

Research Article

Cytomorphological changes in breast carcinomas, after neoadjuvant chemotherapy: a study of twenty cases

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Received: 18 September 2015

Revised: 19 September 2015

Accepted: 08 October 2015

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ABSTRACT

Background: Neoadjuvant chemotherapy administered pre-operatively is the standard of care therapy for locally advanced breast cancers, mainly for clinical down staging. The histopathological evaluation of tumor response is the gold standard. Aims: To study the morphological changes induced with neoadjuvant chemotherapy in breast carcinoma and assess the response or non-response of cancers to systemic therapy, based on a web based calculation script at www.mdanderson.org/breastcancer_RCB and also evaluated basing on NSABP-B18 system.

Methods: 20 cases of radical mastectomies in locally advanced breast carcinomas with neoadjuvant chemotherapy are studied.

Results: All the cases are female breast cancers. Macroscopically, the size of the tumor bed ranges from 10 mm to 90 mm in maximum dimension. The morphological changes: Tumor cellularity, cytomorphological changes. In the present study 20% of cases are pCR/RCB 0, 40% are pNR/RCB III cases and 40% are pPR/RCB I & II (i.e. pCR-pathological complete response, pNR-pathological no response, pPR-pathological partial response, RCB-Residual Cancer Burden).

Conclusions: The spectrum of changes observed in the tumor bed is coagulative necrosis, hyalinisation, dystrophic calcification and intense mononuclear inflammatory cell collections, cytoplasmic vacuolization and bizarre nuclei. Quantification of the residual disease by RCB system and to categorize the residual disease is important, to predict the disease-free relapse rate.

Keywords: Cytomorphology, Carcinoma breast, Neoadjuvant chemotherapy

INTRODUCTION

Neoadjuvant chemotherapy (NAT) administered preoperatively is now the standard of care therapy for locally advanced breast cancers. The major advantages of neoadjuvant therapy are the response or non-response of cancers to systemic therapy can be determined in individual patients, and this information can be used to modify or change the treatment.¹ In most studies of NAT,

the carcinomas are reduced in size with clinical down staging.²

The pathological evaluation of tumor response is the gold standard, as the clinical and radiological responses do not correlate well with residual tumor after treatment.

The pathologist should be familiar with gross examination sampling and the possible nuclear and

cytoplasmic changes induced by chemotherapy and should also be able to assess the residual disease which determines the prognosis.

Aims & objectives

- 1] To study the morphological changes induced with NAT in breast carcinoma.
- 2] To correlate the findings with the literature.
- 3] To evaluate the response to treatment.
- 4] To calculate the residual cancer burden.

METHODS

20 cases of modified radical mastectomies in locally advanced breast carcinomas who received neoadjuvant chemotherapy are studied.

The specimens are carefully sampled and from the tumor bed alone, on an average 5 blocks are submitted for microscopy. The morphological changes are studied under light microscope, in routinely processed, paraffin embedded; H & E stained sections, to assess the tumor cellularity, cytoplasmic and nuclear changes and other associated changes. These observations are compared with other studies.^{1,2,6}

The pathologic response is evaluated and categorized basing on the NSABP-B18 system as pCR, pPR & pNR.³ pCR denotes pathological complete response with no recognizable invasive tumor cells present. pPR denotes pathological partial response with presence of scattered individual or small clusters of tumor cells in a desmoplastic or hyaline stroma and pNR denotes pathological no response, where the tumor is not exhibiting any changes.

The tumor response is also assessed basing on RCB system⁴ and categorized as 0, I, II & III using a web based calculation script at www.mdanderson.org/breastcancer_RCB.

The size of the tumor bed, cellularity of the residual invasive carcinoma, assessed as per the guidelines of RCB (Residual Cancer Burden) system, the number of lymph nodes with metastases and the size of the metastases are submitted and we get the RCB score and Grade. Figure 1 shows the Web page.

By using the RCB system, the residual cancer burden can be quantified and also categorized as RCB 0 which denotes no carcinoma in breast or lymph node, as RCB I & II when there is partial response and as RCB III in chemoresistance.

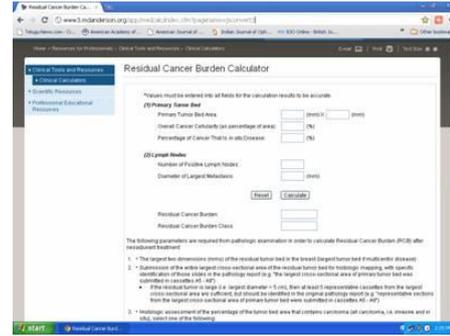


Figure 1: Web page image of RCB system, showing calculation script.

RESULTS

20 cases of locally advanced female breast carcinomas, which received neoadjuvant chemotherapy and later underwent radical mastectomy are studied.

The age group of the patients in the present study ranges from 27-68 years, with a peak incidence in 5th decade.

All the cases are female breast cancers.

Macroscopically, the size of the tumor bed ranges from 10mm to 90mm in maximum dimension.

The morphological changes observed under light microscope, in the sections from the tumor bed, lymph nodes and adjacent breast parenchyma are

- 1] Tumor cellularity - 65 % of the cases show decreased cellularity, including 20% of cases with complete response.
- 2] Cytomorphological changes observed are distortion of glandular architecture enlarged tumor cells due to increased cytoplasm, cytoplasmic vacuolization (Figure 2) eosinophilic change with pleomorphic and bizarre nuclei (Figure 2a).

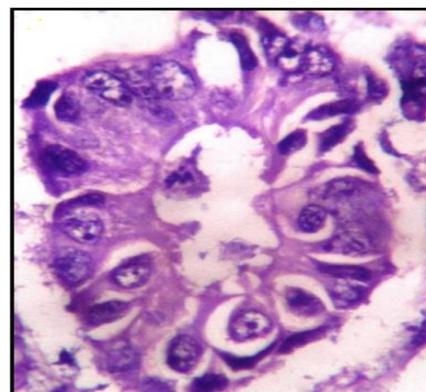


Figure 2: H&E, x40, after NCT, pleomorphic duct epithelial cells, with nucleocytoplasmic vacuolations and cytoplasmic vacuolations.

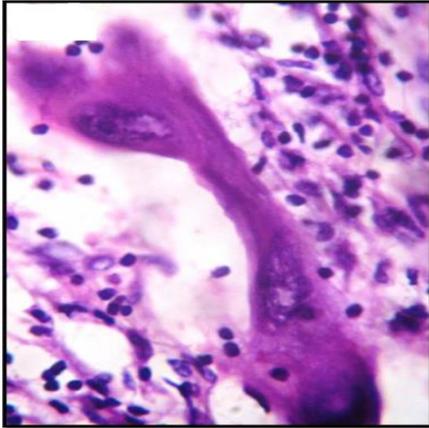


Figure 2a: H&E, x40, after NCT, bizarre tumor cells, suggesting degenerative changes.

Residual tumor cells are distributed either single or in clusters, which tend to shrink away from the stroma (Figure 3). Tumor bed shows areas of hyalinized vascular stroma (Figure 3a). Dense aggregates of lymphocytes, closely abutting the tumor cells, are observed in majority of the cases (Figure 3b). Coagulative type of necrosis and eosinophilic granular necrotic areas are noted (Figure 3c and Figure 4).

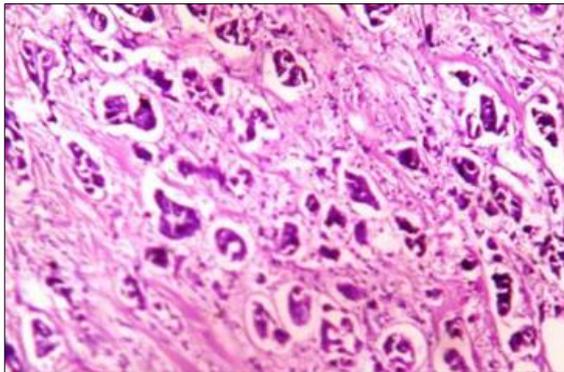


Figure 3: H&E, x10, Residual tumor after NCT, showing tumor cells in clusters, which tend to shrink away from the stroma.

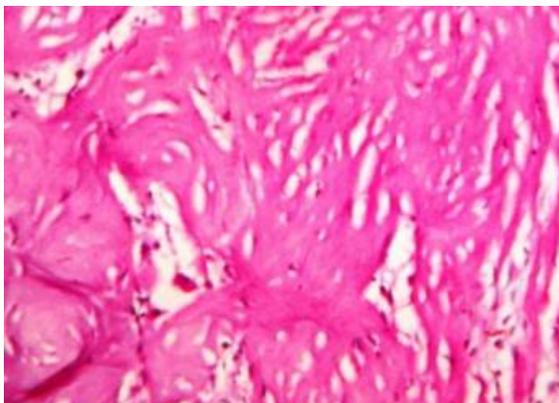


Figure 3a: H&E, x40, tumor bed with extensive areas of hyalinisation.

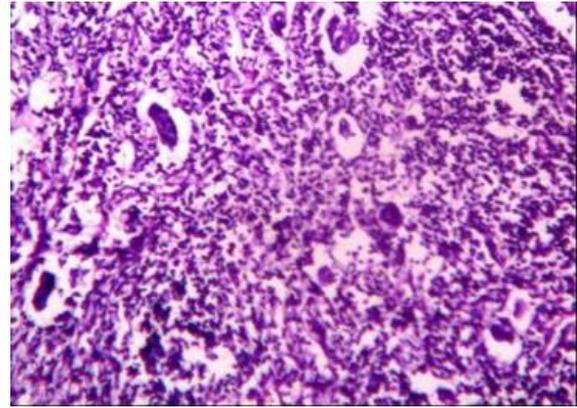


Figure 3b: H&E, x40: Residual tumor after NCT, showing dense lymphocytic infiltrate, closely abutting the tumor cells.

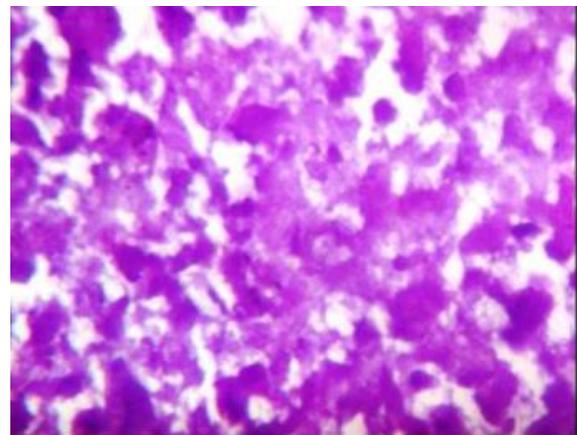


Figure 3c: H&E, x40, tumor bed after NCT showing extensive areas of coagulative necrosis, with pathological complete response (pCR).

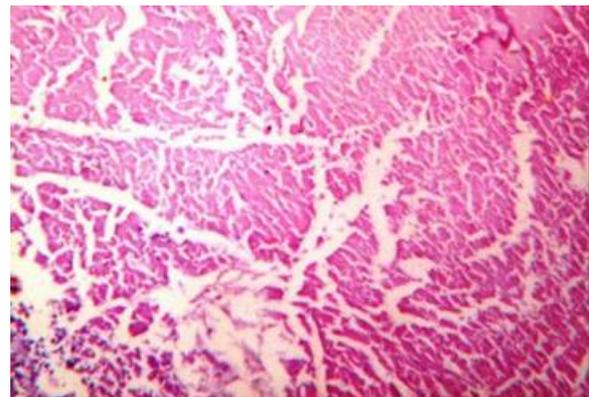


Figure 4: H&E, x40, tumor bed after NCT showing extensive areas of eosinophilic granular necrosis, with pathological complete response (pCR).

Changes in the lymph nodes with complete response to treatment show necrotic areas with rim of histiocytic collections (Figure 4a) and hyaline stromal scars (Figure 4b). Partial response in lymph nodes show isolated or clusters of tumor cells by hyaline stromal fibrosis.

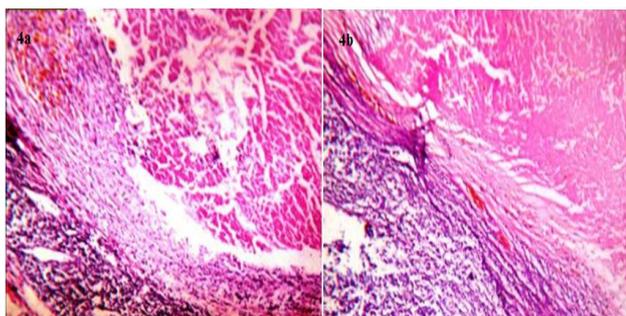


Figure 4a and 4b: H&E, x10, Lymph node: showing tumor necrosis in the deposits, histiocytic collections & hyaline stromal scars.

The changes observed in the adjacent breast parenchyma is sclerosis of basement membranes of the ductal and acinar components, with some epithelial cells showing cytologic and nuclear enlargement (Figure 4c).

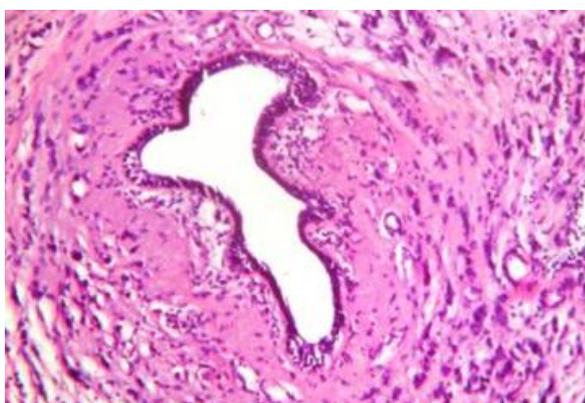


Figure 4c: H&E, x40, adjacent non tumorous breast parenchyma with sclerosis of basement membranes of ducts and duct epithelial cells, showing cytomegaly.

In the present study 20% of cases are pCR/ RCB 0, 40% are pNR / RCB III cases and 40% are pPR/ RCB I & II (Table 1, 2).

Table 1: NSA BP-B18 system.

NSA BP-B18 system category	% of cases
pNR (pathological No response)	40%
pPR (pathological partial response)	40%
pCR (pathological complete response)	20%

Table 2: RCB system.

RCB (Residual cancer burden) system category	% of cases
RCB 0	20%
RCB I	20%
RCB II	20%
RCB III	40%

DISCUSSION

Although there are many different combinations of agents used for NAT, typical changes are seen in most carcinomas with any type of treatment regime. Grading of post chemotherapy breast carcinoma is not a prognostic indicator.¹

The cytomorphic changes after chemotherapy include decrease in tumor cellularity, which is so extreme in 20% of cases of the present study, that no residual tumor cells are detected. Similar response is reported by in 10% of patients of Markis et al.²

The other changes recorded in the present study are architectural distortion, fibrosis, stromal hyalinization, geographic areas of necrosis, dense lymphocytic infiltrate and areas of dystrophic calcification. Similar findings are reported in other studies.¹

In the present study, the variation in the response to treatment can be explained as, in addition to typical adjuvant therapy in which chemotherapy is completed before surgery, some protocols involve short term therapy (weeks instead of months) between diagnosis and definitive surgery. And therapies based on hormonal agents, need a longer duration to develop a maximal response.

It is important to document the changes in lymph node because the patients who have residual metastatic tumor with evidence of treatment effect have better disease-free survival and lower relapse rates than patients who have positive nodes without evidence of such changes.⁶

In the present study, the changes observed in the lymph node metastases are hyaline stromal scars, necrosis and aggregates of histiocytes, without any viable tumor cells.

In lymph nodes with partial response, isolated and clusters of tumor cells surrounded by hyaline stromal fibrosis is observed. Similar observations are reported in other studies.¹

RCB index is prognostic index for distant relapse free survival and the inter-observer agreement of RCB index and RCB categories is high among pathologists.⁵

CONCLUSIONS

From the above study, we can conclude the followings.

- Pathologic evaluation of the tumor response is the gold standard.
- Careful sampling of the post chemotherapy mastectomies is essential with identification of the tumor bed.

- The commonly observed changes after neoadjuvant therapy, in the present study are intense mononuclear inflammatory cell collections, closely abutting the tumor cells, geographic areas of coagulative necrosis, stromal hyalinization, dystrophic calcification and cytological bizarre nuclei with cytoplasmic vacuolations.
- In the non-tumor bearing breast parenchyma, sclerosis of basement membranes of ductal and acinar components and enlargement of the cells is noted.
- Quantification of the residual cancer burden is important, which helps in predicting the distant relapse-free survival and also helps in modification of the treatment and therefore included in the final pathology report.
- Also a detailed checklist of lymph nodal status, including the number of lymph nodes with evidence of treatment response but without tumor cells, should be included in the report.
- Finally, the pathologist should be familiar with the gross examination, sampling and the possible nuclear and cytoplasmic changes induced by chemotherapy, which is extremely important as a prognostic factor for individual patients.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Sumanth MM, Assistant Professor, Department of Community Medicine, M.M.C & R.I., Mysore for assisting with the statistical work.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Ramana Kumari P, Sivarama Krishna TV, NagaKishore MG. Cytomorphological changes in breast carcinomas, after neoadjuvant chemotherapy: a study of twenty cases. Int J Res Med Sci 2015;3:3326-30.