General Surgery

A DESCRIPTIVE OBSERVATIONAL STUDY OF DIFFERENCE OF ESTROGEN & PROGESTERONE RECEPTOR STATUS BEFORE AND AFTER NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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ABSTRACT

Background: Neoadjuvant chemotherapy (NACT) forms the initial modality of treatment for primarily inoperable locally advanced breast cancer (LABC). A change in hormone receptor status after NACT has important therapeutic and prognostic consequences. The primary objective of this study is to compare Hormone Receptor status before and after neoadjuvant chemotherapy (discordance). The secondary objective is to study correlation between tumour response and hormone receptor expression.

Method: This is a descriptive study of 80 LABC patients who received NACT. All patients who underwent core biopsy and ER/PR assessment before and after NACT were included in this study. Data was collected prospectively from each patient in a structured proforma

Results and conclusion: The hormone receptor discordance rate & response to NACT was assessed. ER discordance is 16.4%. in 07 patients estrogen receptor(ER) change positive to negative and in 04patients estrogen receptor change negative to positive. PR discordance is 22.4%. In 12 patients Progesterone receptor (PR) change positive to negative and in 03patients progesterone receptor change negative to positive.

INTRODUCTION:

The breast has always been the symbol of womanhood and feminity. The breast is man's insignia of membership in the class Mammalia. It on one hand is capable of producing the most precious gift of life to the young one, milk and on the other hand it is notorious of giving rise to multitude of pathological conditions causing significant morbidity and mortality and the epitome of all the diseases related to breast in the cancer of breast which is responsible for most of it.

Women from less developed regions (883 000 cases) have slightly more number of cases compared to more developed (794 000) regions.[1] After lung cancer, breast cancer is the second leading cause of cancer-related death in women, accounting for 12% of cancer-related deaths.[2] Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women.[3]

LABC refer to a heterogeneous group of breast cancers without evidence of distant metastases (M0) and represent only 2% to 5% of all breast cancers in the United States. The term LABC encompasses patients with (1) operable disease at presentation (clinical stage T3N1), (2) inoperable disease at presentation (clinical stage T4 and/or N2-3), and (3) clinical stageT4dN0-3, also inoperable.

The role of hormone receptors as a prognostic and therapeutic tool in breast cancer is widely emerging; as Estrogen and progesterone appear to be major hormones involved in regulation of breast tumour growth. Its determination nowadays is becoming an important predictor of response to hormonal therapy and overall prognosis of the patient.[4]

Prognosis is related to a variety of clinical, pathological and molecular features which include classical prognostic factors viz. histological type, histological grade, tumour size and lymph node metastases, status of hormonal receptors—estrogen receptor (ER), progesterone receptor(PR) of the tumour, and more recently, HER-2/Neu status.[5]

Assessment of hormone receptor status and human epidermal growth factor receptor 2 (HER-2) status is routinely conducted at the time of tissue diagnosis to aide in the decision-making of which agents to be utilized in the Neoadjuvant approach. The main goal of this approach is to improve the resectability by shrinking the tumour in locally advanced breast cancer (LABC), possibly allowing for breast conserving surgery.[6]

In developing countries more than 50% of the breast cancer patients as locally advanced breast cancer (LABC) at diagnosis. Neoadjuvant chemotherapy (NACT) forms the first modality of treatment for LABC patients. Neoadjuvant chemotherapy has shown to alter several biological factors of breast cancer. One of the most important biological factors in breast cancer is hormone receptor. Estrogen receptor(ER) and progesterone receptor (PR) are both predictive and prognostic markers.

As they play a crucial role in the treatment of breast cancer, a change in it expression after chemotherapy is of significance. This seems more significant therapeutically, when the discordance is from negative to positive receptor.[7]

METHODS AND AIM:

The study was conducted in the Department of General Surgery and Surgical oncology, SMS Medical College, Jaipur during year 2017-2018.

The aim of this study to study difference of oestrogen and progesterone receptors status in breast cancer patients before and after Neoadjuvant chemotherapy and To evaluate the correlation if any, with oestrogen and progesterone receptor expression and tumour response to primary systemic chemotherapy.

Source Of Data:

Eighty patients with histopathologically proven locally advanced breast carcinoma undergoing surgery after neoadjuvant chemotherapy in division of surgical oncology and department. of surgery, SMS Medical College, Jaipur will be included.

Collection of data:

After explaining about the study to the subjects, an informed consent will be obtained, followed by a detailed history with clinical examination with more emphasis on the parameters given below in outcome variable.

- Hormones receptor(ER,PR) before and after neoadjuvant chemotherapy.
- Pathological complete response correlation with hormones receptor expression.
- Groups (A-ER+,PR+ ,B-ER+PR- , C-ER-PR+, D-ER-PR-) before and after neoadjuvant chemotherapy.

- Histology
- Grade
- Menopausal status
- Age

Statistics:
The data was coded and entered into Microsoft excel spreadsheet. Analysis was done using SPSS version21.0 (IBM SPSS STATISTICS inc. Chicago, Illinois, USA) Window software program. These variables were assessed for normality using the Kolmogorov Smirnov test. Descriptive statistics included computation of numbers and percentages. Chi- square test and Mcnamer test were used for qualitative data whenever two or more than two groups were used to compare. Level of significance was set at P<0.05.

RESULTS:
This is a descriptive study of 80 LABC patients who received NACT. We found 16.25% pathological complete response (13 patients out of 80 patients), so effective population for study is 67 cases of LABC.

Hormones receptor (ER &PR) changes:
estrogen receptor changes after neoadjuvant chemotherapy. We found more estrogen receptor changes from positive to negative (18.9%) as compared to changes from negative to positive (13.3%). Overall estrogen receptor change rate is 16.4%. It had statistically insignificant result. (Table 1a)

Progesterone receptor changes after neoadjuvant chemotherapy. We found more progesterone receptor changes from positive to negative (36.3%) as compared to changes from negative to positive (8.82%). Overall estrogen receptor change rate is 22.4%. It had statistically significant result. (Table 1 b)

Table 1a- Estrogen receptor status before and after chemotherapy.

Receptor status	Pre. Chemo(N)	Post. Chemo(N)	Change rate	ER Change rate
ER positive	37	30	7/37=18.9%	11/67=16.41%
ER negative	30	26	4/30=13.33%	P= 0.77

Table 1b- Progesterone receptor status before and after chemotherapy.

Receptor status	Pre. Chemo(N)	Post. Chemo(N)	Change rate	PR change rate
PR positive	33	21	12/33=36.3%	15/67=22.4%
PR negative	34	31	3/34=8.82%	P= 0.016

Age:
The mean age of patients in this study was 47.1years. (15-78years) all patients were female. We found more hormones receptor changes in younger female (≤50 year) as compared to older female (>50). 32.6% hormones receptor changes were found in patients who are less or equal to 50 year and 16.6% hormones receptor changes were found in patients who are more than 50 years. It had statistically insignificant result

Menopausal Status:
Premenopausal female were more likely hormones receptor changes after neoadjuvant chemotherapy as compared to postmenopausal female. 34.2% hormones receptor changes were found in premenopausal female and 21.8% hormones receptor changes were found in postmenopausal women. It had statistically insignificant result.

Histology:
Hormones receptor changes after neoadjuvant chemotherapy as there was only one case of lobular carcinoma no inference regarding hormones receptor changes according to histology could be made.

Grade:
Hormones receptor changes were more likely in high grade as compared to lower grade. 66.6% hormones receptor changes were found in grade lll and 14.2%, 25.6% hormones receptor changes were found in grade l and grade ll respectively. It had statistically significant result. (Table 2)

Table 2- Relation of hormones receptor changes to tumour grade in breast cancer.

GRADE	No. Of patient (n=67)	Receptor stable (n=48)	Receptor change any
I	07(10.44%)	06(85.8%)	01(14.2%)
II	39(58.20%)	29(74.4%)	10(25.6%)
III	12(17.91%)	04(33.4%)	08(66.6%)
NA	09(13.43%)	09	0

P= 0.006

Initial tumour stage:
Hormones receptor changes were more likely in high tumour stage as compared to lower tumour stage. 36.8% hormones receptor changes were found in T4 and 25% hormones receptor changes were found in T2 and T3 respectively. It had statistically insignificant result. (Table 3)

Table 3- Relation of hormones receptor changes to initial tumour stage in breast cancer.

Tumour stage	No. Of patient(n=67)	Receptor stable(n=48)	Receptor change any(n=19)
T1	0	0	0
T2	12(17.9%)	09(75%)	03(25%)
T3	36(53.7%)	27(75%)	09(25%)
T4	19(28.3%)	12(63.2%)	07(36.8%)

P=0.625

Neoadjuvant chemotherapy regimens:
Hormones receptor changes were more likely in patients who were treated with anthracyclines regimen as compared to treated with taxanes alone and anthracyclines and taxanes combination. 30.6% hormones receptor changes were found in patients who were treated with anthracyclines alone and 25%, 16.6% hormones receptor changes were found in patients who were treated with anthracyclines and taxanes combination and taxanes alone respectively. It had statistically insignificant result. (Table 4)

Table 4 - Relation of hormones receptor changes to chemotherapy regimen in breast cancer.

Regimen	No. Of patients(n=67)	Receptor stable(n=48)	Any receptor change(n=19)
Anthracyclines based	49	34(69.4%)	15(30.6%)
Anthracyclines +taxanes based	12	09(75%)	03(25%)

P= 0.74

DISCUSSION:
Age:
The mean age in our study was 47.1 years and range from 15-78 years. All patients were female. More number of patients was in the age group of ≤50 yr. this is compatible with the study done by Libo yang et al (2018) [8] in which mean age was 46.4 years and maximum numbers of patients were in the age group≤50 yr.

In our study we correlate ER/PR changes after neoadjuvant chemotherapy with age and found that younger patient were more likely to have ER/PR changes (≤50yr) as compared to older patients (>50).

In less than or equal to 50 years old cases 32.6% ER/PR changes were found and in > 50 years old cases 16.6% ER/PR changes were found. These result agrees with result of the study conducted by Libo yang et al (2018).[8] According to these study younger (≤ 50 years) patients tended to convert in receptor status more frequently (P = 0.014). In less than or equal 50 years old cases 28.4% ER/PR changes occur and in >50 years old cases 13.6% ER/PR changes occur.

Menopausal status:
In our study premenopausal patients were more likely to have hormones receptor changes after neoadjuvant chemotherapy as compared to postmenopausal patients. 34.2% hormones receptor changes were found in premenopausal patients and in postmenopausal patients 21.6% hormones receptor changes were found. if only consider absolute change (positive to negative or negative to positive only). These results agree with result of the study done by Marco colleoni et al (2004) [9] premenopausal patients were more likely ER/PR changes (33.5%) as compared to premenopausal (21.9%).

Histology:
Histology as a prognostic factor as has been well documented. Infiltrating duct carcinoma (IDC) was the predominant morphological

category with IDC NOS (not otherwise specified) 98.75% cases and lobular carcinoma 1.25% cases in our study.

In our study hormones receptor changes after chemotherapy as there was only one case of lobular carcinoma no inference regarding hormones receptor changes according to histology could be made. However 100% hormones receptor changes were found in invasive lobular carcinoma and in infiltrating duct carcinoma 27.2% hormones receptor changes were found in our study. These result agree with result of the study done by Libo yang et al(2018) [8] according to these study 23.3% hormones receptor changes were occur in infiltrating duct carcinoma cases and 30.7% hormones receptor changes were occur in other type(invasive lobular carcinoma ,mucinous adenocarcinoma ,cribriform carcinoma).these result also agree with result of study conducted by Ahmed s Ezzat et al (2017) [10] according to these study ER changes two (33%) cases changed from negative to positive in ILC, compared with no cases in IDC. This was statistically significant. Moreover, five (31%) cases changed from positive to negative in IDC compared with three (50%) cases in patients with ILC; however, this was statistically insignificant. And PR changes four (25%) cases changed from negative to positive in patients with IDC compared with two (33%) cases in ILC. Moreover, five (31%) cases changed from positive to negative in IDC compared with two (33%) cases in patients with ILC.

Grade:
When ER/PR changes was compared with tumour grades we found that patient with high tumour grade were more likely to be ER/PR changes as compared to patients with lower grade tumour.

In our study 66.6% hormones receptor changes were found in grade III tumour compared to 14.2%, 25.6% hormones receptor changes were found in grade I and grade II respectively. These result agree with result of the study conducted by Libo yang et al (2018) [8] according to these study 18.9% cases were show hormones receptor changes in grade l and grade ll, 25.8% cases were show hormones receptor changes in grade lll. These results also agree with result of the study done by Ahmed s Ezzat et al (2017) [10] in which 100% cases were show hormones receptor changes in grade lll.

Initial tumour stage:
when hormones receptor changes was compared with initial tumour stage we found that patients with higher stage were more likely to hormones receptor changes as compared to lower stage.

In our study 25% hormones receptor changes were found in T2 stage compared to 36.8% hormones receptor changes in T4 stage. These result agree with study done by Libo yang et al (2018) [8] in which 17% hormones receptor changes were found in T1 stage, 24.3% in T2 stage and 26.7% hormones receptor changes in T3 or T4 stage.

Neoadjuvant chemotherapy regimen:
when hormones receptor changes were correlate with chemotherapy regimen we found that those patients treated with anthracyclines alone were more likely to hormones receptor changes as compared to treated taxanes alone and with anthracyclines and taxanes combination.

In our study 30.6% hormones receptor changes in patients treated with anthracyclines alone and 25%, 16.6% hormones receptor changes in patients treated with anthracyclines and taxanes combination and taxanes alone respectively. According to study conducted by Libo yang et al (2018) [8] 25.3% hormones receptor changes in patients treated with anthracyclines, 23.5% hormones receptor changes in patients treated with anthracyclines and taxanes combination, 20% hormones receptor changes in patients treated with taxanes alone.

According to study done by Olivier tacca et al (2007) [11] Among the 420 tumours, 145 (35%) were HR negative and 275 (65%) were HR positive before NCT. When HR status was retested on the surgical specimen (HR status post- NCT), it had changed in 98 patients (23%) among these 420 tumours: 61 patients (42%) initially HR negative became HR positive, and 37 patients (13%) initially HR positive became HR negative. Among the 61 tumours that had switched to a positive status, 51 (84%) were treated with an anthracycline during NCT, five (8%) were treated with a taxane, and five (8%) were treated with both. Among the 37 tumours that had switched to a negative status, 28 (76%) were treated with an anthracycline during NCT, five (13%) were treated with a taxane, and four (11%) were treated with both.

According to study done by Guangchao jin et al (2015) [12] In anthracyclines treated patients, 28.6% (20/70) of the patients showed ER status changes, 22.9% (16/70) of the patients showed PR status changes. in taxanes treated patients, 16.2% (11/68) of the patients showed ER status changes, 22.1% (15/68) of the patients showed PR status changes. Our results compatible with study done by Libo yang et al (2018). [8]

Hormones receptor changes:
In our study we were found estrogen receptor change rate is 16.4%. 07patients who were ER positive on CNB (core needle biopsy) were found to be ER negative upon resection, and 04 patients were ER negative on CNB were found to be ER positive upon resection. Progesterone receptor change rate was found to be 22.4%, out of which 12 patients were PR positive on CNB turn out to be PR negative on resection and 03 patients were PR negative on CNB turns out to be PR positive on resection. (Table 5)

Table 5: Our results compared with other studies.

STUDY	METHOD	ER CHANGES	PR CHANGES
Aravindh sivanandan anand et al (2016)[7]	Cases-69 No control group IHC cut-off≥1	8.7% changes in status Change: 50% positive to negative, 50% negative to positive	13.04% changes in status Change: 88.9% positive to negative, 11.1% negative to positive
Ramteke p et al (2016)[13]	Cases-100 Control group-50 IHC cut off score≥3	17% Change: 88.2% positive to negative, 11.8% negative to positive	13% Change: 69.2% positive to negative, 30.8% negative to positive
Basak oven ustanlioglu et al (2014)[14]	Cases -80 Control group-53 IHC cut off ≥1	12.5% 90% positive to negative	21.2% 58.8% positive to negative
Jin g et al(2015)[15]	Cases-68 No control group IHC cut-off ≥1	16.2%	22.1%
Shet et al(2007)[16]	Cases-73 No control group IHC cut-off ≥5	13% Change: 5% positive to negative, 8% negative to positive	22% Change: 7% positive to negative, 15% negative to positive
Kasami et al(2008)[17]	Cases-173 Control group-117 IHC cut-off ≥10	11% Change: positive to negative	15.6% Change: positive to negative
Neubauer et al (2008)[18]	Cases-87 No control group IHC cut-off ≥10	8% Change: 43% negative to positive, 57% positive to negative	18% Change: 19% negative to positive, 81% positive to negative
Jain et al (1996)[19]	Cases- No control group IHC cut-off ≥10	17% Change: 67% negative to positive, 33% positive to negative	22% Change: all positive to negative

CONCLUSION:
1. The mean age of presentation of breast cancer in our study was 47.1 years. Range from 15 to 78 years. All patients were female. We compared hormones receptor changes with age and found that hormones receptor changes were more likely in younger patients as compared to older patients after neoadjuvant chemotherapy.
2. Postmenopausal women were more likely to have ER/PR changes after chemotherapy as compared to premenopausal women.
3. Patient with high tumour grade were more likely to have ER/PR changes after chemotherapy as compared to patients with lower grade tumour.
4. We compared hormones receptor changes with initial tumour stages is found that Patient with high tumour stage (T4) were more likely to have ER/PR changes after chemotherapy as compared to patients with lower tumour stage (T2&T3).
5. Patients treated with anthracyclines regimen were more likely to have ER/PR changes as compared to who were treated with anthracyclines and taxanes combination and taxanes regimen.
6. In our study ER discordance is 16.4%. In 7patients estrogen receptor(ER) change positive to negative and in 4patients estrogen receptor change negative to positive. PR discordance is

22.4%. in 12 patients Progesterone receptor(PR) change positive to negative and in 03patients progesterone receptor change negative to positive

7. Patients treated with anthracyclines and taxanes combination were more likely to have pathological complete response as compared to who were treated with anthracyclines and taxanes alone.

8. Patients with high tumour grade were more likely to have pathological complete response after chemotherapy as compared to patients with lower grade tumour.

9. We compared pathological complete response with initial tumor stage and found that Patients with high tumour stage (T4) were more likely to have pathological complete response after chemotherapy as compared to patients with lower tumour stage (T2&T3).

REFERENCES:

1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: E359– 86.

2. *Siegel RL; Miller KD; Jemal A CA Cancer J Clin. 2017; 67(1):7-30 (ISSN: 1542-4863)*

3. Shreshtha Malvia [1], Sarangadhara Appalaraju Bagadi [1], Uma S Dubey [2], Sunita Saxena [1] Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017 Aug;13(4):289-295.doi: 10.1111/ajco.12661.

4. Desai SB, Moonim MT, Gill AK, Punia RS, Naresh KN, Chinoy RF. Hormone receptor status of breast cancer in India: a study of 798 tumors. Breast. 2000; 9:267– 270. doi: 10.1054/brst.2000.0134

5. Rampaul RS, Pinder SE, Elaston CW, Ellis IO,. Prognostic and Predictive Factors in primary breast cancer and their role in patient. Eur J Surg Oncol. 2001 Apr;27(3):229-38.

6. Zhang N, Moran MS, Huo Q, et al. The hormonal receptor status in breast cancer can be altered by neoadjuvant chemotherapy: a meta-analysis. Cancer Investig. 2011;29:594–8.

7. Aravindh Sivanandan Anand1 & Sandeep Thekoot Velayudhan1, Discordance of Estrogen & Progesterone Receptors After Neoadjuvant Chemotherapy in Breast Cancer an Indian Study Indian J Surg Oncol (September 2016) 7(3):316–319

8. Libo Yang1,3, Xiaorong Zhong2, Tianjie Pu1,3, Yan Qiu1,3, Feng Ye3 and Hong Bu. Clinical significance and prognostic value of receptor conversion in hormone receptor positive breast cancers after neoadjuvant chemotherapy Yang et al. World Journal of Surgical Oncology (2018) 16:51

9. Colleoni M, Viale G, Zahrieh D, Pruneri G, Gentilini O, Veronesi P, et al Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: A study of preoperative treatment. Clin Cancer Res 2004;10:6622-8.

10. Ahmed S. Ezzata, Hassan K. Souenia, Hala A. Agenab, Ahmed M. Nowara, Ahmed M.F. Salamaa Changes of biomarkers expression between preoperative biopsy and after definitive surgical treatment in patients with invasive breast cancer who receive neoadjuvant chemotherapy Benha Medical Journal 2017, 34:130–139

11. Tacca O, Penault-Llorca F, Abrial C, Mouret-Reynier MA, Raoelfils I, Durando X, et al. Changes in and prognostic value of hormone receptor status in a series of operable breast cancer patients treated with neoadjuvant chemotherapy. Oncologist 2007;12:636-43.

12. Guangchao Jin1, Yu Han2, Cun Liu3, Liansheng Chen1, Butong Ding4, Shijin Xuan1, Xianqiang Liu1, Guohui Ma1, Jun Gao1, Xingsong Tian5 Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer Int J Clin Exp Pathol 2015;8(1):914-921

13. Ramteke P, Seenu V1, Prashad R1, Gupta SD, Iyer V, Deo SVS2, Gogia A3, Mathur S Alteration in steroid hormone and Her-2/neu receptor status following neoadjuvant chemotherapy in locally advanced breast cancer: Experience at a tertiary care centre in India Indian J Cancer 2016;53:366-71.

14. Basak Oven Ustaalioglu B, Aker Vardar F, Bilici A, Gurleyik G, Erkol B, Kefeli U, et al. Clinical importance of discordance of hormone receptors and Her2/neu status after neoadjuvant chemotherapy in breast cancer J BUON 2014;19:879-86

15. Jin G, Han Y, Liu C, Chen L, Ding B, Xuan S, et al. Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer. Int J Clin Exp Pathol 2015;8:914-21.

16. Shet T, Agrawal A, Chinoy R, Havaldar R, Parmar V, Badwe R. Changes in the tumor grade and biological markers in locally advanced breast cancer after chemotherapy – Implications for a pathologist. Breast J 2007;13:457-64.

17. Kasami M, Uematsu T, Honda M, Yabuzaki T, Sanuki J, Uchida Y, et al. Comparison of estrogen receptor, progesterone receptor and Her-2 status in breast cancer pre- and post-neoadjuvant chemotherapy. Breast 2008;17:523-7.

18. Neubauer H et al (2008) Changes in tumour biological markers during primary systemic chemotherapy. Anticancer Res 28:1797–1804

19. Jain V, Landry M, Levine EA. The stability of estrogen and progesterone receptors in patients receiving preoperative chemotherapy for locally advanced breast carcinoma. Am Surg 1996;62:162-5.