Assessment of Pathological Complete Response in Patients with Breast Cancer Receiving Neoadjuvant Systemic Therapy

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ABSTRACT

Objective: To quantify the rate of pathological complete response (PCR) in a tertiary care hospital in Pakistan, and to explore the association of pathological complete response with tumour histology, tumour grade, and histological subtype based on receptors.

Study Design: Descriptive study.

Place and Duration of Study: Combined Military Hospital, Rawalpindi, Pakistan from January 2016 to December 2018.

Methodology: Data for 110 patients was retrospectively extracted from the medical records for the last three years. Inclusion criteria comprised of patients with non-metastatic breast cancer staged as cT1- 4 N0-1-2 breast cancer who received neoadjuvant systemic therapy, and undergone subsequent surgical procedures and adjuvant treatment as required. Assessment of pathological response was performed on the final (surgical) histopathology specimen. Complete pathological response (PCR) was evaluated according to Austrian Breast and Colorectal Cancer Study Group, and Neo–Breast International Group criteria as no invasive cancer in the breast or nodes; noninvasive breast residuals allowed (ypT0/is ypN0).

Results: The mean age of the study group was 47.21±9.5 years with an age range of 27 – 68 years. Among 110 patients undergoing neoadjuvant systemic therapy and surgery, the rate of pathological complete response was found to be 27.2% (30/110). Univariate analysis showed that pathological complete response was significantly associated with age category, tumour grade, cancer subtype, lymphovascular invasion, and Trastuzumab administration. The occurrence of pathological complete response was significantly different among different cancer subtype groups, being highest (42.8%) among triple-negative cancer subtype, followed by HR-ve/Her+ve, HR+ve/Her+ve, and HR+ve/Her-ve (40.0%, 34.4%, and 13.0% respectively, p=0.022).

Conclusion: Achieving PCR after neoadjuvant chemotherapy is quite promising keeping into consideration that PCR a potential marker for progression-free survival and overall survival. Tumour grade, age of the patient, Her2 positive subtype, anti-Her2 directed therapy, and negative lymphovascular invasion are found to be potential predictors of complete pathological response.

Key Words: *Breast cancer, Chemotherapy, Neoadjuvant systemic therapy, Pathological complete response, Surgery.*

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INTRODUCTION

Breast cancer is one of the most common and frequently diagnosed cancers among women of all ages.[1,2] Global health estimates published by World Health Organization in 2013 stated that around 50% of all breast cancer cases occur in developed countries while 58% of all the deaths caused by breast cancer occur in developing countries.[3]

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High mortality rate in less developed countries like Pakistan is contributed to a lack of early cancer detection, which results in the advancement of cancer stage and a lack of proper diagnosis and treatment facilities.[4]Currently, Pakistan carries the highest incidence rate of breast cancer in Asia affecting every 1 in 9 women.[1,2]

Neoadjuvant systemic therapy given initially for locally advanced breast cancer has now taken a paradigm shift by its use in the treatment of early-stage breast cancer as well, especially with unfavorable tumour histology.[5]Advantages of neoadjuvant chemotherapy have been reported in terms of increasing resectability and breast conservation surgeries, decreasing a number of positive lymph nodes, and most importantly resulting in achieving pathological complete response (PCR) in breast and axilla.[6]

Literature depicts pathological complete response, following neoadjuvant systemic therapy, to be a potential surrogate

marker for progression-free survival and overall survival, especially in advanced tumours[7,8] but there also lies a disparity when it comes to breast tumours with favorable receptors therefore it is currently under debate.[9,10]

Keeping in view survival benefits, the aim of this study was to quantify the rate of pathological complete response (PCR) in a tertiary care hospital in Pakistan, and to explore the association of pathological complete response with tumour histology, tumour grade and histological subtype based on receptors.

METHODOLOGY

This retrospective descriptive study was conducted in the Department of Breast Surgery, Combined Military Hospital Rawalpindi from January 2016 to December 2018. The sample size required for this study was calculated by using the formula $n=z^2x(p)(1-p)/\alpha^2$ with 95% level of confidence, 80% study power and the prevalence of breast cancer in Pakistan was taken to be 0.069%.[4] Data for 110 patients with informed consent was retrospectively extracted from the medical records from January 2016 to December 2018 in which patients with non-metastatic breast cancer treated with neoadjuvant chemotherapy were included. The study was approved by the Institutional Review Board of the hospital, prior to data collection.

Patients' disease was appropriately staged after thorough investigations and a treatment plan was decided in a multidisciplinary meeting. Inclusion criteria comprised of patients staged as cT1- 4 N0-1-2 breast cancer, received neoadjuvant systemic therapy, and undergone subsequent surgical procedures and adjuvant treatment (radiation therapy, monoclonal antibody agents, or endocrine therapy) as required. Patients with inflammatory breast cancers, recurrent disease, or who had undergone excision biopsy were excluded from the study.

The diagnosis of invasive breast cancer was made on core biopsy and receptor status was determined thereafter. A staging workup was performed to exclude metastasis which included CECT chest, abdomen and pelvis, and bone scans. American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumour-node-metastasis (TNM) staging criteria (8th edition) were considered for staging the disease in these patients.

Standard chemotherapy protocols as per institutional policy were allowed including 1) Adriamycin, Cyclophosphamide (AC) x 4 cycles followed by paclitaxel for 12 cycles. 2) AC x 4 cycles followed by docetaxel x 4 cycles. The surgical procedures, performed 3-4 weeks after neoadjuvant chemotherapy, consisted of Modified Radical Mastectomy or Breast Conservation Surgery. Axillary dissection, included in both above-mentioned procedures, was performed up till level II/III. Patients who had undergone breast conservation surgery received mandatory adjuvant whole breast radiotherapy thereafter. Post-mastectomy radiation therapy was considered for the patients with high-risk factors decided by radiation-oncologist as per ASCO guidelines. Adjuvant endocrine therapy was administered to all patients with hormone receptor-positive tumours for 5 - 10 years. Patients with positive her2 neu status who received trastuzumab prior to surgery completed their one-year course of Her 2 directed therapy.

Assessment of pathological response was performed on the final (surgical) histopathology specimen by analyzing the treatment response of neoadjuvant chemotherapy in breast and lymph nodes commonly using Sat all off classification. Complete pathological response (PCR) was evaluated according to Austrian Breast and Colorectal Cancer Study Group, and Neo–Breast International Group criteria as no invasive cancer in the breast or nodes; noninvasive breast residuals allowed (ypT0/is ypN0).

Table I: Baseline demographic and clinical characteristics of study population (n=110).

Baseline characteristics	Frequency	Percentage
Age group		
Less than 40 years	30	27.3%
40 years and above	80	72.7%
Family history	21	19.1%
Tumour grade		
Grade II	95	86.4%
Grade III	15	13.6%
Tumour size		
T1	3	2.7%
T2	15	13.6%
T3	30	27.3%
T4 (including a,b,c sub stages)	62	56.4%
Lymph node involvement		
N0	24	21.8%
N1	71	64.5%
N2	15	13.6%
Tumour histology		
Invasive ductal carcinoma (IDCA)		
Invasive ductal + Ductal in-situ carcinoma (IDCA+DCIS)	65	59.1%
	42	38.2%
Invasive ductal carcinoma with no specific type (IDCA NST)	3	2.7%
Lymphovascular invasion	66	60.0%
Breast cancer subtype		
HR+ve/Her-ve	46	41.8%
HR+ve/Her+ve	32	29.1%
HR-ve/Her+ve	25	22.7%
HR-ve/Her-ve	7	6.4%
Chemotherapy drug class		
Anthracyclines	20	18.2%
Taxanes	9	8.2%
Antracyclines+Taxanes	81	73.6%
Trastuzumab	23	20.9%
Breast surgery		
Modified Radical Mastectomy	89	80.9%
Breast conservation surgery + axillary lymph node dissection	21	19.1%

Statistical analysis was performed by using IBM SPSS (version 23.0) software. Descriptive statistics were expressed as the mean and standard deviation for quantitative data, while frequency and percentages were used to express qualitative data. Group comparisons were made by using independent samples T-test or Chi-square test for quantitative and qualitative variables respectively. Multivariate analysis was performed via logistic regression where a pathological complete response was

considered as a dependent/outcome variable, to find a significant association of various demographic and clinical variables with the outcome variable. A two-sided p value of less than 0.05 was reported to be significant in this study.

RESULTS

Medical records of 110 female patients who had undergone neoadjuvant systemic therapy followed by surgery for non-metastatic breast cancer were considered for analysis in this study. The mean age of the study group was 47.21±9.5 years with an age range of 27 – 68. In terms of age groups, 30 (27.3%) patients belonged to the age group of less than 40 years, while the remaining 80 (72.7%) patients belonged to age group of 40 years or above. Baseline characteristics of the study group along with family history and cancer histology are mentioned in Table I.

Most of the patients (n=95, 86.4%) had grade II invasive carcinoma and remaining 15 (13.6%) had grade III carcinoma. Sixty-two (56.4%) patients had T4 tumour stage; while 30 (27.3%), 15 (13.6%), and 3 (2.7%) patients had tumour sizes belonging to T3, T2 and T1 stages respectively. Lymph node involvement of the N2 stage was present in 15 (13.6%) patients, N1 in 71 (64.5%) patients while 24 (21.8%) had N0 stage. Breast cancer subtypes based on receptor status showed that 46 (41.8%) patients were HR+ve/Her-ve, and 32 (29.1%) were HR+ve/Her+ve; while 25 (22.7%) and 7 (6.4%) patients were HR-ve/Her+ve and triple-negative respectively. All the patients underwent surgery after neoadjuvant chemotherapy, 89 (80.9%) patients had modified radical mastectomy whereas 21 (19.1%) had breast conservation surgery.

The rate of pathological complete response was found to be 27.2% (30/110). Univariate analysis showed that pathological complete response was significantly associated with age category, tumour grade, cancer subtype, lymphovascular invasion, and Trastuzumab administration as shown in Table II. The higher number of patients belonging to the age group of more than 40 years were found to have better PCR rates as compared to the age group of less than 40 years (33.8 *vs.* 10.0%, p=0.013), while grade III tumours had a greater PCR rate as compared to grade II tumours (73.3% *vs.* 20.0%, p<0.001). Similarly, the occurrence of pathological complete response was significantly different among different cancer subtype groups, being highest (42.8%) among triple-negative cancer subtype, followed by HR-ve/Her+ve, HR+ve/Her+ve and HR+ve/Her-ve (40.0%, 34.4%, and 13.0% respectively, p=0.022). Patients with positive lymphovascular invasion experienced a lower rate of PCR as compared to patients with negative lymphovascular invasion (13.6% *vs.* 36.4%, p=0.009). Similarly, Trastuzumab administration was found to be associated with the higher PCR response rate (56.5% *vs.* 19.5%, p<0.001).

Multivariate analysis revealed the age of the patient and tumour grade to be potential predictors of pathological complete response. With a one-unit increase in the age of the patient, the chances of achieving PCR rate increased by 1.10 times (OR=1.10, 95% CI 1.01 – 1.287, p=0.018). Patients with grade III tumour were 9.98 times more likely to achieve a pathological complete response as compared to patients with grade II tumour (OR=9.98, 95% CI 2.49 – 39.9, p=0.001).

Table II: Association of pathological complete response with clinic pathological variables.

Clinicopathological variables	Pathological Complete Response		p-value
	No (n=80)	Yes (n=30)	
Age category			
Less than 40 years	27 (90.0%)	3 (10.0%)	0.013
40 years and above	53 (66.3%)	27 (33.8%)	
Tumour grade			
Grade II	76 (80.0%)	19 (20.0%)	<0.001
Grade III	4 (26.7%)	11 (73.3%)	
Cancer subtype			
HR+ve/Her-ve	40 (87.0%)	6 (13.0%)	
HR+ve/Her+ve	21 (65.6%)	11 (34.4%)	0.022
HR-ve/Her+ve	15 (60.0%)	10 (40.0%)	
HR-ve/Her-ve	4 (57.1%)	3 (42.8%)	
Trastuzumab administration			
No	70 (80.5%)	17 (19.5%)	<0.001
Yes	10 (43.5%)	13 (56.5%)	
Lymphovascular invasion			
Positive	38 (86.4%)	6 (13.6%)	0.009
Negative	42 (63.6%)	24 (36.4%)	
Surgery type			
MRM			
Breast-conserving surgery + axillary lymph node dissection	71 (79.8%) 9 (42.9%)	18 (20.2%) 12 (57.1%)	0.001

DISCUSSION

In this study, the authors have reported the rate of complete pathological response among breast cancer patients undergoing neoadjuvant chemotherapy followed by surgery at a tertiary care hospital in Pakistan. The rate of complete pathological response was reported to be 27.2% (30/110), which is quite similar to some studies, while a little bit higher than many others. Spring *et al.* reported a complete pathological response rate of 31.7% among 53 patients out of 170.[11] LeVasseur *et al*. reported that 74 patients out of 267 achieved PCR (28.0%).[12] Groots *et al.* reported a PCR rate of 20.5% in 420 breast cancer patients out of a total of 2046.[13] A study conducted in Iran by Sasanpour *et al.*, reported a quite higher PCR rate of 39.2% which might be attributable to the higher percentage of ER/PR negative patients in the study group.[14]

An inverse association has been reported by various clinical studies between positive hormone status and PCR rate and also in results of the current study. A meta-analysis conducted by Houssami *et al.,* included 11,695 cases from 30 high-quality studies, and reported the highest odds of achieving PCR among triple-negative subtype patients.[15] Similarly, another meta-analysis conducted by Wu *et al.,* also reported a higher PCR rate among such patients.[16]

This study supports the biological standpoint that ER/PR positive and Her negative patients are relatively less likely to

achieve a higher PCR rate, as 13.0% of such patients are reported to achieve PCR in the present study. Similarly, other studies also reported a lower PCR rate among such patients supporting the fact that such tumours are generally found to be resistant to chemotherapy but have more favorable outcomes in general and thus efforts should be focused on other treatment options and possible ways to overcome chemotherapy resistance.[17,18] On the other hand, the present results showed a remarkable PCR rate among breast cancer patients of triple-negative subtype *i.e*. 42.8%, supports the fact that tumours with high proliferation rate like triple-negative breast cancers respond well to chemotherapy as chemotherapy targets rapidly dividing cells the most. Similar results were reported by Yao *et al.* and Xu *et al.* in their research studies which is indeed reassuring considering the aggressive biology of such tumours.[19,20] However, considering a small number of patients of this subgroup in this study, it is difficult to draw a strong conclusion making it a limitation of this study.

Results of the current study showed that breast cancer patients with high tumour grade, hormone receptor-negative tumours are more likely to achieve a complete pathological response. Similar results had been reported by Spring *et al.* where the author has reported 47.3% PCR rate among Her2 positive patients and 39.6% in triple-negative breast cancer subtype.[11] Groots *et al*. reported that high tumour grade (p=0.001), positive Her status (p<0.001), and negative ER/PR status (p<0.001) were significant predictors of achieving a high PCR rate,[13] which are quite similar to what the authors have found in univariate analysis of the current study. The PCR rate among Her positive patients in this study is reported to be 34.4% and 40.0% with HR-positive and negative status respectively, whereas Groots *et al.* reported an overall PCR rate of 35.6% among Her positive patients.[13] Hormone negative Her 2 positive tumours may not achieve remarkable pathological response as the response of anti Her2 directed therapy is not uniform and a proportion of HER2-positive patients do not respond. Studies have reported discordance of Her2 status between the pre-treatment biopsy and the post-treatment surgical specimen. Loss of HER2-positivity in the residual tumour has been reported to be associated with a poorer outcome compared to tumours that remain HER2--positive following neoadjuvant treatment.[21] Existence of intratumoral heterogeneity in breast cancers also contributes to chemotherapy resistance.

Many studies have reported a significant association of tumour size with PCR rate but the current study failed to demonstrate any such association, which might be due to the difference in tumour sizes of this study population as compared to other studies.

No significant association of the type of surgery chosen and lymph node status was found with PCR in this study, results of which are comparable with other studies. Fayanju *et al*. also reported that achieving pCR in both breast and axilla is driven by the response to neoadjuvant chemotherapy rather than presenting clinical node (cN) stage.[24]

Other potential predictor variables for achieving a good PCR rate, identified in the results of this study, include lymphovascular invasion as patients with no such invasion had a better PCR rate, anti-HER2 directed therapy as patients who were administered the drug Trastuzumab had a relatively better PCR rate, and lastly age as patients belonging to age more than 40 years had a better response rate. Others also reported similar predictor variables associated with a better PCR rate including HER2+/HR– and triple-negative cancer subtype, higher tumour grade, higher age, Trastuzumab administration, and no lymphovascular invasion.[14,15,22,23]

CONCLUSION

Achieving PCR after neoadjuvant chemotherapy is quite promising keeping into consideration that PCR a potential marker for progression-free survival and overall survival. Tumour grade, age of the patient, Her2 +/HR -ve subtype, anti-Her2 directed therapy, and negative lymphovascular invasion are found to be potential predictors of complete pathological response.

ETHICAL APPROVAL:

Ethical approvals were obtained from the 'Ethical Committee / Institutional Review Board Combined Military Hospital Rawalpindi' prior to initiation of the research work.

PATIENTS' CONSENT:

Informed consent was obtained to publish the data from the patients prior to data collection.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

NF: Conception of work along with data collection, analysis, interpretation, and drafting of the final document.
RB, SRQN: Contributed to conception and design of work and reviewed the content critically for final approval.
HL: Contributed to data collection and drafting of the document for final approval.
All authors took complete responsibility and accountability for all aspects of the work.

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