

# Determination of Tumor Pathological Response in Post-Neoadjuvant Chemotherapy Breast Carcinoma Resection Specimens

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### ABSTRACT

**Objective:** To determine the tumor pathological response in post-neoadjuvant chemotherapy resected breast carcinoma specimens.

**Methodology:** It was a cross-sectional study conducted in the Department of Histopathology, Shifa International Hospital (SIH), Islamabad from 1<sup>st</sup> October 2014 to 30<sup>th</sup> April 2016. The study was approved by the Hospital ethics committee. All formalin fixed resection specimens with or without axillary lymph nodes dissection (ALND) were processed according to the standardized grossing techniques. Slides were prepared from the tissue blocks. Previous biopsies were reviewed for assessment of neoadjuvant chemotherapy (NACT) response using Pinder et al. system for pathological response.<sup>1,2</sup> Results were verified by another consultant histopathologist. The statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 24.0.

**Results:** A total of 77 previously diagnosed patients who received NACT were analyzed. Seventy five (97.4%) cases underwent modified radical mastectomy (MRM) with ALND and 2(2.6%) cases had a lumpectomy with ALND. All of the cases were females. The age range was 26-75 years (48.55±11.66 years). Clinical/radiological tumor size was 1.1 to 16.0 cm (4.68±2.63 cm). Invasive mammary carcinoma of no special type was the commonest tumor type and was seen in 73(94.8%) cases. Most of the cases of invasive mammary carcinoma of no special type 53(72.6%) showed partial response while 10(13.7%) cases had complete pathological response (cPR) and 10(13.7%) had no response. Post-NACT tumor histological grade I was identified in 2 cases (3.0%), grade II in 46 cases (68.6%) and grade III in 19 cases (28.4%). Post-NACT grade could not be assessed in 10 cases due to cPR. In MRM specimen after NACT, there was no residual tumor in 11(14.3%) cases and no significant decrease in cellularity in 9(11.7%). Tumor cellularity of <10% partial pathological response (pPR) was noticed in 15(19.5%), 10-50% cellularity (pPR) in 19(24.7%) of cases and >50% of cellularity (pPR) in 22(28.5%) cases. No evidence of metastatic disease and no evidence of response in lymph nodes (LN) was seen in 14 cases (18.2%) while 27 cases (35%) had the metastatic disease but no evidence of response. In 11 cases (14.3%), no metastatic tumor was present, however, histological features of NACT response were observed. Rest of 25 cases (32.5%) had metastatic carcinoma along with the evidence of response.

**Conclusion:** Breast carcinoma showed a good response to neoadjuvant chemotherapy with the majority of the cases showing partial pathological response in both breast and lymph nodes. The response in both breast and lymph nodes was not found to be related to age or histologic grade. Invasive mammary carcinoma of no special type was the commonest tumor with the majority of cases showing grade II category of tumor.

**Keywords:** Breast carcinoma. Lymph node. Neoadjuvant chemotherapy. Pathological response.

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### INTRODUCTION

Breast carcinoma is the most common cancer in women with an incidence of 23% and 27% of all cancers in developed and underdeveloped world respectively.<sup>3</sup> The commonest histological types of breast cancer include invasive mammary carcinoma of no special type (IMC, NST) and invasive lobular carcinoma (ILC). In Pakistan, it is more common at a younger age contrary to the West where it is more common after 60 years. Approximately one in every nine Pakistani women is likely to suffer from breast cancer and show an incidence rate of 50/100,000. This is one of the highest incidence rates in Asia.<sup>4</sup> Breast cancer is being managed increasingly by

neoadjuvant chemotherapy (NACT) which means that breast cancer patients will receive chemotherapy for down staging the disease before surgical excision of the tumor with the probability of breast conserving surgery (BCS) in selected patients. Survival correlates with the response of primary breast carcinoma to NACT. The response can vary from complete to no response both clinically and microscopically on histopathology. Patients achieving a complete pathological response are reported to have significantly improved disease-free survival and overall survival rate. Accurate and standardized evaluation of invasive carcinoma is mandatory prior to initiation of therapy. Clinical and radiological information followed by biopsies of the main carcinoma in breast and suspicious lymph nodes (LN) is performed.<sup>5</sup>

Pathologic assessment of the final surgical resection specimen is still the gold standard for determining a cPR since 60-80% cases with apparent complete clinical response have the residual tumor in resection specimen.<sup>5</sup> Two commonly used systems for documenting post-NACT response in breast carcinoma are Miller-Payne and Pinder et al. Miller-Payne system described post-NACT response changes only in breast

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Received: October 20, 2018; Accepted: December 10, 2018

resection specimens while Pinder et al. system also addressed changes observed in LN after NACT.<sup>6</sup> Response correct to NACT include a spectrum of morphologic changes in the main tumor and LN i.e. from cPR or partial regression to no response. The cPR is defined as no residual tumor or presence of ductal carcinoma in situ (DCIS) with no invasive component plus no residual LN metastasis while no response refers to persistent tumor cells with no treatment changes. The pPR means the presence of the scattered individual or small clusters of tumor cells in the desmoplastic stroma.<sup>7,8</sup> Assessment of tumor cellularity post-NACT is somewhat subjective. Presence of ductal carcinoma in situ (DCIS) has to be mentioned. However, it is not clinically significant if surgical margins are clear.<sup>6</sup> There is no published national study available on tumor pathological response in post-NACT breast resection specimens. This study will help us to evaluate the differences of tumor pathological response in our population as compared to developed countries.

**METHODOLOGY**

It was a cross-sectional study conducted in the Department of Histopathology, Shifa International Hospital (SIH), Islamabad from 1<sup>st</sup> October 2014 to 30<sup>th</sup> April 2016. The study was approved by the Hospital ethics committee. A total of 77 formalin-fixed breast resection specimens with or without axillary lymph nodes (ALND) from diagnosed patients of breast carcinoma who received NACT were analyzed. The specimens were processed according to the standardized grossing techniques. Slides were prepared from the tissue blocks. Previous biopsies were reviewed for assessment of NACT response using Pinder et al. system for pathological response.<sup>1,2</sup> Results were verified by another consultant histopathologist.

**STATISTICAL ANALYSIS**

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 24.0.

Mean and the standard deviation (SD) were calculated for quantitative variables like patient age and clinical size. Frequencies and percentages were calculated for qualitative variables like tumor cellularity, grade of tumor and pathological response in the main specimen and axillary lymph nodes (ALND).

**RESULTS**

A total of 77 previously diagnosed patients who received NACT were analyzed. Seventy five (97.4%) cases underwent MRM with ALND and 2(2.6%) cases had a lumpectomy with ALND. All of the cases were females. The mean age of patients was 48.55±11.66 years with the age range of 26-75 years.

Pre-NACT clinical/radiological tumor size range was 1.1 to 16.0 cm (mean 4.68±2.64). Differences observed between pre-NACT and post-NACT tumor size elaborating pathological response are illustrated in table 2.

Invasive mammary carcinoma of no special type was the commonest tumor type and was seen in 73(94.8%) cases. One (1.33%) of these cases in addition, showed mixed mucinous and micropapillary morphology while one case (1.33%) showed apocrine differentiation. Most of the cases of invasive mammary carcinoma of no special type i.e. 53(72.6%) cases showed partial response while 10(13.7%) cases had cPR and 10(13.7%) had no response. These results are shown in table 3.

Pre-NACT tumor histological grade I was seen in 3(3.9%) cases, grade II in 59(76.6%) cases and grade III in 15(19.5%) cases. Post-NACT tumor histological grade I was identified in 2(3.0%) cases, grade II in 46(68.6%) cases and grade III in 19(28.4%) cases. Post-NACT grade could not be assessed in 10 cases due to cPR. The pathological response in post-NACT MRM specimen in terms of tumor cellularity is illustrated in figure 1. Lymphovascular invasion was identified in 57(74%) cases and not identified in 20(26%) cases. The pathological response in post-NACT lymph nodes is elaborated in figure 2.

**Table 1: Pinder et al. System for Pathological Response**

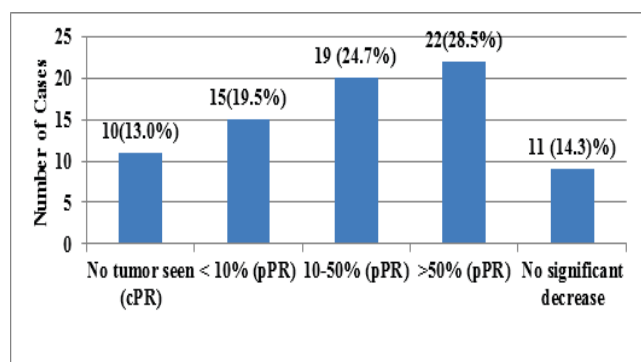
Breast Specimen	
a	Complete pathologic response, either no residual carcinoma or no residual invasive tumor but ductal carcinoma in-situ present.
b	Partial response to therapy, either (i) minimal residual disease/near total effect (e.g. < 10% of tumor remaining) or (ii) evidence of response to therapy but with 10-50% of tumor remaining or (iii) > 50% of tumor cellularity remains evident, when compared with the previous core biopsy sample, although some features of response to therapy present.
c	No evidence of response to therapy
Lymph nodes	
a	No evidence of metastatic disease and no evidence of changes in the lymph nodes
b	Metastatic tumor not detected but evidence of response/down-staging, e.g. fibrosis
c	Metastatic disease present but also evidence of response, such as nodal fibrosis
d	Metastatic disease present with no evidence of response to therapy

**Table 2: Comparison of Pre and Post-NACT Tumor Size (n=77)**

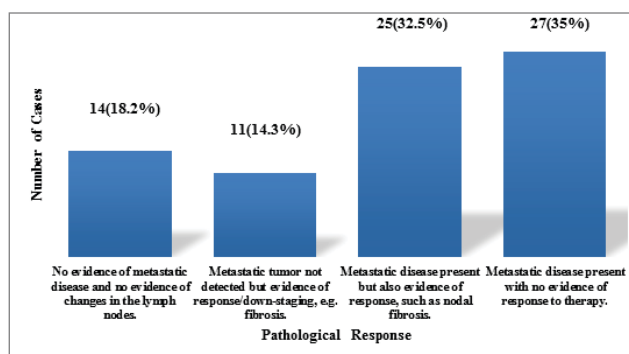
Pretreatment Tumor Size & Number of Cases		Post-NACT Tumor Size			
Tumor Size	Number of Cases	< 2 cm	2 - 5 cm	> 5 cm	No evidence of residual carcinoma
<2 cm	6	4	1	0	1
2 - 5 cm	46	9	31	3	3
> 5 cm	25	7	3	9	6
Total	77	20	35	12	10

**Table 3: Pathological Response in Breast Specimen according to Histological Tumor Type (n=77)**

Histological Tumor Type	Complete Pathological Response	Partial Pathological Response, <10%	Partial Pathological Response, 10-50%	Partial Pathological Response, >50%	No response	p-Value
Invasive mammary carcinoma of no special type	10(13.7%)	15(28.3%)	18(34.0%)	20(37.7%)	10(13.7%)	<b>0.586</b>
Invasive lobular carcinoma	0 (0%)	0 (0%)	0 (0%)	1(4.5%)	0 (0%)	
Invasive mammary carcinoma of no special type with apocrine differentiation	0 (0%)	0 (0%)	1(5.3%)	0 (0%)	0 (0%)	
Invasive mammary carcinoma of no special type with mixed mucinous and micropapillary morphology	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1(3.1%)	
Metaplastic carcinoma with mesenchymal (chondroid) differentiation	0 (0%)	0 (0%)	0 (0%)	1(4.5%)	0 (0%)	



**Figure 1: Post-NACT Tumor Cellularity & Pathological Response in Breast Specimen (n=77)**



**Figure 2: Pathological Response in Lymph Nodes (n=77)**

**DISCUSSION**

In this study, 75(97.4%) patients underwent MRM with ALND and 2(2.6%) patients had a lumpectomy with ALND. The most likely reason of majority of cases which underwent MRM is a late presentation with locally advanced disease. Ibarra et al. evaluated 18 partial mastectomies and 22 MRM specimens.<sup>15</sup> A study conducted at King Fahad Medical City, Riyadh by Iqbal et al. included 40 MRM and 14 BCS along with ALND in all cases.<sup>8</sup>

During a survey of the literature, it was found that several studies which analyzed post-NACT changes

included females like in this study.<sup>1,9</sup> The age range of patients was 26-75 years in this study with the majority of being more than 40 years (72.7%) of age. Various studies have observed post-NACT effects in the age group 26 to 78 years.<sup>8,10</sup> A study published in 2014 has evaluated 54 patients with 38 patients being more than 40 years of age.<sup>8</sup>

This study had 10 cases with cPR and out of these 7 were above 40 years. Similarly, 46 cases out of 60 cases with the partial response of variable degree were above 40 years. Patients with no response to therapy were 11 and out of these, 7 were above 40 years. Keeping in

view that the majority of luminal type A breast carcinoma is observed in older women while HER2/Neu triple negative and luminal type B are noticed in younger women, age carries substantial weight.<sup>3</sup> A lot of current published literature has evaluated breast carcinoma molecular subtype against NACT response.<sup>1,11,12</sup> The difference in response in our cases might be due to the difference in molecular subtype which was not evaluated in this study.

As evidenced from the literature review, residual tumor size measurement is essential for precise estimation of response to NACT.<sup>13</sup> Corben et al. reported a mean reduction in tumor size.<sup>1</sup> Alvarado-Cabrero and his colleague observed reduction in tumor size in 60% of their total cases with 16 patients showing cPR.<sup>14</sup> Sethi et al. and Gharbi et al. mentioned 47% and 50% of their patients with a decrease in tumor sizes respectively.<sup>7,10</sup>

In the current study, a total of 29 cases (37.6%) showed downstaging after NACT. The current study had only 25(32.5%) tumors of more than 5 cm but these responded quite well to NACT in comparison with tumors of smaller pre-NACT size. Invasive mammary carcinoma of no special type was the commonest tumor type in this study and was seen in 73(94.8%) cases. One (1.33%) of our cases showed mixed mucinous and micropapillary morphology while one case (1.33%) showed apocrine differentiation. In an Asian study by Iqbal et al. 50(92.6%) cases had invasive mammary carcinoma of no special type.<sup>8</sup> Corben et al. in 2013 evaluated 54 cases of invasive mammary carcinoma of no special type in their study.<sup>1</sup> An Indian study also conducted in 2013 had invasive mammary carcinoma of no special type as the commonest tumor type.<sup>7</sup> In a study by Ibarra et al. histologic tumor type included 31 cases of invasive mammary carcinoma of no special type, 8 cases of invasive lobular carcinoma (ILC) and 1 case of mixed invasive carcinoma of no special type and ILC.<sup>15</sup> Another study conducted by Sullivan et al. in 2009 showed 40 cases of invasive mammary carcinoma of no special type and 9 of ILC.<sup>16</sup> Hence invasive mammary carcinoma of no special type remained the commonest tumor in the literature review and matched with results of this study.

In numerous studies, it has been published that invasive mammary carcinoma of no special type responded better than ILC carcinoma as well as metaplastic carcinoma.<sup>3,16,17</sup> In this study, majority (73) cases were of invasive mammary carcinoma of no special type while there was only 1(1.3%) case each of ILC and metaplastic carcinoma. The latter tumors showed >50% residual tumor cellularity after NACT concurring with poor response to therapy.

Histologic grading of breast carcinoma is one of the important prognostic markers so pre-NACT biopsy tumor grading should be reviewed before assuming that

present findings are due to therapy.<sup>11,18-20</sup> In our study, grade II was the commonest (76.6%) followed by grade III (19.5%) tumor. Gharbi et al. observed 60% cases of histological grade II and 18% cases of grade I as well as grade III.<sup>10</sup> Iqbal et al. in a recently conducted study documented grade II in 55.6% cases and grade III in 44.4% cases.<sup>8</sup> In an older study by Moreno et al., grade II remained highest (66.4%) followed by grade III (20.1%) and grade I (6.9%).<sup>21</sup>

According to the literature, high-grade tumors responded well to NACT and were more likely to show pPR as compared to low-grade tumors.<sup>1,19,22,23</sup> In the current study, 20 cases with histologic grade II and 1 case of grade I showed a response. However, the majority of cases had no change in tumor histologic grade. Due to cytomorphologic changes post-NACT, tumor grade may increase in 1/3rd cases unit. Some studies reported an increase in nuclear grade in one-third of the cases.<sup>24,25</sup> Similarly, an increase of histologic grade in 4 cases to grade III was seen in the current study and this might be either due to limited pre-NACT sample or therapy-related cytomorphologic changes. Tumor cellularity does not relate to tumor size due to its heterogeneity.

Tumor cellularity may decrease significantly but a minimal decrease in the size of the tumor is seen in few cases. Combined assessment of tumor size and cellularity may provide more accurate measure of pathologic response.<sup>5</sup> Tumor cellularity results of this study showed that the majority of cases (28.5%) had evident cellularity of > 50%. Reduction of cellularity to <10% was seen in 19.5% cases which is similar to results of a study by Frierson et al.<sup>26</sup> Rajan et al. documented 75% reduction in cellularity in post-NACT resection specimens compared to pre-NACT core biopsy.<sup>5</sup> This study had no residual tumor in 13% of cases and 10-50% residual tumor cellularity in 24.7% cases. Additional 14.3% of cases had no significant decrease in tumor cellularity.

In two student the NACT treated patients showed cPR in around 30% cases or less.<sup>9,10</sup> The MRM specimens showed 13% cases with cPR which is close to the results of National Surgical Adjuvant Breast and Bowel Project (NSABP B18 trial) results as well as two other prospective studies findings conducted in this context. Studies conducted by Sethi et al. and Mazouni et al. had results of 20% and 3.4% cPR respectively.<sup>7,27</sup> The results of the study by Cianfrocca et al. however, showed a significant difference in cPR with results reaching up to 41.2%.<sup>19</sup> This variation in cPR rates is probably related to variability in sample size. Larger sample size studies had lower cPR and vice versa.

In this study, the partial pathological response in breast specimen was present in 72.7% of cases. Vast variation in response rate was noticed when compared with other

studies. Gharbi et al. and Ibarra et al. had their results close to the results of this study.<sup>10,15</sup> Results of studies conducted by Sethi et al., Iqbal et al., Kim et al. and ElBakary et al. had lower partial pathological response of 37.5%, 25.9%, 56% and 51.5% respectively.<sup>7,8,25,28</sup>

Cases of partial pathological response in lymph nodes of the current study were 67.5% which showed a marked difference compared to findings of Sethi et al. (37.5%).<sup>8</sup> About 68% of cases in this study showed the residual tumor in LN after NACT which is close to the results of Gharbi et al. who had positive LN in 78% cases.<sup>10</sup> General pathological response to therapy with or without metastatic deposit was present in 32.5% of the cases in this study. This is relatively slightly higher than the results seen in studies of Moreno et al. and Newman et al. with responses of 28.6% and 26.8% respectively.<sup>21,29</sup>

A significant number of cases (14.3%) in this study had no pathological response. Sethi et al. observed no response in 42.5% of cases of breast carcinoma and this difference might be due to a smaller sample size of only 40 cases.<sup>7</sup>

### CONCLUSION

Breast carcinoma showed a good response to neoadjuvant chemotherapy with the majority of the cases of partial pathological response in both breast and lymph nodes. The response in both breast and lymph nodes was not found to be related to age or histologic grade. Invasive mammary carcinoma of no special type was the commonest tumor with more tumors in grade II category.

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