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POSTCHEMOTHERAPY EVALUATION OF BREAST CARCINOMA USING RESIDUAL TUMOR BURDEN SCORE-A PROSPECTIVE STUDY AND REVIEW OF LITERATURE

Pathology

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ABSTRACT

This study evaluates the value of residual tumor burden scoring in patients who have received neoadjuvant chemotherapy followed by mastectomy in locally advanced breast carcinoma. The average age of presentation with breast cancer was 51.7 years. Partial response after neoadjuvant chemotherapy was seen in 10% and 40% of patients with RCB score1and 2 respectively.48% of patients exhibited a RCB score 3. Complete response was seen in 2% of patients. There was a strong correlation between ER AND PR. Subjects with ER positive have a higher probability of being PR positive.Subjects with Her 2neu positive and ER negative have a higher probability of chemoresistance .

KEYWORDS:

Locally advanced breast cancer, neoadjuvant chemotherapy, residual cancer burden.

INTRODUCTION:

Breast cancer is the most common malignancy among women which accounts to 33% of all female cancers. Neoadjuvant chemotherapy followed by mastectomy is the standard protocol for advanced infiltrating breast carcinoma so as to ensure better survival. Measurement of residual cancer burden index following neoadjuvant chemotherapy is helpful in evaluating pathological response to improve the prognosis in such patients. Residual cancer burden scoring system was taken up for this study as a prognostic indicator as it includes tumour size and nodal status and is advantageous over other systems due to its easy applicability.

MATERIALS AND METHODS:

:This prospective study was done in the Government Stanley Medical College between May 2014-May 2015. 50 patients with locally advanced breast cancer treated by neoadjuvant chemotherapy followed by mastectomy were analysed. The clinical, histomor phological, immunohistochemical analysis and residual cancer burden scoring using the MD Anderson online cancer burden calculator were observed in such cases. Statistical analysis was done by SAS JMP 7 method.

50 patients with locally advanced breast cancer treated with neoadjuvant chemotherapy followed by mastectomy were taken up for the study.We received the mastectomy specimens from patients treated for 3 to 4 weeks with neoadjuvant chemotherapy from the Department of Surgery, Stanley Medical College.Pertaining clinical data and mammographic findings were obtained for all these cases. Pretreatment core biopsy report,axillary lymphnode status, history of chemotherapeutic regimen, size of the tumour, prior and after neoadjuvant chemotherapy was assessed and recorded.

Mastectomy specimens received in formalin were evaluated macroscopically to identify the tumour bed. Deeper clearance margin was inked and the specimens were serially sectioned at 5 mm interval from the posterior surface leaving the skin intact. Cut surface was examined for the tumour bed. Cross sectional dimensions of residual tumour bed was assessed and the distance from the resected margins were measured. Tumour bed was extensively sampled. Axillary lymph nodes were dissected out .Number of lymph nodes and diameter of the largest node was noted. Residual cancer burden score was calculated by using the online residual tumor burden calculator and was evaluated and scored accordingly.

RCB-0: No carcinoma in breast or lymphnode.
RCB-1: Partial response
RCB-2: Partial response
RCB -3:Chemoresistant
RCB score was distributed as follows in this study

RCB SCORE	PERCENTAGE
0	2%
1	10%
2	40%
3	48%

ER, PR, HER2NEU values were distributed as follows:

Marker	Negative	Positive
ER	34%	66%
PR	24%	76%
HER2NEU	56%	44%

DISCUSSION:

Invasive mammary carcinomas are a group of malignant tumors of the breast which have the potential to invade the adjacent tissues and also have a marked tendency to metastasize to distant sites. Frei in the year 1982 introduced the term neoadjuvant chemotherapy to treat solid tumours that were extensive and locally advanced.(1).He highlighted the advantage of using neoadjuvant chemotherapy in the treatment of solid tumours as 1) reduction in the tumour size and 2) prevention of early metastatic deposits.

Recently neoadjuvant chemotherapy is instituted for patients with early stage operable breast cancers to enable breast conservation surgery. The prime aim of such a therapy is to conserve the breast and to prevent micrometastatic disease .The efficacy of systemic therapy in vivo is also considered as a prognostic tool and is assessed by means of pathologic response, highlighting the importance of pathologic examination which is considered a gold standard. Patients obtaining a pathological complete response (pCR) after neoadjuvant chemotherapy have the best prognosis.

Pathological complete response (pCR) after neoadjuvant chemotherapy is characterized by shrinkage of tumor size with complete absence of tumor cells in the mastectomy specimen and in the axillary lymph nodes.This response is found to be highest in patients with high grade tumor,estrogen and progesterone receptor negativity and in Her 2 positive tumors.(2).Tumors more than 2cms and locally advanced breast carcinoma cases are amenable to neoadjuvant chemotherapy.Deo et al has proved that neoadju vant chemotherapy is equally efficient as adjuvant chemotherapy in locally advanced tumors.(3). Pathological partial response is when the residual tumor in the mastectomy specimen is more than 50% smaller in size than the pretreatment size. Complete response to neoadjuvant chemotherapy was seen in 2% of patients and partial response was seen in 10% and 40% of subjects with partial response in this study.

Assesing the therapeutic response and measurement of residual disease in the breast and /or the axillary node is important as it predicts

the survival and also helps in instituting further management.About 60-80% patients with complete pathological response have residual tumor in the resected specimen while 20% patients with clinically suspected residual disease have complete pathological response(4). Hence pathologic assessment of the final resected specimen is essential for assessing the complete pathologic response.

Histomorphology shows a spectrum of changes in the residual tumour cells such as nuclear hyperchromasia, cytoplasmic and or nuclear vacuolisation, hypereosinophilia of the cytoplasm, pleomorphic nuclei, multinucleation and vesicular chromatin. Cell borders are typically well defined.(5)

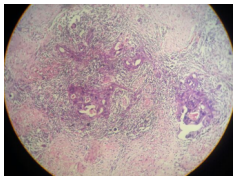


Fig 1: Partial response: Neoplastic cells showing residual tumor cells (10X)

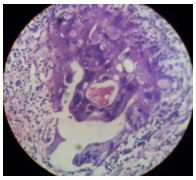


Fig 2: Partial response: Neoplastic cells showing pleomorphism, hyperchromasia and cytoplasmic vacuolization (40X)

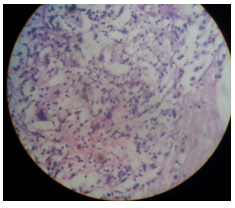


Fig3.Complete response showing foamy histiocytes and inflammatory response (10x)

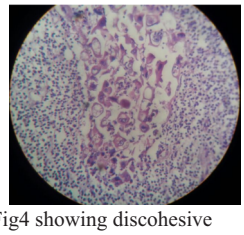


Fig4 showing discohesive tumour cells with cytoplasmic and nuclear vacoulation

Regarding the grade of the tumor,some tumors may appear as higher grade and in rare instances may be of lower grade because of the cytomorphological changes seen in the residual tumour cells from the treatment effect.(6,7). In comparison with the classical axillary dissection prior to neoadjuvant chemotherapy a lesser number of lymph nodes are retrived after the treatment protocol.

National Surgical Adjuvant Breast and Bowel Project(NSABP) Protocol -18 trial was one of the largest studies and had an easy applicability, a better disease free survival and overall survival and proved that the preoperative therapy was efficient as that of the adjuvant therapy, but carried a disadvantage of including only one category of partial response,survival was similar to patients without response ,does not separate well pPR patients from pNR patients and lymph node status was not included(4)

45 women with inflammatory breast carcinoma were reviewed in a study by Chevallier et al. According to this clinical trial patients were grouped into 4 categories with 1 category of partial response.(8) Residual ductal carcinoma in situ cases were categorized separately from cases with no residual carcinoma.This system of grading combined the partial response category with the no response category.

Sataloff conducted a clinical trial in 36 patients and included the examination of both the primary carcinoma and the lymph nodes .This system did not include lymphovascular invasion and did not show the difference in the 2 categories of partial response.(9).

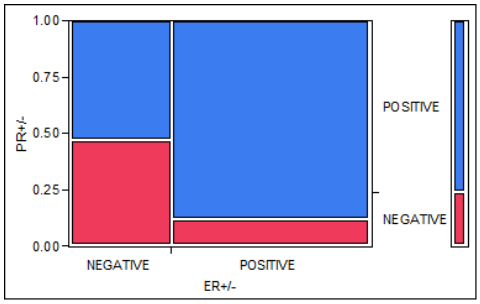
About 176 patients with tumor of size more than 4cms were treated with chemotherapy and 5 grades based on cellularity,before and after treatment were assessed for 5 years and was corroborated with disease free survival and overall survival(10) .

It was Symmans et al who proposed the use of RCB to quantitate the extent of residual tumour in breast cancer(11) . Based on the RCB classes evaluated by David J Dabb ,patients with minimal residual disease RCB1 were found to have the same 5year survival as those with pCR (RCB0) ,irrespective of the type of neoadjuvant chemotherapy administered.Extensive residual disease (RCB3) had poor prognosis,in patient who did not receive adjuvant hormone therapy. Patients who had moderate response to chemotherapy (RCB2) with subsequent hormone therapy appeared to have a better survival rate. (12)

Following are the findings in this study:

1.In this study, there is strong correlation between ER and PR. Subjects with ER+ have a higher probability of being PR+

Contingency Analysis of PR+/- By ER+/-
Mosaic Plot



Contingency Table

ER+/- By PR+/-

Count Total % Col % Row %	NEGATIVE	POSITIVE	
NEGATIVE	8 16.00 66.67 47.06	9 18.00 23.68 52.94	17 34.00
POSITIVE	4 8.00 33.33 12.12	29 58.00 76.32 87.88	33 66.00
	12 24.00	38 76.00	50

Tests

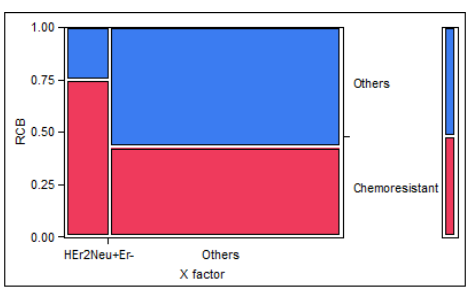
N	DF	-LogLike	RSquare (U)
50	1	3.6119301	0.1311

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	7.224	0.0072
Pearson	7.509	0.0061

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	0.9988	Prob(PR+/-=POSITIVE) is greater for ER+/-=NEGATIVE than POSITIVE
Right	0.0094	Prob(PR+/-=POSITIVE) is greater for ER+/-=POSITIVE than NEGATIVE
2-Tail	0.0123	Prob(PR+/-=POSITIVE) is different across ER+/-

2. ***Markers are such as PR, ER and HER2NEU individually are not a good indicator of RCB class.***
3. ***Subjects with HER2NEU+ and Er- have a higher probability of Chemoresistance, ie, if the subject is not HER2NEU+ and Er-, the probability of responding to Chemotherapy is larger.***

Contingency Analysis of RCB By X factor
Mosaic Plot



X factor divides the population in to two categories: a) HER2NEU+and ER-, b) others

Contingency Table

X factor By RCB

Count Total % Col % Row %	Chemoresistant	Others	
HEr2Neu+Er-	6 12.00 25.00 75.00	2 4.00 7.69 25.00	8 16.00
Others	18 36.00 75.00 42.86	24 48.00 92.31 57.14	42 84.00
	24 48.00	26 52.00	50

Tests

N	DF	-LogLike	RSquare (U)
50	1	1.4365268	0.0415

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	2.873	0.0901
Pearson	2.782	0.0954

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	0.9819	Prob(RCB=Others) is greater for X factor=HEr2Neu+Er- than Others
Right	0.0996	Prob(RCB=Others) is greater for X factor=Others than HEr2Neu+Er-
2-Tail	0.1319	Prob(RCB=Others) is different across X factor

CONCLUSION:

This study was analysed with 50 cases of breast carcinoma treated with neoadjuvant chemotherapy. The residual cancer burden score is a simple and easily quantifiable method used to assess the pathological response and therby can be used as a uniform reporting system with ease and broad applicability.We inferred that about 2% of cases had a complete tumor response and 50% patients had partial response with 48% of patients showing no pathologic response. It is found that patients ER+ have a higher probability of being PR+. Among the markers, the combination HER2NEU+ and ER- indicates higher probability of chemoresistance.

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