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ORIGINAL ARTICLE

Assessment of heterogeneous response of primary tumor and nodal disease to neoadjuvant therapy in invasive breast cancer

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ABSTRACT

Objective: To assess heterogeneous pathological responses of the primary tumor and axillary lymph nodes following neoadjuvant therapy (NAT) in invasive breast carcinoma and to identify clinicopathological factors associated with variable response patterns, including pathological complete response (pCR).

Methods: This cross-sectional study included node-positive, non-metastatic patients with invasive breast cancer who received NAT followed by definitive surgery between October 2024 and June 2025. Tumor and nodal responses were assessed on final histopathology and categorized as pCR, heterogeneous response, or non-complete response. Clinicopathological and biological variables were recorded. Associations were evaluated using univariate analysis, while multinomial logistic regression identified independent predictors of tumor and nodal response.

Results: Among 169 patients, heterogeneous response occurred in 53 (31.4%), non-complete response in 95 (56.2%), and pCR in 21 (12.4%). Within the heterogeneous group, 24 (45.3%) patients achieved breast pCR with residual nodal disease, while 29 (54.7%) showed nodal pCR with residual breast tumor. A significant association was observed between breast and nodal responses ($p < 0.001$). Tumor grade III (50.9%, $p=0.017$), triple-negative receptor status (41.5%, $p < 0.001$), and type of NAT ($p=0.032$) were significantly associated with heterogeneous response. Residual tumor size ($p=0.010$), lymphovascular invasion ($p=0.023$), ductal carcinoma in situ ($p=0.007$), and extranodal extension ($p<0.001$) independently predicted tumor and nodal response, but not heterogeneous response specifically.

Conclusion: Discordant pathological responses between primary breast tumors and axillary lymph nodes after NAT are frequent and reflect biological heterogeneity. Recognizing these patterns is crucial for individualized surgical planning and optimization of post-neoadjuvant treatment strategies.

Keywords: Breast Neoplasms (MeSH); Neoadjuvant Therapy (MeSH); Heterogeneous response (MeSH); Pathologic Complete Response (MeSH); Drug Therapy (MeSH); Antineoplastic Agents (MeSH); Mastectomy (MeSH); Neoplasm Staging (MeSH); Treatment Outcome (MeSH); Biomarkers, Tumor (MeSH).

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INTRODUCTION

Neoadjuvant therapy (NAT) is the use of systemic therapy including, chemo and hormonal therapy before undergoing definitive surgery. It was initially used for the treatment of inoperable, locally advanced disease; however NAT is now an indispensable component of treatment in early-stage disease as well. Since the introduction of this concept, the significance of neoadjuvant therapy in improving breast conservation, decreasing morbidity and enhancing self-image has been well recognized.[1-5] Administration of NAT is primarily based on factors like size of the tumor, extent of disease, biology of tumor, receptor and nodal status.[6] Axillary lymph node status is still the most significant factor responsible for the overall end result of primary breast tumor. Positive axillary lymph node status after conclusion of therapy is a firm indicator of potential disease recurrence.[7] Response to Neoadjuvant systemic therapy can be assessed both clinically (clinical examination and radiologic findings) and pathologically. Clinically RECIST (Response evaluation criteria in solid tumors) can be used to estimate the response.[8] Multiple grading systems have been used to categorize response to treatment.[9] National surgical adjuvant breast and bowel project (NSABP) protocol B-18 provides a simple pathological classification of complete (pCR), partial (pPR) and no response (pNR) in primary tumor and axillary lymph nodes. According to this protocol, pPR is defined as the presence of scattered individual or small clusters of tumor cells while the pNR is no change or some alteration in tumor cells. pCR is the absence of invasive tumor cells.[10] For Pathologic Complete Response, Food and Drug Administration (FDA) recommends either of two definitions of pCR on the basis of data analysis, pCR (ypT0/Tis ypN0) absence of residual invasive cancer on hematoxylin and eosin, evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy and pCR-no DCIS (ypT0 ypN0) as the absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimens and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy.[11-13]

The objective of the treatment is focused on improving and reducing the primary tumor and nodal tumor cells burden. High rates of complete pathologic response (ypCR), reaching up to 67%, have been documented in certain subgroups of breast cancer, specifically in cases of Human Epidermal

Growth Factor Receptor 2 (HER2)-positive tumors. In the present era, discordance between primary tumor and nodal response has been observed which has adverse implications on patient survival. Fleming AC, et al., and Wang Y, et al., reported dissonance in responses to the Neoadjuvant therapy. They reported discordance in terms of complete response in breast while still having nodal disease.[6,14]

This study aimed to assess the heterogeneous response to NAT of primary tumor and nodal disease in Invasive Breast Carcinoma and to identify characteristics linked to variable response in primary tumor and nodal disease, including pathological complete response.

METHODS

This prospective cross-sectional study was conducted at Breast Surgery Unit, Department of Surgery, Khyber Teaching Hospital, Peshawar, Pakistan from 16th October 2024 to June 2025, using consecutive non-probability sampling. A formal permission from ethical board and head of the department was obtained (letter #: 795/DME/KMC dated 16/10/2024). The sample size was calculated by means of OpenEpi with 95% confidence interval. A total of 169 patients with biopsy proven Invasive breast cancer (irrespective of type and receptor status) with positive nodal status at the time of diagnosis planned for neoadjuvant therapy and subsequently definitive surgery registered with the multidisciplinary team for breast cancer were enrolled. Exclusion criteria consisted of cases with initial workup and surgery at another institution, patients who did not receive neoadjuvant treatment, negative nodal disease, inoperable status and distant metastasis. Negative nodal disease was established on the basis of radiological and histopathological evaluation. Confirmation of exact tumor size before administration of neoadjuvant therapy was done radiologically. Biological characteristics of breast cancer, including receptor status were determined through histological and immunohistochemical (IHC) evaluation. Breast cancer staging was performed in accordance with the 8th edition of the AJCC staging system. The type of neoadjuvant therapy (NAC or NAHT) proceeded by type of surgery was decided by the breast multidisciplinary team. Follow-up with maintenance of record started from the day of index diagnosis, until the final post-operative histopathology evaluation. Strict exclusion criteria were followed to control confounders and bias in study results.

Data collection was carried out through a self-administered, semi-structured proforma designed for the study. Purpose and benefits of the study were explained to the patients. A written informed consent was obtained. The confidentiality of participants was ensured at every stage of the research process. All patients were subjected to detailed history, examination and work up. Post-operative care was provided in accordance with established institutional protocols.

SPSS version 26 was used for data analysis. Post-operative histopathology was used to assess the pathological response to neoadjuvant therapy. Pathologic response was recorded in three categories complete (pCR), heterogenous (HR) and non-complete response (N-pCR), to examine variable associations separately. Mean ± SD was calculated for continuous variables like age, parity and size of tumor. Frequency and percentage calculation of each variable was performed. Pearson chi-square and Fishers exact tests were applied in univariate analysis to assess the association of pre-NAT breast and nodal characteristics with treatment response. Chi-square test was also employed to evaluate the association between primary tumor and nodal pathological response in the heterogeneous response category. Multinomial logistic regression was performed to identify independent predictors among post-operative variables like residual tumor size, number of involved axillary lymph nodes in relation to tumor and nodal response. While multinomial regression was also employed to evaluate independent predictors of heterogenous response, the small sub-group sizes, wide confidence intervals and lack of statistical significance suggested instability of estimates, in addition univariate analysis was performed.

RESULTS

A total of 169 patients meeting the inclusion criteria were analysed. Median follow-up was 6.5 months. Population characteristics are summarized in Table I. The median age at the time of diagnosis was 48 years, n=12 (7.1%). The age group of 46 to 60 years had the maximum number of diagnosed breast cancer patients. The youngest diagnosed patient was 25 years old. In

Table I: Population characteristics

Characteristics		Frequency (%)
Age groups (years)	≤30	6 (3.6)
	31-45	63 (37.3)
	46-60	78 (46.2)
	61-75	19 (11.2)
	>75	3 (1.8)
Menopausal status	Pre-menopausal	63 (37.3)
	Peri-menopausal	11 (6.5)
	Post-menopausal	95 (56.2)
Marital Status	Single	12 (7.1)
	Married	155 (91.7)
	Widow	2 (1.2)
	Parity (Median, 3)	35 (31.8)

Table II: Breast cancer histopathological characteristics

Histopathological Characteristics	Category	Frequency (%)
Histological type	IDC	150 (8.8)
	IDC with mucinous features	5 (3.3)
	IDC with micropapillary features	3 (1.8)
	IDC with DCIS	2 (1.2)
	IDC with squamous differentiation	2 (1.2)
	ILC	7 (4.1)
Grade	1	2 (1.2)
	2	104 (61.5)
	3	63 (37.3)
Ki-67 Proliferative index	Mean	35.76
Receptor status	ER/PR Positive	53 (31.4)
	ER positive	19 (11.2)
	PR Positive	2 (1.2)
	ER/HER-2 Positive	5 (3.0)
	PR/HER-2 Positive	1 (0.6)
	ER/PR/HER-2 positive	16 (9.5)
	ER/PR/HER-2 Negative	48 (28.4)
	HER-2 Positive	25 (14.8)

IDC=Invasive ductal carcinoma; DCIS=ductal carcinoma in-situ; ER=estrogen receptor, PR=progesterone receptor; HER-2 = human epidermal growth factor receptor-2.Values are presented as number (percentage)

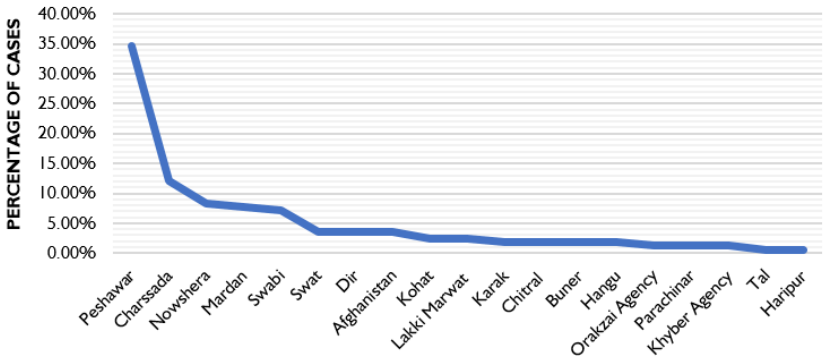

Figure I: Geographic distribution

our study population, majority of the patients were post-menopausal, 95 (56.2%) followed by 63 (37.3%) pre-menopausal. Most patients had given birth to two or more children, with a median parity of 3 (IQR 2.00-3.25).

Figure I shows the geographic distribution of diagnosed patients. Highest number of the patients belonged to Peshawar, 57 (34.6%) followed by Charssada, 20 (12%) patients. Table II describes the histopathological characteristics of breast cancer, as determined through histological and immunohistochemical (IHC) evaluation of biopsy samples. Invasive ductal carcinoma (IDC) was the most common histological type contributing 148 (87.6%) cases. Invasive lobular carcinoma was the second most common having a total of 7 (4.1%) cases. Moderately differentiated tumors or Grade 2 encompassed the majority of cases, n=104 (61.5%). The Ki-67 Proliferative index had a mean value of 35.76, showing that majority had a high proliferative index. Most tumors were ER/PR positive followed by triple negative (ER/PR/HER-2, Negative) and HER-2 positive subtypes.

Stage 2B constituted the largest proportion of cases, 70 (41.4%) as shown in Table III. Bulk of aggressive disease occurred in Stage 3B, 48 (28.4%) patients. T2 (tumor≤5cm) was the predominant tumor size category, while N1 (ipsilateral involved mobile axillary lymph nodes) was the most common nodal status.

Neoadjuvant chemotherapy (NAC) was the commonest treatment modality used for Tripple Negative (ER/PR/HER-2-ve), HER-2 positive, Tripple Positive (ER/PR/HER-2+ve) and Hormone receptor positive (ER/PR+ve) sub types,161 (95.2%) except among few cases of hormone receptor positive, 7 (4.1%) had Aromatase inhibitors and 1 (0.6%) had Tamoxifen as the primary therapy. Anthracycline and taxanes were a part of treatment regimen used for hormone receptor positive and triple negative breast cancer patients. They were given either in the form of 8 cycles, n=91 (56.5%) or 6 cycles, n=21 (13.04%). HER-2 positive patients were administered a combination of 6 cycles of taxanes, cisplatin and trastuzumab, n=47 (29.1%). There were only two cases who also had pembrolizumab in TNBC patients. In neoadjuvant hormone therapy, aromatase inhibitors and tamoxifen were administered, where applicable given for 6 months.

Modified radical mastectomy was performed in 70.4% of patients, while 11.8% underwent wire-guided local excision, 14.8% had wide local excision, 1.8% received perforator flap reconstruction, and 1.2% underwent vertical mammoplasty. Axillary clearance was carried out in 80% of cases, whereas 20% underwent sentinel lymph node biopsy. Twenty one (12.4%) patients achieved pathologic complete response in both breast and axilla after neoadjuvant therapy. 95 (56.2%) patients could not achieve pCR in breast or axilla, while in 53 (31.4%)

Table III: Pre-treatment clinical staging profile

Clinical Features	Category	Frequency (%)
Stage	2A	17 (10.1)
	2B	70 (41.4)
	3A	28 (16.6)
	3B	48 (28.4)
	3C	6 (3.6)
Tumor size	cT1	T1a (1), T1b (9), T1c (9)=19 (11.2)
	cT2	75 (44.4)
	cT3	30 (7.8)
	cT4	T4a (11), T4b (26), T4c (8)]=45 (26.7)
Nodal Status	cN1	140 (82.8)
	cN2	23 (13.6)
	cN3	6 (3.6)

2A=T0N1M0/T1N1M0/T2N0M0;2B=T2N1M0/T3N0M0; 3A=T0N2M0/T1N2M0/T2N2M0/T3N1M0/T-3N2M0; 3B=T4N0M0/T4N1M0/T4N2M0; 3C=Any T N3M0; cT1=less or equal to 2cm; cT1a=tumor> 1mm but <5mm; cT1b =tumor >5mm but ≤10mm; cT1c = tumor >10mm but ≤ 20mm;cT2=tumor ≤5cm; cT3=tumor ≥ 5cm; cT4a=extension to chest wall ; cT4b=skin ulceration, same side satellite nodules, edema which do not meet criteria for inflammatory carcinoma; T4c=both T4a and b; cN1= metastasis to mobile ipsilateral level I and 2 axillary lymph nodes; cN2 = metastasis in ipsilateral level I, 2 axillary lymph nodes fixed or matted or in clinically detected ipsilateral internal mammary lymph nodes in absence of clinically evident level I,II axillary lymph nodes; cN3 = metastasis in ipsilateral infraclavicular lymph nodes with or without level I,II axillary lymph node involvement or in clinically detected ipsilateral internal mammary lymph nodes with clinically evident level I,II axillary lymph node metastasis or metastasis in ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement. Values are presented as number (percentage).

Table IV: Pathologic response

Pathologic Response	Frequency (n=169)	Percentage
Heterogeneous response (HR)	53	31.4
Non- pathologic complete response (N-pCR)	95	56.2
Pathologic complete response (pCR)	21	12.4

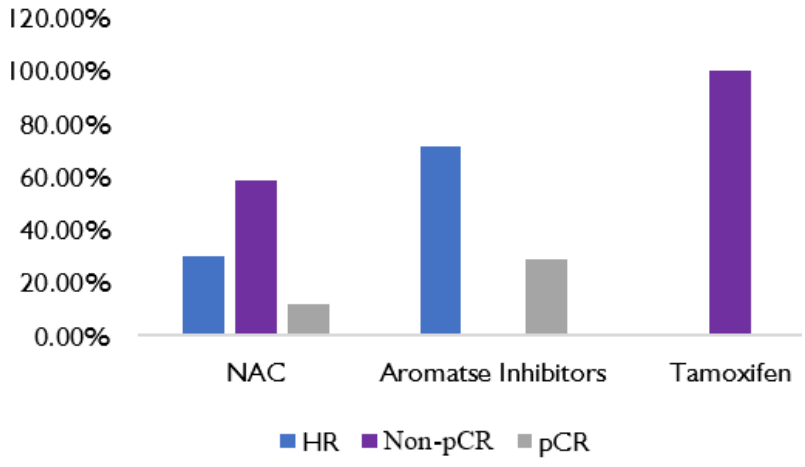

Figure 2: Association between type of neoadjuvant therapy and pathologic response [HR=heterogeneous response; Non-pCR=pathologic non-complete response; pCR=pathologic complete response; NAC=neoadjuvant chemotherapy. Values are presented as percentages]

cases heterogenous response was seen, as shown in Table IV. Treatment effect was further divided into complete, partial and no response in both primary tumor and axillary lymph nodes, as reported in the final histopathology. 45 patients had ypT0 (no residual tumor) and 50 patients achieved ypN0 (no involved lymph nodes). In the category of Non-pCR, majority exhibited partial response to NAT in breast while in axilla, cases were distributed almost evenly between partial and no response. There was statistically significant association between pathologic response in breast and axilla (Pearson Chi-Square, p< 0.001, df=4, all cell counts expected >5). Complete breast responders frequently achieved nodal response (21/45), non-responders often had persistent nodal disease (29/48) and partial responders showed high concordance (36/76).

Regardless of the above stated concordance, the sub-section of heterogenous response had varied results. Despite complete response in breast, there was residual nodal disease and vice versa, as depicted in Table V. Among cases of heterogeneous response, 24 patients had ypT0 while still having residual nodal disease. None achieved a complete response in axilla, showed either a partial (20.8%) or no response (24.5%) in the axilla. In contrast, all patients with no breast response (n= 9) exhibited a complete axillary response (100%). Patients with partial breast response (n=20), demonstrated complete axillary response. Statistically significant association was found between both groups (Fisher exact, p<0.00, df=4, 55.6% cells count <5), indicating that distribution of discordant responses was not independent but reflect underlying biological variability.

Table VI demonstrates relation between receptor status and total response. Highest number of cases achieving total pCR belonged to TNBC, n=10 (47.6%), followed by HER-2 positive n=7 (33.3%). The greatest rate of discordant response was also noted in triple negative breast cancer, but over all cases of ER/PR+ve with inclusion of triple positive cases had maximum heterogenous response, 26 (49.1%) In Non-pCR group maximum

Table V: Stratification of pathologic breast and nodal response vs pathologic response

Pathologic Response	Breast Pathologic Response [n (%)]	Axillary Pathologic Response [Frequency (%)]			Total [n (%)]
		Complete response	No response	Partial Response	
HR	Complete Response	0 (0.0)	12 (50.0)	12 (50.0)	24 (100)
	No-response	9 (100)	0 (0.0)	0 (0.0)	9 (100)
	Partial Response	20 (100)	0 (0.0)	0 (0.0)	20 (100)
Total, n (%)		29 (54.7)	12 (22.6)	12 (22.6)	53 (100)
Non-Pcr	No-response	-	29 (74.4)	10 (25.6)	39 (100)
	Partial response	-	20 (35.7)	36 (64.3)	56 (100)
Total, n (%)			49 (51.6)	46 (48.4)	95 (100)
pCR	Complete Response	21 (100)	-	-	21 (100)
Total, n (%)		21 (100)	-	-	21 (100)

HR=heterogeneous response; Non-pCR=pathologic non- complete response; pCR=pathologic complete response. Values are presented as number (percentage).

Table VI: Pathologic response after neoadjuvant treatment in terms of receptor status

TPR	Receptor status, Frequency (%)								
	ER+ve	ER/HER-2+ve	HER-2+ve	ER/PR+ve	PR+ve	PR/HER-2+ve	TNBC	TPBC	Total
HR	7 (13.2)	3 (5.7)	5 (9.4)	13 (24.5)	0 (0.0)	0 (0.0)	22 (41.5)	3 (5.7)	53 (100)
Non-pCR	12 (12.6)	2 (2.1)	13 (13.7)	39 (41.1)	2 (2.1)	0 (0.0)	16 (16.8)	11 (11.6)	95 (100)
pCR	0 (0.0)	0 (0.0)	7 (33.3)	1 (4.8)	0 (0.0)	1 (4.8)	10 (47.6)	2 (9.5)	21(100)

TPR=total pathological response; HR=heterogeneous response; Non-pCR=pathologic non-complete response; pCR=pathologic complete response; ER=estrogen receptor, PR=progesterone receptor; HER-2=human epidermal growth factor receptor-2; TNBC=triple negative breast cancer, TPBC=triple positive breast cancer; +ve=positive. Values are presented as number (percentage).

Table VII: Univariate analysis of heterogeneous response by pre-treatment variables

Variable	Test Used	DF	P-value	Note
Histological type	Fishers exact	10	0.610	83.3% cells count <5
Grade	Fishers exact	2	0.017	33.3% cells count <5
T status	Fishers exact	8	0.617	68.2% cells count <5
Ki-67 Proliferative index	Fishers exact	2	0.710	33.3% cells count <5
Type of NAT	Fishers exact	2	0.032	66.7% cells count <5

df=degrees of freedom; p values obtained using univariate Fishers exact test; p <0.05 was considered statistically significant

cases belonged to hormone receptor +ve sub-type. This reflects that sub-type has an effect on tumor response to NAT. Statistically strong association was shown by (Fisher exact, p<0.001).

As shown in Figure II, in the non-pCR group, majority had neoadjuvant chemotherapy, while the patients with NAC and AIs treatment options, heterogeneous response comprised of n= 48, 29.8% and n=5, 71.4%. In the NAC group, patients who had pCR were n=19,11.8%. A small proportion of receiving aromatase inhibitors had complete pathologic response (n=2, 28.6%). A statistically significant association was found between pathologic response and NAT. Owing to small expected cell counts in several cells (66.7% <5), Fishers exact test was used (p = 0.005).

The association between pathologic response and histological type was evaluated. In the heterogeneous group, n=48 (90.6%) had IDC, n=2 (3.8%) ILC and one each case of IDC with DCIS, IDC with micro papillary features and IDC with squamous features was seen. Among Non-pCR group, n=86 (90.5%) belonged to IDC followed by n =3 (3.2%) ILC and n=2 (2.1%) IDC with mucinous features. IDC with DCIS and squamous features had one case. In the pCR group, maximum number of cases n=16 (76.2%) were having invasive ductal carcinoma, n=3 (14.3%) IDC with mucinous features. Few cases n=2 (9.5%) belonged to invasive lobular carcinoma. No case was reported in other types of breast cancer. In all the response groups Invasive ductal carcinoma was the most common type. Fisher exact test (p= 0.185) indicated no statistically strong association between cancer type and response. Heterogeneous response was most frequent in cases with Grade 2 (47.2%) and Grade 3 (50.9%). Only one case was reported in Grade I breast cancer. Non-pCR was also predominantly associated with Grade 2 (67.4%) and Grade 3 (31.6%) tumors. pCR rate was (71.4%) in Grade 2 and (28.6%) in Grade 3. Given small counts,

Table VIII: Post neo-adjuvant therapy histopathological features

Variable	Category	Frequency (%)
Histological type	Invasive ductal carcinoma (IDC)	112 (66.3)
	IDC with mucinous features	2 (1.2)
	Invasive lobular carcinoma	6 (3.6)
	Metaplastic carcinoma	3 (1.8)
	Metaplastic carcinoma with squamous features	1 (0.6)
Tumor Grade	Grade 1	2 (1.2)
	Grade 2	66 (39.1)
	Grade 3	56 (33.1)
Lymphovascular invasion	Present	37 (21.9)
	Absent	132 (78.1)
Ductal carcinoma in situ	Present	31 (18.3)
	Absent	139 (82.2)
Tumor size	Mean=3.051	-
Involved Axillary lymph nodes	Mean±Standard deviation 3.93±4.595	-
Size of largest nodal deposit	Mean±Standard deviation 0.925±1.17	-
Extra nodal extension	Present	68 (40.2)
	Absent	101 (59.8)

Table IX: Post-treatment association between breast pathologic response, caner type and residual tumor sizeles

Breast Pathologic Response	Histological Type [n (%)]		Tumor size [n (%)]		
	IDC	ILC	≤2cm	2.1-5cm	≥5cm
Partial	71 (91)	5 (6.4)	30 (38.5)	38 (48.7)	8 (10.3)
No response	41 (85.4)	1 (1.2)	3 (6.2)	21 (43.8)	24 (50.0)

IDC=invasive ductal carcinoma; ILC=invasive lobular carcinoma.Values are presented as number (percentage)

Table X: Association between post- nat breast pathologic response and tumor pathological features

Breast Pathologic Response	LVI [n (%)]		DCIS [n (%)]		Grade [n (%)]	
	Yes	No	Yes	No	2	3
Partial	15 (19.2)	63 (80.8)	20 (25.6)	58 (74.4)	46 (59.0)	28 (35.9)
No response	22 (45.8)	26 (54.2)	9 (18.8)	90 (81.2)	20 (41.7)	28 (58.3)

LVI = lymphovascular invasion; DCIS = ductal carcinoma in-situ. Values are presented as number (percentage)

Fisher exact test (p=0.088) did not show a statistically significant relation. Although a border line association was revealed. Across all response categories, maximum number of patients (55%) exhibited a high Ki-67 proliferative index, >25%. In the pCR group, 66.7% had high proliferative index, 28.6% had intermediate (10-25%) and 4.8% had low index (< 10 %). N-pCR, HR had 51.6% and 56.6% cases of high index respectively. Despite the descriptive trend suggested that a greater proportion of high proliferative index was associated with pCR, no association was obtained (Fishers exact, p=0.542).

Association of these factors were separately tested in heterogeneous group.Garde of the tumor and type of neoadjuvant therapy were found to have association with heterogeneous response, depicted in Table VII. We examined primary tumor and nodal pathological determinants post-operatively after completion of neo adjuvant therapy. Table VIII demonstrates frequency of each variable. There was absence of these features in complete response. IDC was the commonest breast cancer in both partial and no response categories. Majority of the cases of invasive lobular carcinoma had partial response. Metaplastic variety illustrated no response to NAT. Primary tumor with partial response comprised of most cases with grade 2, residual tumors of T2 and T1 along with presence of DCIS. Grade 3, T3 and presence of LVI were mostly associated with poor response shown in table IX and X. Perineural invasion was identified in 5 of 169 cases (2.9%), all of which showed either partial (n=2) or no pathologic response (n=3). No cases of complete response were reported. Dermo lymphovascular invasion was seen in 15 cases out of 169. Among patients with out DLVI (n= 154), 27.9% achieved complete response, while none with DLVI had complete response, most cases showed no response (66.7%) or partial response (33.3%).

Table XI shows that the presence of extra nodal extension and ypN2a-N3a, caused no nodal response in majority of cases. ypN1a contributed to a better response. A multinomial logistic regression analysis was conducted to evaluate predictors of pathologic response in breast and axilla (complete, partial or no response). The model demonstrated a statistically significant improvement over the intercept-only model (χ^2=230.404, df=20, p< 0.001), with a strong explanatory capacity (Nagelkerke R2=0.845). Key determinants of response included

Table XI: Association between post- nat nodal pathologic response and lymph node pathological features

Nodal Pathologic Response	Extra nodal extension [n (%)]		Nodal status [n (%)]		
	Yes	No	pN1	pN2	pN3
Partial	25 (43.1)	33 (56.9)	42 (72.4)	10 (17.2)	4 (6.9)
No response	43 (67.2)	21 (32.8)	21 (32.8)	25 (39.1)	18 (28.1)

Note: pN1=metastasis in 1-3 axillary lymph nodes; pN2a=metastasis in 4-9 axillary lymph nodes; pN3a=metastasis in 10 or more axillary lymph nodes or to infraclavicular nodes. Values are presented in number (percentage).

post-operative tumor size (p=0.010), type of breast cancer (p=0.006), presence of lymphovascuar invasion (p =0.023), presence of DCIS (p=0.007) and DLVI (0.001). Post operative grade was not a significant predictor (p= 0.885). Fisher exact test was used for PNI showing statistically not significant association (p=0.210). Number of involved lymph nodes was a strong predictor in both no and partial pathologic response in axilla (p=0.025 and 0.033), with higher node involvement increasing the odds of poor response. Extent of extra nodal extension (ENE) also showed a strong inverse association with response (p < 0.001). Size of largest nodal deposit and Pre-NAT nodal status were not found to be significant predictors of response.

Independent predictors of pathologic response in breast and axilla found on multinomial logistic regression test were separately examined in the heterogenous response group. The frequency of each variable reported was, residual tumor size (T0 [n=22, 41.5%], T1 [n=12, 22.6%, T2 [n=16, 30.2%], Tis [n=1, 1.9%]), LVI (present =13, 24.5%), DCIS (present=11, 20.8%), DLVI (present =4, 7.5%), ENE (present =22, 41.5%) and number of involved axillary lymph nodes (N0 [n = 24, 45.3%, N1a [n= 19, 35.8%, N1mi, micro-metastasis [n=2, 3.8%], N2a [n=7, 13.2%], N3a [n=1, 1.9%]).The preferred test choice to identify independent predictors was multinomial logistic regression, however given the small sub-group sizes, Fisher exact and Pearson chi-square test were used to evaluate association between variables. No significant statistical association was found. Residual tumor size (Fisher exact, p=0.421, df=5, 20% had expected count < 5), LVI (Pearson chi-square, p=0.576, df=1), DCIS (Pearson chi-square, p=0.490, df=1), DLVI (Fisher exact, p=0.77, df=1, 25% had expected count <5), Type of carcinoma (Fisher exact, p=0.895, df= 5, 66.7% had expected count <5), ENE (Pearson chi-square, p=0.820, df=1) and number of involved lymph nodes (Fisher exact, p=0.421, df=4, 20% cells had expected count <5).

DISCUSSION

In our single centre prospective study, we evaluated the heterogeneous pathological response of the primary breast tumor and axillary lymph nodes after receiving neoadjuvant therapy. We observed a notable rate of discordant responses, n=53 (31.4%). In this group, 45.3% (n=24) cases had a complete response in breast with either a partial or no response in the lymph nodes and vice versa. Additionally, a higher rate of complete nodal response (n=29, 54.7%) was noted in this group and overall. This discordance highlights the varying responsiveness of primary tumor and nodal disease. Such variations reflect underlying biological heterogeneity, differences in tumor niche and variable drug sensitivity between primary and nodal disease.[6]

A retrospective study performed by Fleming SC, et al., also showed discordance between response in breast and axillary lymph nodes. In their study, 15% cases had a complete pathologic response in the breast while still having persistently positive axillary lymph nodes.[6] Another study by Chen SC, et al., also revealed such discrepancy in responses between the two groups. 3.2% of patients achieved breast pCR with nodal non-pCR and 25.3% had nodal pCR with breast non-pCR, thereby supporting our study findings.[15]

In this study, we explored the biological characteristics of both tumor and nodal disease that contributed to heterogenous response and compared it with those achieving pCR and non-pCR. Both Receptor status and type of neoadjuvant therapy showed statistically significant association with heterogeneous and total pathological response. Overall Hormone receptor positive (including ER+ve, ER/HER-2+ve and Tripple positive) showed maximum cases of heterogenous response and non-pathologic complete response. Triple negative breast cancer contributed to second most cases, while it was also the sub-group with maximum number achieving pCR. Chen SC, et al., also reported hormone receptor positive breast cancer with maximum discordance in response in their study[15]

As most of the patients received neoadjuvant chemotherapy, 11.8% patients had complete and 29.8% showed discordant response. Notably Aromatase Inhibitors, though a small group when given as a primary therapy demonstrated 71.4% heterogenous response. In our study, Pre NAT tumor type, Ki-67 proliferative index, tumor size and nodal status did not impact heterogenous and total response significantly. Although literature shows association between response, breast cancer stage, tumor type and grade.[16,17] Grade had borderline association with total response mostly cases of Grade 2 showed a better response. Instead, tumor grade demonstrated a significant association with discordant response, there by highlighting a difference between response patterns. Patients in both HR and pCR groups demonstrated high proliferative index.

We also studied the post operative histological parameters after NAT related to responses in breast and axilla separately. Variables such as residual tumor size, type of breast cancer, presence of lymphovascuar invasion, ductal carcinoma in situ and dermo lymphovascular invasion were identified as independent predictors of response in the residual tumor while extra nodal disease and number of involved lymph nodes of nodal burden, but none proved to impact the heterogenous response. These differences in trends again point towards incongruent responses.

Invasive ductal carcinoma was the most common type of breast cancer. Our

study recognized poor response to neo adjuvant therapy in the less common types, like invasive lobular, metaplastic and invasive ductal carcinoma with micro papillary features. Residual tumor of more than 5cm mostly demonstrated poor response while less than 2cm markedly showed partial response in tumor cells. Lymphovascular invasion greatly affected the trend of poor response in primary tumor. 45.8% lead to no response. Takayoshi et al demonstrated in their study the association between LVI and chemo-resistance.[18] Presence of ductal carcinoma in situ and dermal lymphovascular invasion in addition to primary tumor reduced the chance of complete pathological response. We noted an increase in partial response among histological samples of DCIS and no response in DLVI. Eunju Shin et al reported residual DCIS may affect breast cancer outcome after NAT, particularly in terms of distant metastasis.[19] Another important factor having an impact on nodal response was extra nodal extension, producing no response in 67.2% cases. In a study performed by Karyn et al, ENE was found to be a strong predictor of non-sentinel node involvement.[20] No relation between size of the largest nodal deposit and nodal response was found. In early and operable breast cancer, nodal status is the key determinant of response to neoadjuvant treatment and also the worst prognostic predictor.[15] A complete response or decrease in nodal burden led to the concept of de-escalation in axillary surgery.[21] Such discrepancy in responses can lead to challenges in predicting residual nodal disease solely on the basis of primary tumor response. Even small nodal disease in the form of micro-metastasis can cause distant metastasis and affect disease free survival

Recommendation: Most studies on this topic have been retrospective and have not evaluated in particular the association of post NAT pathological variables with heterogeneous response. In future, more prospective studies with large cohorts should be performed to identify features responsible for discrepancy with modification of treatment options accordingly.

Limitations of the study

This study is constrained by small sample size and variability in pathological assessment. A larger sample size is required to evaluate the independent predictors in depth using standardized criteria and biomarker-driven approaches.

CONCLUSION

In conclusion, our study highlights the heterogeneous behavior of responses to neoadjuvant therapy between primary tumor and nodal disease in breast cancer. Thus, emphasizing on the need of comprehensive evaluation when planning surgical and adjuvant treatments.

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AUTHORS' CONTRIBUTION

The Following authors have made substantial contributions to the manuscript as under:

ZA: Conception and study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

ISA & MMK: Acquisition, analysis of data, drafting the manuscript, approval of the final version to be published

FS: Acquisition, analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be 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.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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