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Post-chemotherapy changes in breast with evaluation of residual carcinoma burden

Kavita Tiwari[1], Nidhi Verma[2]

[1]Senior Resident, [2]Professor, Department of Pathology, Lala Lajpat Rai Memorial Medical College, Meerut, Uttar Pradesh, India

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ABSTRACT

Background: Neoadjuvant therapy (NAT) is an important tool for the treatment of patients with breast cancer. The aim of NAT is to make it operable for patients with locally advanced breast cancer, to shrink early-stage tumors – thus allowing for breast conservation. Pathological complete response achieved by post-chemotherapy is an independent factor in the long-term survival of patients. Thus, the histopathological components of post-chemotherapy changes such as cellularity and lymph node (LN) tumor deposits, when combined, help to assess residual carcinoma burden. **Aims and Objectives**: This study aims to analyze various histopathological changes in the breast after neoadjuvant chemotherapy with the objective of evaluating post-chemotherapy response and residual cancer burden. **Materials and Methods**: A total of 34 cases of post-chemotherapy modified radical mastectomy specimens were analyzed for pathological response (pCR) and residual cancer burden were evaluated. Tumor cellularity, stromal changes, lymphovascular invasion, and LN involvement were noted. **Results:** The age group of presentation of 34 cases ranged from 30 to 75 years of age with the mean age being 43.5 years. The most common histomorphological finding was fibrosis/elastosis and vacuolation with 26 (76.5%) and 24 (70.6%) cases, respectively. The number of cases that showed partial pCR was 30 (88.2%) and 1 (2.9%) case showed a pathological complete response which belonged to Stage 0, pathological no response was shown by 3 (8.8%) cases which belonged to Stage II and Stage IV. **Conclusion**: Post-chemotherapy response of neoadjuvant chemotherapy in breast carcinoma is important for prognosis and predictive information for disease relapse.

Key words: Neoadjuvant; Mastectomy; Post-chemotherapy; Residual Cancer Burden

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INTRODUCTION

Breast cancer is the most common cancer diagnosed in women and the second leading cause of death in women globally.[1] Neoadjuvant therapy (NAT) is currently established as a standard therapeutic approach for patients with larger and locally advanced breast cancer. Although there is no gain in survival benefits from NAT for breast cancer, however, the degree of response to NAT can play a prognostic factor.[2-6] NAT downstages the tumor, enables monitoring of the treatment efficacy, and makes it possible to detect and treat the micro-metastasis.[7] Pathological evaluation of therapeutic response of residual tumor in lymph node (LN) is critical as it helps to determine the prognosis, survival, and provides guidance for further therapy to be used after the surgery. Therefore, it is still considered to be the gold standard for determining the pathological response (pCR) or pathological non-complete response (pNR).[8-10]

The residual carcinoma burden (RCB) system was developed to calculate residual cancer burden using residual invasive carcinoma cellularity distributed over the tumor bed, number of LNs with metastasis, and size of the largest LN combined into four categories.[11] Miller–Payne system ignores the tumor size and nodal status altogether and estimates only the decrease in cancer cellularity after treatment. However, the reduction in cellularity is often greatest when the residual tumor is small, suggesting a relationship between residual size and cellularity.[12-14]

Address for Correspondence:
Dr. Nidhi Verma, Professor, Department of Pathology, Lala Lajpat Rai Memorial Medical College, Meerut, Uttar Pradesh, India.
Mobile: +91-9528990006. **E-mail:** drndverma94@gmail.com

Aims and objectives

Aim

- To analyze various histopathological changes in the breast after neoadjuvant chemotherapy
- To calculate RCB using cellularity of residual tumor, its size, and extent of lymph nodal involvement
- To categorize residual tumors by Miller–Payne criteria and RCB criteria along with TNM staging.

Objective

- To evaluate post-chemotherapy changes and their correlation with RCB
- To analyze and evaluate various categories of RCB index and Miller–Payne criteria with a stage of the tumor.

MATERIALS AND METHODS

Study setting

This prospective study was done in the pathology department of our institution from October 2022 to May 2023. In total, the number of cases analyzed was 34 in number. The cases with a history of chemotherapy, complete history, radiological, and previous investigative records were included in the study. The specimens that were autopsied, and did not have any previous investigation records, were not included in the study.

It is emphasized that patient's clinical data along with their radiological report should be essentially obtained. Histological diagnosis of pre-treatment core biopsy or fine needle aspiration cytology should also be sent by the clinician.

Inclusion criteria

All cases with a history of NAT were included in the study.

Exclusion criteria

- Cases without any clinical data and previous reports were excluded
- Cases without any history of NAT were not taken for study
- Cases without any previous biopsy or biopsy reports were excluded from the study.

Gross

Mastectomy specimen[14,15]

According to the dataset (14) published by the Royal College of Pathologists in 2016, the specimen is to be sent immediately to a pathology laboratory, fixed in 10% formation with surgical markings which will aid in orientation. Once received, the entire relevant surgical margins are inked so that the margin of excision can be easily determined histologically. Prior removal of surface lipids is achieved by dipping the specimen in alcohol and drying, then applying appropriate pigment such as Indian ink. In some tertiary units, acrylic dyes could also be used. The paint was fixed using 10% acetic acid.

The specimen was serially sectioned at a 5 mm interval from the posterior surface, leaving the skin intact. Tumor beds were identified, which were poorly defined fibrotic areas or fibrotic bands. The residual tumor was a firm, fleshy nodule, or area. The distance of the tumor bed from all margins was noted. In some cases, extensive sampling was done when the tumor bed was not identified grossly.

Axillary LN

Each LN was identified and thoroughly examined. LNs >4 mm in maximum dimension were sectioned in 2 mm intervals perpendicular to a long axis and sampled in their entirety. LNs <4 mm were bisected.

Microscopy

Tumor bed

Histologically tumor bed was evaluated for fibrosis or elastosis, inflammation (tumor-infiltrating lymphocytes [TILs], histiocytes, and giant cells), epithelial structures either present or absent, and hemosiderin or calcification.

Residual carcinoma

Changes in carcinoma histology were noted as histiocytoid appearance, cytoplasmic vacuolation, eosinophilia, nuclear hyperchromasia, pleomorphism, decreased mitotic activity, cancerization of lobules (lobular-like growth), retraction artifact, heterogeneity, presence or absence of lymphovascular invasion, and tumor cellularity (Figure 1).

RCB was calculated using www.mdandersonRCB calculator and scoring was done. RCB system was developed to calculate residual cancer using

- Residual invasive carcinoma cellularity distributed over tumor bed
- Number of LNs with metastasis and
- Size of largest LN combined into four categories.

Tumor cellularity was assessed by protocols defined by MD Anderson RCB calculator (Figure 2).[16,17]

Residual cancer burden

RCB-0 = No residual invasive cancer, i.e., pathological complete response
RCB-I = Small amount of residual invasive breast cancer, i.e., minimal residual disease
(RCB score ≥0–1.36)
RCB-II = Moderate residual disease (RCB score 1.37–3.28)
RCB-III = Extensive residual disease (RCB score >3.28).

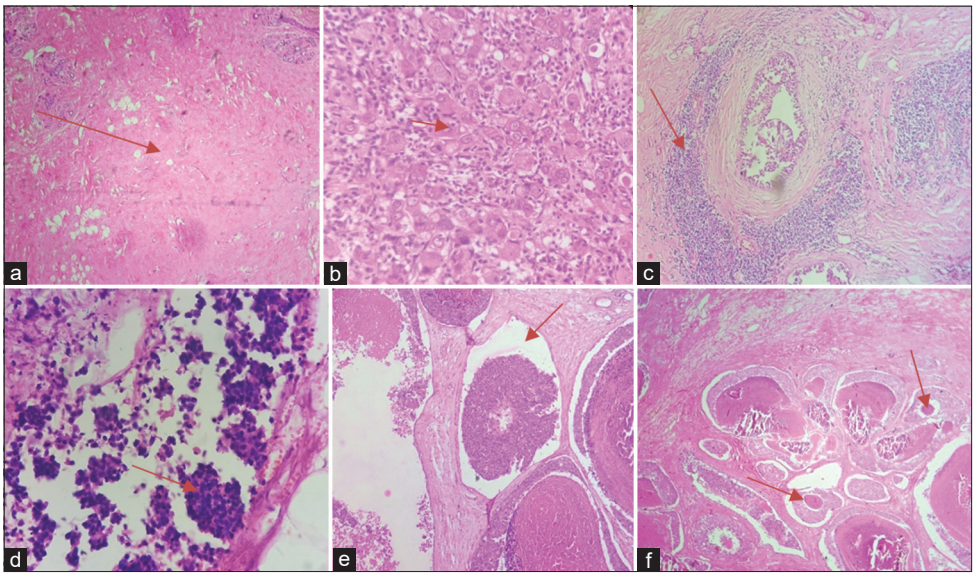

Figure 1: Radiation-induced changes (a) fibrosis (high power, H&E), (b) pleomorphism and giant cells (high power, H&E), (c) tumor-infiltrating lymphocytes (low power, H&E), (d) pyknotic/hyperchromatic nucleus (high power, H&E), (e) retraction artifacts (arrow, low power, H&E), (f) ductal carcinoma *in situ* with comedo-necrosis (low power, H&E)

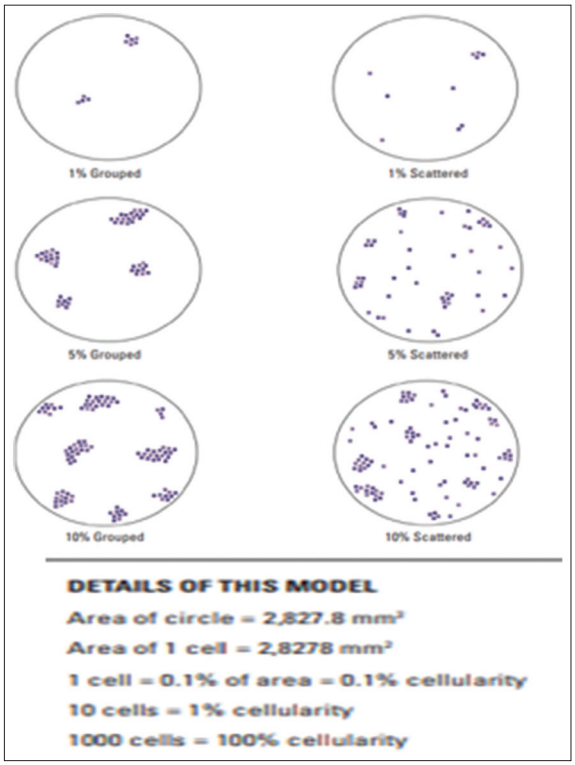

Figure 2: Protocol for evaluation of cellularity according to MD Anderson residual carcinoma burden calculator

Tumor regression grade was evaluated by analysis of tumor cellularity of pre- and post-chemotherapy changes.

Miller–Payne criteria[21,22]

TRG-1 = No change or some alteration to individual malignant cells but no reduction in overall cellularity

TRG-2 = A minor loss of tumor cells but overall cellularity is still high; up to 30% loss

TRG-3 = between an estimated 30–90% reduction in tumor cells

TRG-4 = A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumor cells

TRG-5 = No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastic stroma remains often containing macrophages. However, ductal carcinoma *in situ* (DCIS) may be present.

LN analysis

A total number of LNs was screened for any post-chemotherapy change such as fibrous scarring, lymphocytic depletion, or histiocytic aggregation.

i. The number of positive LNs is counted (LN)
ii. The diameter of the largest metastatic deposit is measured.

Ethics

This study was approved by the institutional ethics committee. No animals or humans were harmed in this study.

Statistical analysis

The findings were evaluated for significance by Chi-square and paired t-test. $P<0.05$ was considered statistically significant.

RESULTS

The total number of cases studied was 34 in this study and the age group of patients ranged from 30 to 75 years. The

mean age was 43.5 years. The number of chemotherapy cycles received in NAT varied from 2 to 8 chemotherapy cycles.

Post-chemotherapy histomorphological changes which were analyzed and evaluated revealed fibrosis 26 (76.47%) in most of the cases followed by inflammation, i.e., TILs 25 (73.53%), cytoplasmic vacuolation 24 (70.58%), cytoplasmic eosinophilia 16 (47.05%), hyperchromatic/pyknotic nuclei 15 (44.11%), pleomorphism 17 (50.00%), lobular growth 13 (38.23%), multinucleation 12 (35.29%), retraction 17 (50.00%), lymphovascular invasion 08 (23.53%), histiocytoid morphology 18 (52.94%), necrosis 20 (58.82%), and calcification 08 (23.53%) cases, respectively. Fibrosis, cytoplasmic vacuolation, and TILs were significant (P<0.05) with RCB grading (Figure 3).

LNs were observed separately and in 22 (64.70%) cases post-chemotherapy changes were noted and 15 (44.11%) cases showed LN involvement with tumor deposits (Figure 4).

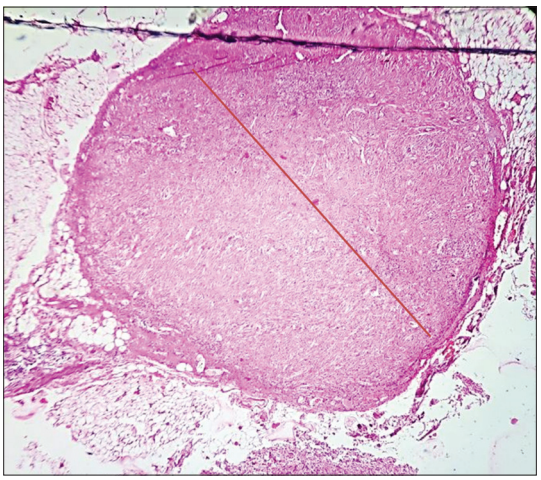

Figure 3: Lymph node showing metastasis (whole lymph node involved) (low power, ×10)

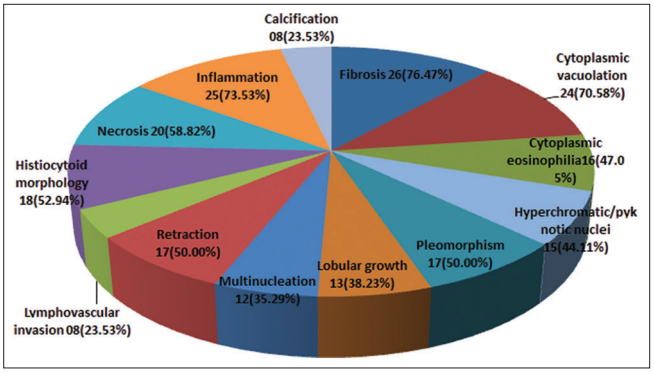

Figure 4: Histomorphological changes in tumor bed and residual carcinoma

The most common subtype observed in the study was Invasive Ductal Carcinoma NOS. However, in one case, RCB-0 was seen in which only a residual DCIS component was seen without invasive carcinoma, which was evaluated as a pathological complete response; pCR – 01 (2.94%). The number of cases that showed partial response to chemotherapy (pPR) was 30 (96.77%) and no response (pNR) was seen in 03(8.82%) cases (Table 1).

In this study, one case that showed complete pCR belonged to Stage 0 and the cases that showed pathological partial response were distributed among all stages except for Stage 0. Only one case of Stage IV showed partial response. The cases that showed no pCR were Stage II and Stage IV (Table 2).

Tumor regression was evaluated using Miller–Payne regression criteria, and it was also evaluated for stage and grade of residual tumor. It showed almost comparable results to residual carcinoma grading (Table 3).

DISCUSSION

The RCB index was first created in 2007 by Symmans et al.,[12] on a cohort of 241 BC patients who completed NAC. The RCB index combines pathological findings in the primary tumor bed and the regional LNs to calculate a continuous index.[18]

We observed several histomorphological changes induced by NAT. All of these histopathological changes have been described and evaluated in various studies. Few have been significantly correlated with RCB. In our study, the most common histological change observed was fibrosis with 26 (76.47%) cases, which was also the most common finding in other studies such as Hemavathi and Sridhar[8] (83%) and Sethi et al.[21] Furthermore, it was significantly correlated with the RCB index. TILs were the second most common pathological finding in our study. There are various literature that have studied the association of TILs with response to NAT, independently. Luen et al.[24] and Denkert et al.[23] suggested and studied that higher pre-treatment TIL levels are associated with higher rates of pCR in response to NAC. Other histopathological features, although observed in our study, were not significantly correlated with the RCB index.

In some other studies such as Sethi et al.,[20] TIL and RCB scores have been described as independent predictors for the outcome of residual carcinoma after chemotherapy. This study showed the maximum number of cases, 30 (88.24%) with pPR, which was also seen in a study done by Hemavathi and Sridhar,[8] Van der Wall et al.,[25] and Hamy et al.,[19] with 27 (90%), 42 (68%), 374 (72.6%) cases in pPR, respectively. However, the study of Sheereen et al.[1]

Table 1: Evaluation of pathological response in correlation with modified Bloom–Richardson grading system

Grade	RCB-0	RCB-I	RCB-II	RCB-III	No of cases (N)
Grade 1	00	05	04	00	09 (26.47%)
Grade 2	00	07	11	01	19 (55.88%)
Grade 3	00	01	02	02	05 (14.70%)
	01 (2.94%)	13 (38.24%)	17 (50.00%)	03 (8.82%)	34 (100%)

RCB: Residual carcinoma burden

Table 2: Evaluation of pathological response with post-chemotherapy staging (yT)

Stage	RCB-0	RCB-I	RCB-II	RCB-III	No of cases (N)
yT*in situ*	01	00	00	00	01 (2.94%)
yT0	00	00	00	00	00 (0.00%)
yT1	00	08	03	00	11 (32.35%)
yT2	00	03	07	02	12 (35.29%)
yT3	00	02	06	00	08 (23.53%)
yT4	00	00	01	01	02 (5.88%)
	01 (2.94%)	13 (38.24%)	17 (50.00%)	03 (8.82%)	34 (100%)

Table 3: Evaluation of post-chemotherapy response by Miller–Payne regression criteria with post-chemotherapy staging (yT)

Tumor regression grade	yT0	yT*in situ*	yT1	yT2	yT3	yT4	No of cases (N)
TRG1	00	00	00	00	00	01	01 (2.94%)
TRG2	00	00	02	05	04	00	11 (32.35%)
TRG3	00	00	08	07	03	01	19 (55.88%)
TRG4	00	00	01	00	01	00	02 (8.82%)
TRG5	00	01	00	00	00	00	01 (2.94%)
		01 (2.94%)	11 (32.35%)	12 (35.29%)	08 (23.52%)	02 (5.88%)	34 (100%)

and Sethi et al.[19] showed most cases with pNR. Only one case showed pCR which belonged to Stage 0 similar to Hemavathi and Sridhar[8] whereas 3 (8.82%) showed pNR one of which belonged to Stage IV and the other two cases to Stage II. There were only 2 (6.7%) cases of Stage II which showed pNR in Hemavathi and Sridhar[8] whereas Van der Wall et al.[25] showed 07 (11%) cases which were evenly distributed among all stages except Stage 0 cases.

In this study, 15 (44.11%) cases showed LN involvement, which was comparable to the study done by Symmans et al.,[12] in which positive LNs were 41%. LN status predicts the recurrence and disease-free survival rate in patients.

Therapy and prognosis in breast cancers largely depend on the stage at which the cancer is diagnosed. Breast cancer stage is one of the most important prognostic indicators and significant determinant of the patient's overall survival.[1] In the present study, maximum number of cases was seen in Stage II. Stage II breast carcinoma was found to be the most predominant with 35.29% after NACT. These findings were in accordance with the numerous other studies conducted including the one conducted by Sheereen et al.,[1] Faneyte et al.,[26] and von Minckwitz et al.,[27] with 61.5%, 41%, and 52%, respectively, wherein Stage II breast carcinoma was found to be the most predominant type. Hemavathi and Sridhar[8] reported Stage III cases to be most predominant in their study, similar to Ahmed et al.,[28] which also showed Stage III tumors to be most common. The maximum number of cases found in our study belonged to Stage II and Stage III (32.35%).

Immunohistochemical analysis of residual tumors was done by ER, PR, HER2neu, and Ki67 antibodies in a few cases where their previous biopsy was done in our setting. However, due to the low sample size (eight cases), results could not be fully validated. The other cases were analyzed and calculated based on previous radiological and biopsy reports available to the patient. One case with Miller–Payne grade-1 and RCB grade-3 relapsed and recurred. However, the study of more cohorts is needed to confirm the findings, and rigorous follow-up is needed in patients with high RCB scores or low Miller–Payne grades.

Limitations of the study

Low sample size and lack of correlation with immunohistochemical markers which affect the predictve and prognostic value of breast carcinoma are limitations of this study. Thus to validate the data follow up of the cases with ihc markers are needed.

CONCLUSION

Histomorphological changes following adjuvant therapy are important predictors for assessing the burden of the tumor. In this study, we showed that fibrosis, cytoplasmic vacuolation, and TILs were present in most cases which showed chemotherapy response. All the variables of RCB help to evaluate the remaining tumor which tells the burden of disease in the patient. Assessment of RCB is important to plan further management and follow-up to ensure relapse-free survival.

However, this study revealed fibrosis, TILs, and vacuolation as the most common findings in patients with a complete response and partial response to NACT. However, a study with a much larger cohort is needed to validate the results. Various other factors such as immune-phenotyping of tumors also affect the prognostication of breast carcinoma. Thus, the association of these predictive markers with RCB is also needed. The aggressive nature of breast carcinoma could be predicted using the Ki67 Labeling Index. The metastasis in the LNs could be missed by bare eyes, especially by novel pathologists. Thus, the use of CK5/6 helps detect tumor cells dispersed within LNs. Similarly, CD34 can be used to confirm lympho-vascular invasion in case of confusion as it is also one of the important factors for the prognosis of breast carcinoma. Immunochemical examination with predictive markers is important. However, RCB scores using histomorphological changes after chemotherapy can also be helpful to assess and plan follow-up management of the patient. It is necessary to predict the nature of lesions in breast carcinoma to ensure relapse-free survival and to improve the quality of life of patients as it is one of the menaces that is causing exquisite deterioration in standards of life.

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Authors Contribution:
KT- Concept design, proforma of study, literature survey, data collection, data analysis, manuscript preparation, and submission of the article; **NV-** Proofreading and review of the manuscript.

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Lala Lajpat Rai Memorial Medical College LLRMMC, Meerut, India

Orcid ID:
Dr. Kavita Tiwari- https://orcid.org/0009-0007-3748-9697
Dr. Nidhi Verma- https://orcid.org/0009-0003-2260-3769

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