Original Article

Histomorphological Changes and Pathological Response Following Neoadjuvant Chemotherapy in Breast Carcinoma: A Cross-Sectional Study

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Abstract

Background: Neoadjuvant chemotherapy (NACT) is widely used in the management of locally advanced breast carcinoma to downstage tumors and improve surgical outcomes. Histopathological evaluation of post-NACT specimens and assessing pathological response using the Miller–Payne grading system provides critical information regarding therapeutic response and prognosis.
Methods: This cross-sectional study included 50 patients with biopsy-proven breast carcinoma who received two or more cycles of neoadjuvant chemotherapy followed by surgical excision. Post-therapy specimens were examined for nuclear, stromal, and inflammatory changes using routine hematoxylin and eosin staining. Tumor regression was graded according to the Miller–Payne system. Statistical analysis was performed using SPSS version 20, with $p < 0.05$ considered statistically significant.
Result: The mean age of patients was 52.78 ± 10.43 years. Invasive ductal carcinoma, no special type, was the most common histological subtype (88%). A significant reduction in tumor size was observed following neoadjuvant chemotherapy, with mean tumor size decreasing from 4.87 ± 1.14 cm pre-NACT to 1.94 ± 1.16 cm post-NACT ($p < 0.0001$). Histomorphological changes included nuclear alterations in 60% of cases, stromal fibrosis or sclerosis in 52%, tumor necrosis in 64%, and inflammatory infiltrate in 90%. Pathological complete response was achieved in 14% of cases, while partial response was observed in 64%.
Conclusion: Histopathological evaluation remains the most reliable method for assessing response to neoadjuvant chemotherapy in breast carcinoma. Therapy-induced nuclear and stromal changes correlate with pathological response and have important prognostic implications.

Keywords: breast carcinoma; neoadjuvant chemotherapy; histomorphology; Miller–Payne grading; pathological response

Introduction

Breast cancer is the most common malignancy among women worldwide and a leading cause of cancer-related mortality.[1] In India, breast cancer incidence continues to rise, with many patients presenting at a locally advanced stage. Neoadjuvant chemotherapy (NACT) has become an integral component of treatment, offering tumor downstaging, improved operability, and increased rates of breast-conserving surgery.[2, 3]

While clinical and radiological assessments provide an estimate of tumor response, histopathological evaluation of post-NACT surgical specimens remains the most reliable method for assessing therapeutic efficacy.[3, 4] Accurate recognition and interpretation of these changes are essential for determining pathological response and prognosis.

Among various tumor regression grading systems, the Miller–Payne grading system is widely accepted for evaluating response in breast carcinoma following neoadjuvant therapy.[10] This study aims to assess histomorphological changes induced by NACT and to determine pathological response in breast carcinoma patients treated at a tertiary care center.

Materials and Methods

This cross-sectional study was conducted in the Department of Pathology, Government Medical College and Rajindra Hospital, Patiala, a tertiary care center over a period of one year, after obtaining approval from the Institutional Ethics Committee.

Study population

Fifty consecutive patients with histologically confirmed breast carcinoma (core biopsy or surgical specimen) who received two or more cycles of neoadjuvant chemotherapy followed by surgical excision were included. In a limited number of cases where initial diagnosis was based on FNAC, subsequent histopathological confirmation was available in surgical specimens.

Patients received neoadjuvant chemotherapy as per standard institutional and referring-center protocols for breast carcinoma. The commonly used regimens included anthracycline- and taxane-based combinations.

Inclusion criteria

Histologically confirmed breast carcinoma Receipt of at least two cycles of neoadjuvant chemotherapy

Exclusion criteria

Patients who did not receive neoadjuvant chemotherapy Patients who received only one cycle of chemotherapy

Variables

The primary outcome variable was pathological response to neoadjuvant chemotherapy, assessed using the Miller–Payne grading system. Secondary variables included histomorphological changes (nuclear alterations, stromal fibrosis/sclerosis, necrosis, and inflammatory infiltrate). Clinicopathological variables such as age, tumor size, and histological subtype were also recorded.

Histopathological evaluation

Surgical specimens were fixed in 10% neutral buffered formalin and processed according to standard protocols. Representative sections from tumor bed and surgical margins were examined. Hematoxylin and eosin–stained sections were evaluated for nuclear changes, stromal alterations, necrosis, and inflammatory response.

Interobserver agreement

Histopathological evaluation and Miller–Payne grading were performed independently by two experienced pathologists. In cases of discrepancy, a consensus diagnosis was reached after joint review. Immunohistochemical data regarding ER, PR, and HER2 status were not available for all cases as immunohistochemical evaluation for ER, PR, and HER2 was not performed uniformly at our institute, and hence molecular subtype–based analysis was not performed.

Pathological response assessment

Tumor regression was assessed using the Miller–Payne grading system, categorizing response from Grade 1 (no response) to Grade 5 (pathological complete response).[10]

Statistical analysis

Data were analyzed using SPSS version 20. Descriptive statistics were expressed as mean ± standard deviation and percentages. Paired t-test was used to compare pre- and post-NACT tumor size. Chi-square test or Fisher's exact test, as appropriate, was used to assess associations between categorical variables. A p value < 0.05 was considered statistically significant.

Bias

Efforts were made to minimize bias by including all consecutive eligible cases during the study period. However, as this was a single-center hospital-based study, the possibility of selection bias cannot be excluded. Additionally, observer variability in histopathological interpretation may represent a potential source of information bias.

Results

All patients meeting the inclusion criteria during the study period were included in the analysis. No eligible cases were excluded.

The mean age of patients was 52.78 ± 10.43 years (range: 31–66 years). Invasive ductal carcinoma, no special type, was the predominant histological subtype (88%). Most tumors measured more than 5 cm prior to chemotherapy (62%) (Table 1).

A significant reduction in tumor size was observed following neoadjuvant chemotherapy. The mean tumor size decreased from 4.87 ± 1.14 cm pre-NACT to 1.94 ± 1.16 cm post-NACT, representing a 60.16% reduction (p < 0.0001) (Table 1).

Table 1: Comparison of tumour size pre and post NACT.

Tumour size	Before NACT n (%)	After NACT n (%)
<2 cm	0 (0%)	7 (14%)
2–5 cm	19 (38%)	33 (66%)
>5 cm	31 (62%)	0 (0%)
Not seen	0 (0%)	10 (20%)*
Total	50 (100%)	50 (100%)
Mean ± SD	4.87 ± 1.14	1.94 ± 1.16
Range	2–7	0–4
% change	2.93 (60.16%)	
p value	< 0.0001	

Post-chemotherapy specimens demonstrated a spectrum of histomorphological changes. Nuclear alterations were seen in 60% of cases. Stromal fibrosis or sclerosis was noted in 52% of cases, while tumor necrosis was present in 64%. An inflammatory infiltrate was observed in 90% of cases (Table 2).

Table 2: Major histomorphological changes observed in breast carcinoma following neoadjuvant chemotherapy.

Histomorphological feature	Frequency	Percentage (%)
Nuclear changes*	30	60
Stromal fibrosis / sclerosis	26	52
Tumor necrosis	32	64
Inflammatory infiltrate	45	90

*Nuclear changes include hyperchromasia, karyorrhexis, nuclear enlargement, prominent nucleoli, and altered N:C ratio.

Pathological response assessment using the Miller–Payne grading system revealed Grade 3 response in 46% of cases. Pathological complete response (Grade 5) was observed in 14% of patients, while 22% showed minimal or no response. Overall, partial response (Grades 2–4) was observed in 64% of cases (Table 3) (Table 4).

Discussion

Neoadjuvant chemotherapy has become an integral component in the management of breast carcinoma, particularly in patients presenting with locally advanced disease, as it allows tumor downstaging and provides an opportunity to assess in vivo tumor response to systemic therapy [2, 3]. In the present study, a statistically significant reduction in tumor size

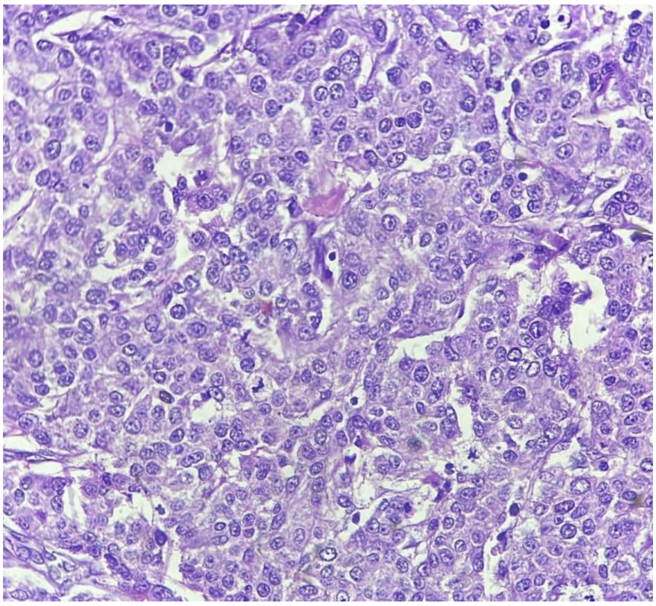

Figure 1: IDC-NST: nuclear features following NACT including nuclear hyperchromasia, prominent nucleoli, karyorrhexis. (H&E, 400×)

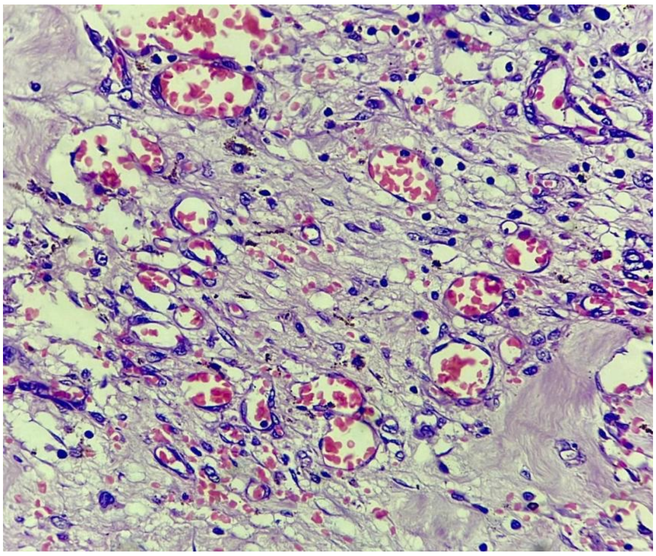

Figure 2: Stromal alterations following NACT in breast carcinoma showing angiogenesis. (H&E, 400×)

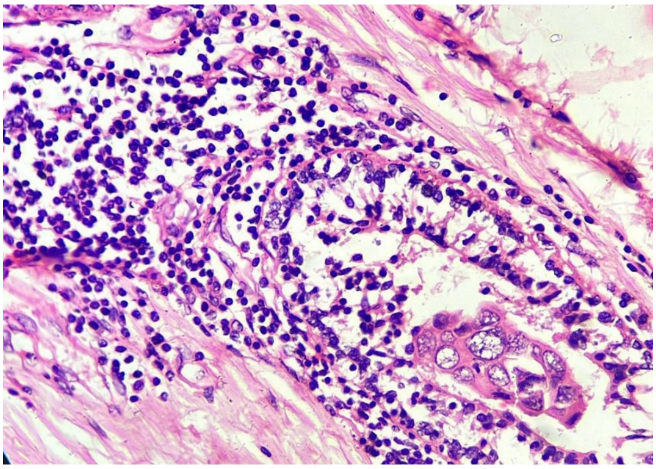

Figure 3: Inflammatory response following NACT in breast carcinoma showing lymphoplasmacytic infiltrate and residual tumor cells. (H&E, 400×)

Table 3: Pathological response to neoadjuvant chemotherapy assessed by Miller–Payne grading.

Miller–Payne grade	Tumor regression	Frequency	Percentage (%)
Grade 1	No/minimal response	11	22
Grade 2	<30% tumor loss	6	12
Grade 3	30–90% tumor loss	23	46
Grade 4	>90% tumor loss	3	6
Grade 5	No residual invasive tumor	7	14

Table 4: Pathological response (n=50).

Pathological Response	Frequency	Percentage
Pathological complete response	7	14%
Pathological partial response	32	64%
Pathological no response	11	22%
Total	50	100%

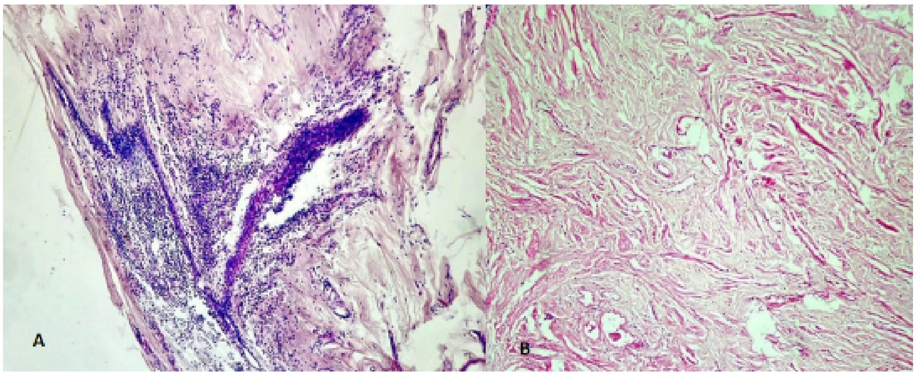

Figure 4: Pathological complete response of breast cancer: A – post-therapy evaluation of tumor showing areas of sclerosis and chronic inflammatory infiltration (H&E, 100×); B – fibrotic stroma and absence of tumor cells (H&E, 400×).

following neoadjuvant chemotherapy was observed, highlighting the effectiveness of this therapeutic approach in reducing tumor burden prior to surgery.

The predominance of invasive ductal carcinoma in the present study is consistent with the global and Indian epidemiological pattern of breast cancer [1]. The mean age of presentation observed in our cohort is comparable to that reported in other Indian studies, where breast carcinoma commonly presents in the fifth to sixth decade of life. These findings emphasize the relevance of neoadjuvant therapy in the typical demographic profile of breast cancer patients encountered in routine clinical practice.

Histomorphological evaluation of post-chemotherapy specimens revealed a wide range of therapy-induced changes. Nuclear alterations such as hyperchromasia, karyorrhexis, nuclear enlargement, and altered nuclear-cytoplasmic ratio were observed in a significant proportion of cases. These changes reflect direct cytotoxic effects of chemotherapy on tumor cells and have been well documented in earlier studies [4]. Such nuclear features indicate ongoing tumor cell damage and regression and are considered important microscopic indicators of therapeutic response.

Stromal changes, particularly fibrosis and sclerosis, were observed in more than half of the cases in the present study. Stromal fibrosis represents a reparative response following tumor cell destruction and has been correlated with favorable pathological response in several studies [4, 6]. Tumor necrosis, which was noted in 64% of cases, is another important marker of chemotherapy-induced tumor regression. Extensive necrosis reflects effective tumor cell kill and has been associated with improved pathological outcomes [4].

An inflammatory infiltrate was observed in the majority of cases, predominantly composed of lymphocytes with admixed plasma cells and histiocytes. The presence of tumor-associated inflammatory response is believed to represent host immune reaction to therapy-induced tumor cell injury and necrosis [4]. This inflammatory milieu may play a role in further tumor clearance and has been suggested as a favorable prognostic indicator in some studies.

Pathological response was assessed using the Miller–Payne grading system, which evaluates tumor regression based on reduction in tumor cellularity [10]. In the present study, Grade 3 response was the most common, while pathological complete response (Grade 5) was observed in 14% of patients. These findings are comparable to those reported in the literature, where pathological complete response rates vary widely depending on tumor biology, stage at presentation, and chemotherapy regimen used [6, 7, 8, 9]. Tiwari K et al (2024) showed partial pathological response in 88.2% patients and 2.9% cases with a pathological complete response, while pathological no response was shown by 8.8% patients.[11] Ahuja S et al (2024) found that the response to chemotherapy showed pathological complete response (55%), partial response (35%), and limited non-response (10%).[12]

The achievement of pathological complete response is considered an important surrogate marker for improved long-term outcomes, including disease-free and overall survival [6, 7]. Although survival analysis was not performed in the present study due to lack of follow-up data, the observed pathological response patterns suggest a favorable therapeutic impact of neoadjuvant chemotherapy in a substantial proportion of patients.

The Miller–Payne grading system was found to be a practical and reproducible method for assessing tumor regression in routine histopathological practice [10, 11]. It is simple to apply, does not require special techniques, and provides clinically meaningful information regarding therapeutic efficacy. Compared to more complex systems such as residual cancer burden scoring, the Miller–Payne system is particularly suitable for resource-limited settings and high-volume pathology laboratories.

Overall, the findings of the present study reinforce the importance of detailed histopathological examination of post-neoadjuvant chemotherapy specimens. Recognition and documentation of nuclear, stromal, and inflammatory changes, along with standardized pathological grading, provide valuable prognostic information and aid in guiding further patient management.

Although molecular subtype (ER, PR, HER2 status) is known to significantly influence response to neoadjuvant chemotherapy, such data were not available for all patients in the present study. This limitation restricted correlation of pathological response with tumor biology and represents an important area for future research.

Conclusion

Histopathological examination of post-neoadjuvant chemotherapy specimens provides invaluable information regarding treatment response in breast carcinoma. Recognition of therapy-induced histomorphological changes and accurate pathological grading are essential for prognostication and guiding further management. The present study has certain limitations. Being a cross-sectional study, it does not allow assessment of temporal relationships or causal inferences between histomorphological changes and treatment outcomes. The study was conducted at a single tertiary care center, which may limit generalizability. Additionally, molecular subtyping and receptor status correlation were not included, which could influence pathological response. Interobserver variability in histopathological interpretation is another potential limitation. Furthermore, the relatively small sample size and lack of long-term follow-up precluded correlation of pathological response with survival outcomes. Despite these limitations, the findings are applicable to similar tertiary care settings managing locally advanced breast carcinoma in resource-limited environments.

Abbreviations: NACT: Neoadjuvant chemotherapy; IDC-NST: Invasive ductal carcinoma, no special type; FNAC: Fine needle aspiration cytology; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; H&E: Hematoxylin and eosin; SPSS: Statistical Package for the Social Sciences; pCR: Pathological complete response; N:C ratio: Nuclear to cytoplasmic ratio.

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