

Assessment of Histopathological response to neoadjuvant chemotherapy in breast cancer patients undergoing mastectomy at a tertiary care hospital in pakistan.

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Abstract

Objective; To assess histopathological response to neoadjuvant chemotherapy in breast cancer patients undergoing mastectomy at a tertiary care hospital.

Material and Methods; Histopathological features were assessed for a total of 39 breast carcinoma cases post-therapy. Statistical analysis was done using IBM SPSS statistics 17 (Chicago, USA). Presence of viable tumor cells was checked.

Results; The results of the present study revealed that only 6 out of 39 breast carcinoma cases showed complete response to chemotherapy (ie absence of cancer cells completely). Intracellular changes commonly noted after chemotherapy included nuclear enlargement, hyperchromasia and an increased N:C ratio which were found in upto 85% of the cases followed by presence of prominent nucleoli and karyorrhexis/karyolysis. The predominant stromal changes seen post-therapy included necrosis (74.4%), fibrosis (64.1%), desmoplasia (59%) and degenerative changes (33.3%).

Conclusion; Our study concludes that majority of breast cancer patients showed no or minimal response to neoadjuvant chemotherapy. Only 15% patients showed complete response to chemotherapy in our population group while in western world, this percentage is around 50-60%. This shows different population groups respond differently to chemotherapy in breast cancer and management options should be revisited in each different population group.

Introduction

Breast cancer is the most common malignancy among women worldwide, accounting for approximately 25% of all female cancers. It remains a leading

cause of cancer-related mortality globally, with significant geographical variation in incidence and outcomes. Developed regions tend to have higher incidence rates due to lifestyle factors, genetic predisposition, and advanced screening programs, while mortality rates are higher in low- and middle income countries due to late diagnosis and limited access to treatment.

Neoadjuvant chemotherapy has been thought of playing a vital role in modern breast cancer management, particularly in aggressive subtypes and advanced stages. Its epidemiological significance reflects its ability to improve surgical outcomes, assess tumor biology, and enhance long-term survival, underscoring the need for equitable access to this therapeutic approach globally.

Neoadjuvant chemotherapy (NAC) has become an essential component of breast cancer management, particularly for locally advanced and aggressive subtypes. Administered before surgery, NAC aims to reduce tumor size, enable breast-conserving surgery, and provide early systemic treatment for micrometastatic disease. Additionally, it allows for the assessment of tumor chemosensitivity, offering valuable prognostic information based on pathological response.

The assessment of histopathological response to neoadjuvant chemotherapy (NAC) in breast cancer patients undergoing mastectomy is essential for evaluating treatment efficacy and predicting prognosis. A strong pathological response to NAC is associated with improved outcomes, including recurrence-free survival (RFS) and overall survival (OS). This evaluation also guides treatment planning by determining the need for additional adjuvant therapies and providing insight into the tumor's chemosensitivity and

biological behavior.

Several systems are commonly used to classify and quantify histopathological responses. The Residual Cancer Burden (RCB) index, for instance, evaluates the extent of residual disease by considering the size of the primary tumor, cellular composition, and lymph node involvement, categorizing responses into RCB-0 (pathological complete response, pCR) to RCB-III. The Miller-Payne grading system assesses the percentage reduction in tumor cellularity, ranging from Grade 1 (no reduction) to Grade 5 (complete regression). Other grading methods, such as the Chevallier and Sataloff systems, focus on the presence or absence of invasive cancer in the breast and lymph nodes, while the AJCC ypTNM staging provides a pathological staging post-NAC based on tumor size (ypT), nodal involvement (ypN), and metastases (M).

This assessment has significant clinical implications. Patients achieving pCR often have the best prognosis, while partial responders may require tailored adjuvant therapies. For non-responders, alternative therapeutic strategies or clinical trial participation may be necessary. The evaluation of histopathological response not only helps in understanding treatment efficacy but also supports individualized patient care.

Material and Methods

This study included 39 patients with locally advanced breast cancer characterized by axillary lymph node involvement and no evidence of distant metastasis. Patients with a history of prior lumpectomy were excluded. Breast carcinoma diagnosis was confirmed in all patients through cytology or trucut biopsy. Before starting chemotherapy, clinical data and the tumor's pretherapeutic size were recorded. Tumor

grading was performed on cytology smears or trucut biopsy sections, with histological grading based on the Bloom-Richardson system and cytological grading using Robinson's method.

Patients received three courses of paclitaxel-based chemotherapy, including adriamycin, cyclophosphamide, and paclitaxel, followed by modified radical mastectomy (MRM) with axillary lymph node dissection. Postchemotherapy changes were analyzed using MRM specimens. Tumor tissues were studied from paraffin embedded H&E-stained sections derived from the tumor bed. For complete responders, the tumor bed was identified by sampling fibrotic areas extensively. For partial and nonresponders, the tumor was identified grossly or microscopically, and comprehensive sampling was conducted. Tumor grade, histological type, and response to chemotherapy were assessed using Chevallier's method. Data entry was done using SPSS version 23 for analysis of study variables.

Results

This study included 39 cases of breast carcinoma, with a median patient age of 55 years. The most common presenting symptom was a palpable lump in the affected breast, followed by mastalgia (38.5%), nipple discharge, and ulceration. The right breast was more frequently involved (66.7%), with the upper outer quadrant being the most common tumor location (74.4%), followed by the upper inner quadrant (8%). In 13% of cases, more than one quadrant was affected. Most patients (69%) received four to six cycles of neoadjuvant chemotherapy, while 31% underwent more than six cycles. The most commonly administered regimen was AC (doxorubicin and cyclophosphamide followed by paclitaxel) in 26 cases (64.1%), followed by CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) in 8 cases (20.5%), and CEF

(cyclophosphamide, epirubicin, and 5-fluorouracil) in 6 cases (15.4%).

The average tumor size decreased only minimally from 3.75 cm before chemotherapy to 3 cm afterward ($p < 0.001$), reflecting poor response to following treatment. Stage II breast carcinoma was the most prevalent (61.5%), with stage IIA accounting for 38.5% of cases, while 23% of patients presented with stage III disease. Younger women were observed to have more aggressive disease, predominantly at stage III. The most common histological type was infiltrating ductal carcinoma—not otherwise specified (IDC-NOS), comprising 94.87% of cases before therapy and 76.92% after therapy. Rare cases included one instance each of lobular carcinoma and metaplastic carcinoma.

Tumor grade changed (increased) in 32 of the 39 cases, ($p < 0.05$).

Pathologic complete response (pCR) was observed in 15% of cases only and 85% had no response to chemotherapy. Common intracellular changes included nuclear enlargement, hyperchromasia, and an increased nuclear-to-cytoplasmic (N:C) ratio, observed in 85% of cases. Other changes, such as prominent nucleoli and karyorrhexis/karyolysis, were noted in 70–75% of cases.

Discussion

Neoadjuvant chemotherapy induces variable morphologic changes in breast carcinoma cells and surrounding stromal tissue. This study analyzed the histopathologic changes in a series of 39 breast cancer cases before and after therapy, correlating clinical and histopathologic findings. Breast cancer, the second most common cancer globally, accounts for approximately 7% of the global burden, with its incidence increasing with age. The median age of patients in this study was 55 years, contrasting with studies by Sethi et al. and Faneyte et al., which reported median ages of 46 and 45 years, respectively.^{1,2}

The most common presenting complaint was a palpable lump, followed by mastalgia (38.5%), nipple discharge, and ulceration. The right breast was affected more frequently (66.7%), with the upper outer quadrant being the most common tumor location (74.4%), consistent with other studies. The mean tumor size decreased significantly from 3.75 cm pre-chemotherapy to 3 cm post-chemotherapy ($p < 0.001$), indicating a 15% reduction. These findings differ from those reported by Fisher et al., where 70–

80% of patients showed a > 50% reduction in tumor size.³ Infiltrating ductal carcinoma—not otherwise specified (IDC-NOC) was the predominant histologic type before (94.87%) and after (76.92%) therapy. Rare types included one case each of lobular and metaplastic carcinoma.

The study found stage II breast carcinoma to be the most prevalent (61.5%), with stage IIA accounting for 38.5% of cases, while 23% presented with stage III disease. Younger women were more likely to have aggressive stage III cancers, aligning with findings from Orucevic et al.⁴ Chemotherapy-induced morphologic changes were first described in 1960 by Waller and later expanded upon by Kennedy et al. Despite extensive research, relatively few studies have comprehensively detailed the effects of chemotherapy on tumor cell viability, necrosis, and stromal changes.⁵

This study observed significant stromal changes post-therapy in healthy tissue, including necrosis (74.4%), fibrosis (64.1%), desmoplasia (59%), and degenerative changes (33.3%). Other notable changes included mucinous alterations, vascular hyalinization, neoangiogenesis, calcifications, loss of cellular architecture, and inflammatory infiltrates, such as hemosiderin-laden macrophages, giant cells, and histiocytes. These findings are consistent with studies by Sethi et al. and Honkoop et al., which reported similar post-chemotherapy changes in breast tissue.^{1,6} However, other studies have not demonstrated significant histopathologic alterations following chemotherapy.⁷ Lobular carcinomas have been reported to be less responsive to chemotherapy, possibly because of their greater stromal component; however, this could not be substantiated in the present study because of the limited number of lobular carcinoma cases.

A minimal decrease in tumor cellularity was the primary effect of therapy, accompanied by nuclear enlargement, hyperchromasia, increased nuclear-to-cytoplasmic ratios, prominent nucleoli, and karyorrhexis/karyolysis in 70–85% of cases. These cytologic changes result from cellular damage caused by neoadjuvant chemotherapy and may vary according to tumor type and chemotherapy regimen.^{5,6} Inflammatory responses, including lymphocytic reactions and plasma cell infiltration, were also observed. Stromal elastosis was another significant post-therapy change.

Response to chemotherapy was classified using the International Union Against Cancer (UICC) criteria. Pathologic complete response (pCR) was observed in 15% of cases, pathologic partial response (pPR) in 15%, and increased disease in 70%. Overall, this study highlights the diverse histopathologic changes induced by neoadjuvant chemotherapy, providing insights into tumor biology and response to treatment.^{8–10}

Conclusion

Our study concludes that histopathological examination of the tumor bed

post chemotherapy showed no significant decrease in cancerous cells in Pakistani women with breast cancer as compared to women of western world with breast cancer. Breast cancer therapy causes no significant morphologic alterations in the

cancerous in our study. Further studies need to be done in our country to verify the effects of neoadjuvant chemotherapy in breast cancer patients in Pakistan.

Declarations

Ethics approval: This retrospective study was approved by the Institutional Review Board (IRB) of Nishtar Medical University, Pakistan (IRB approval No. 23446).

Consent to participate: The requirement for informed consent to participate was waived by the Institutional Review Board of Nishtar Medical university because this was a retrospective study using existing clinical and histopathological data.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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