanıt veren hastalar, yanıt vermeyen veya kısmi yanıt verenlerle karşılaştırıldığında yaş, menopoz durumu, başlangıç tümör boyutu açısından anlamlı bir fark bulunmadı. NACT, hormon negatif, HER2 pozitif ve üçlü negatif popülasyondan sonra klinik olarak nod negatif hastalarda tam patolojik yanıt oranı daha yüksekti.

Sonuç: Sonuçlarımız, memede tam patolojik yanıt gelişen hastaların %53'üne gereksiz aksiller girişimi yapıldığını gösterdi. Histopatolojik örnekte rezidüel tümör varsa, meme cerrahisinden sonra aksiller cerrahi evrelendirilebilir. pCR durumunda, aksiller cerrahinin ihmal edilmesi düşünülebilir; ancak tedavi kılavuzları için daha geniş popülasyonlu, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Neoadjuvan kemoterapi, aksiller nodal yanıt, meme kanseri

DOİ: 10.47717/turkjsurg.2023.5708