



RETROSPECTIVE STUDY OF THE EFFECT OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCINOMA AT OUR INSTITUTE

Oncology/Radiotherapy

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ABSTRACT

Background: - Breast cancer is most common site-specific cancer in women worldwide. The introduction of NACT has dramatically changed the treatment of LABC improving the surgical resectability and histopathological tumor response. **Material And Method:** - 66 patients of inoperable biopsy confirmed LABC were included in the study. Patients with complete investigation and metastatic work up done were evaluated. After 3-4 cycles of NACT patients underwent surgery. Post operative assessment was done on the basis of MD Anderson scale and CRP score. The pathological response was evaluated. The complete data was documented and analysed statistically. **Result:** - Post NACT and surgery, MD Anderson grade 0 in 7.5% patients, grade I in 4.5% patients, grade II in 45 % patients and grade III in 45% patients. ECE present only in 18% patients. Margins free in 80% of patients. 91% of patients having less than 10 axillary lymph nodes positive for metastasis. 62% patients of TNBC showed good response to chemotherapy. **Conclusion:** - NACT is a reasonable alternative to upfront surgery in the management of LABC. NACT has shown a good pathological response which can be satisfactory correlated with receptor status, lymph nodes, extracapsular extension and margins which can change the treatment decisions and lead to a better outcome. Long-term Disease-Free Survival, Overall survival and Progression Free Survival are under assessment.

KEYWORDS

Locally advanced breast cancer (LABC), Neoadjuvant Chemotherapy (NACT), MD Anderson Grade.

INTRODUCTION:-

Breast cancer is the most common site-specific cancer in women worldwide. Locally advanced breast cancer is defined by presence of a large primary tumor more than 5 cm with or without skin or chest wall involvement or with fixed axillary lymph nodes or with disease spread to ipsilateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastasis. In India it accounts for 30- 35% of all the cases.^[1] NACT is the administration of systemic chemotherapy in locally advanced breast cancer patients in order to convert inoperable tumor into operable tumor. As now with scientific and innovative era NACT is proved to be a boon for the society in increasing the rate of breast conservation surgery with reduced morbidity and better cosmetic outcome.^[2] NACT offers an opportunity for the evaluation of treatment response and assessment of the efficacy of new therapeutic agents so that dose or change to another drug if no response is there can be early and effectively done to save patients from the burden of toxicity.

The spectrum varies from complete response, partial response to nonresponse. Patients who achieve complete response after NACT have better outcomes in terms of long-term disease-free survival and better overall survival.^[3]

The pathology report forms the foundation on which the final response assessment depends and follow up management of breast cancer patients is planned.^[4] After surgery either in the form of BCS or MRM adjuvant treatment of chemotherapy and radiotherapy and hormonal totally depends on the histopathological report and ER, PR, Her2 neu

receptor studies.

Aims And Objectives:-

- 1) To assess the pathological response of Neoadjuvant chemotherapy in cancer Breast.
- 2) To evaluate the effect of NACT on the type of surgery in cancer Breast.
- 3) To assess the correlation of NACT with clinical outcome and to determine the predictive role of tumour characteristics.

MATERIAL AND METHODS:-

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this study was conducted on 66 patients of age between 25-75 years of inoperable locally advanced biopsy confirmed breast cases receiving NACT. Patients with ECOG more than two or with metastatic disease or previously treated for Ca. Breast were excluded from the study. As the treatment of breast cancer is a multidisciplinary approach a complete evaluation of patient before administration of NACT is required. The definitive diagnosis of breast cancer with information regarding tumor type, tumor grade, presence, or absence of necrosis, lymphatic or vascular invasion and receptor status is required so that appropriate selection of NACT could be done along with the status of axillary lymph node. Response to neoadjuvant chemotherapy can be evaluated clinically, radiologically, and pathologically.

Clinical examination is performed by palpation but is difficult for the accurate assessment of tumor response to NACT due to inter observer

variations. Breast imaging modalities include mammography, ultrasound, MRI and PET. Imaging was done in appropriate timings as before starting NACT and before surgery to properly evaluate the comparison of the images and for the assessment of tumor response so that when repeat imaging is used the same modality for breast imaging should be used as the previously used.

Metastatic work up done along with 2D echo. Hormone receptor status i.e. ER, PR and Her2 neu with IHC was done. NACT started depending on stage and receptor status. Most of the patients received NACT 3-4 cycles in the form of inj Cyclophosphamide and Doxorubicin or inj Paclitaxel and Carboplatin or inj Docetaxel, Carboplatin and Trastuzumab. Imaging was done before and after NACT for response evaluation. Surgery in the form of BCS or MRM performed after 2 weeks of NACT. Pathologically response assessment was done post operatively on the basis of MD Anderson scale and CRP score in collaboration with pathology department. The response grading along with the clinicopathological profile of all the patients were noted in masterchart. Detailed histopathological examination was carried out especially looking for chemotherapy induced histopathological changes like necrosis, fibrosis and inflammatory reactions and other changes. The tumor cells were evaluated for dissociation, dyscohesion and loss of organisation along with changes such as necrosis, vacuolation of nucleus and cytoplasm, karyorrhexis, pyknosis and karyolysis. Any change in pattern or type of carcinoma was noted. The stroma was examined for host response including fibrosis, elastosis, collagenization and infiltration by lymphocytes, plasma cells, fibroblast, histiocytes and giant cells.

The spectrum of changes after therapy was defined as complete response i.e. no residual tumor identified, partial response i.e. residual tumor seen singly or in clusters and non-response i.e. no changes identified. Complete pathological response involved the disappearance of all the invasive carcinoma in the breast and axillary lymph node after completion of the therapy.^[5] Post NACT the lymph node evaluation involved the recognition of pronounced lymphoid depletion, atrophy, and fibrosis when there was complete response. Residual tumor was better identified by immunostaining for cytokeratin. The pathology report must include the number of lymph nodes, no of lymph node with metastases, size of largest deposit, the status of tumor response and the presence or absence of extranodal involvement.

The complete data was documented and analysed statistically. The patients were then followed up after surgery for further adjuvant treatment on the basis of histopathological report and receptor status following chemotherapy. Patients requiring radiotherapy were given as per protocol. After radiotherapy hormonal treatment was started as per receptor status.

RESULT:-

The average age of the patients included in the study was 49.7 years. 40 (51%) patients were premenopausal and 32 (49%) were postmenopausal. 40 (61%) patients presented with right laterality and most of the tumors were located in the upper outer quadrant of the breast in 37 (56%) patients. 33 (50%) of patients received AC as NACT, 21 (32%) patients received EC, 7 (10%) patients received FAC, 3 (4.5%) patients received FEC, and 2 (3.5%) patients received TCH as neoadjuvant chemotherapy. 40 (61%) patients underwent BCS after NACT [Table 1].

Table 1: Demographic And Clinical Data Of Patients Selected.

Variables		No. of Cases (n)	Percentage (%)
Age in years	25-40	18	27%
	41- 55	28	43%
	56 - 70	17	25%
	>70	03	5%
Menopausal Status	Premenopausal	34	51%
	Postmenopausal	32	49%
Laterality	Right	40	61%
	Left	26	39%
	Bilateral	00	0%
Tumor Location	Upper outer quadrant	37	56%
	Upper inner quadrant	14	21%
	Lower outer quadrant	04	6%
	Lower inner quadrant	02	3%

Type of Surgery	Nipple areolar complex	09	14%
	BCS	40	61%
	MRM	26	39%
NACT Received	A + C	33	50%
	E + C	21	32%
	FAC	07	10%
	FEC	03	4.50%
	TCH	02	3.50%
BCS - Breast conservative surgery, MRM - Modified Radical Mastectomy, NACT - Neoadjuvant Chemotherapy, A- Adriamycin, C- cyclophosphamide, E- Epirubicin, F- 5-Fluorouracil, TCH regimen: - Docetaxel, Coarboptatin, Trastuzumab.			

Another combination which was common was ER positive, PR positive and Her 2neu negative in 16 (24%) patients out of which 11 (69%) patients were having MD Anderson grade III. 21 (32%) patients had triple negative breast cancer out of which 13 (62%) patients showed good response to chemotherapy [Table 2].

Table 2: Hormonal Receptor Status Of Patients Selected.

Hormonal Status	No. of Cases (n)	Percentage (%)
TNBC	21	32%
TPBC	09	11%
ER +, PR +, HER2neu -	16	24%
ER +, PR-, HER2neu -	08	12%
ER -, PR +, HER2 neu -	01	1.50%
ER +, PR -, HER2 neu +	00	0%
ER -, PR +, HER2 neu +	02	3%
ER -, PR-, HER2 neu +	08	12%
ER +, PR+, HER2 neu not done	02	4.50%

TNBC- Triple negative breast cancer, TPBC - Triple positive breast cancer, ER- estrogen receptor, PR- Progesterone receptor, HER2neu- Human epidermal growth factor receptor 2,

The predominant histological subtype was infiltrating ductal carcinoma in 55 (84%) patients with 33 (50%) patients having grade III carcinoma. After surgery 19 (29%) patients were having pathological stage ypT2N0M0. MD Anderson grade 0 was in 5 (7.5%) patients, grade I in 3 (4.5%) patients, grade II in 30 (45%) and grade III in 28 (43%) patients. Extracapsular extension was present only in 12 (18%) patients and was not found in 54 (82%) patients while LVSI was present in 33 (50%) patients, absent in 32 (48%) patients and unknown status in 1 (2%) patient. Margins were free in 53 (80%) patients. 60 (91%) patients had less than 10 axillary lymph nodes positive for metastasis [Table 3].

Table 3: Histopathological Data Of Patients Selected.

Variables		No. of Cases (n)	Percentage (%)
MD Anderson Score	Score 0	05	7.50%
	Score I	03	4.5
	Score II	30	45%
	Score III	28	43%
Histological Subtype	Ductal Carcinoma	3	3.50%
	Invasive ductal Carcinoma	55	84%
	Lobular Carcinoma	1	1.50%
	Medullary Carcinoma	0	0%
	Others	7	11%
Grade	Grade I	0	0%
	Grade II	7	10.50%
	Grade III	33	50%
	Undifferentiated	26	39.50%
Extracapsular Extension	Present	12	18%
	Absent	54	82%
Lymphovascular Space Invasion	Present	33	50%
	Absent	32	48%
	Unknown	1	2%
Margins	Close	9	14%
	Positive	4	6%
	Free	53	80%
No of Axillary Lymph Node	Less than 10	60	91%
	More than 10	6	9%

19 (29%) patients are now on treatment. 38 (62%) patients completed follow up of nine months out of which only one patient developed brain and bone metastasis for which the radiotherapy treatment is going on. 6 (9%) patients completed follow up of one year six months who are now on remission. Long-term disease-free survival, overall survival and progression free survival are under assessment.

DISCUSSION:-

NACT is beneficial for the patients for downstaging the LABC. The aim of our study was to assess the effect of NACT clinically and pathologically. The median age of patients in our study was 49 years which is a common age for presentation.^[6] The majority of patients were having histological subtype of infiltrating duct carcinoma 84% which is again a common proved histological variant in breast carcinoma. 56% of patients had tumors in the upper outer quadrant of the breast which is the most common situation of breast cancer. 32% of patients were having TNBC showing its increasing trend. 51% of patients were premenopausal. The average number of NACT cycles used in our patient was 4-6. There is a lot of variation in the number of NACT cycles given in neoadjuvant settings. The advantage of giving chemotherapy upto maximal response is that if the patient has achieved good complete response in less than planned cycles continuation of further chemotherapy consolidates the complete response by maintaining the dose intensity. If NACT is given upto the maximal response further regression of the tumor continues which makes BCS more feasible.^[7] Most of the patients 96.5% received anthracycline based chemotherapy as per our institutional protocol. Breast conservative surgery was possible in 61% of cases. The rates reported in the literature ranges from 16% to 80%.^[8] Hence, BCS can be good option after NACT in locally advanced breast cancer patients instead of radical surgery which can add to the better quality of life and better cosmesis.

As per consideration of prognostic factors pathological stage i.e ypT2N0M0 was found to be in 29% patients again showing favourable response to NACT. As per MD Anderson score 7.5% were in class 0 i.e complete response, 4.5% patients were in class I i.e partial response and 45 % patients in class II i.e partial response and 43% in class III i.e chemoresistant.^[9] Overall 57% showed good response to NACT. 62% of patients with TNBC showed good response to NACT and as per literature also TNBC are more chemosensitive tumors.^[10]

The pathological changes were studied in two groups as changes in the tumor cells and changes in the stroma. In the tumor cells necrosis was the most common event observed along with nuclear shrinkage, nucleus vacuolation, pyknotic changes, degenerative changes, loss of architecture, dyscohesion and shrinkage of tumor cells with retrogressive changes like karyorrhexis, karyolysis and pyknosis.^[11]

In the stroma changes like fibrosis, elastosis, collagenization, hyalinisation, microcalcification, neovascularisation, stromal fibrinoid necrosis and mucinous changes were observed. The lymphocytes were the most common inflammatory host response seen. (Figures 1, 2, 3, 4, 5 and 6 show the pathological changes).

Extracapsular extension was absent in 82% of patients' histopathological reports showing favourable response to chemotherapy. LVI was absent in 48% patients, margins were free in 80% patients and 91% patients were having less than 10 axillary lymph nodes positive. All these prognostic factors document the effective role of NACT in LABC.

CONCLUSION:-

Breast cancer remains a heterogenous disease that is present with several different clinical presentations, morphologic features, and molecular characteristics. There is now sufficient evidence to prove the role of NACT in locally advanced breast cancer patients. Assessment of the response to NACT requires an established integrated multidisciplinary care among pathologist, radiologist, surgeon, and oncologist. For proper pathological response assessment responsibilities of a pathologist in proper handling and processing of post treatment surgical specimen play a crucial role. Majors should be taken to standardise pathological reporting and monitor the adherence to already established guidelines in breast cancer. Pathologic evaluation of tumor response to neoadjuvant chemotherapy is of critical importance in the treatment planning and prognosis of the patient. NACT is a reasonable alternative to upfront surgery. In the management of LABC NACT has shown a good pathological response

which can be satisfactory correlated with receptor status, lymph nodes, ECF and margins which can change the treatment decision and lead to a better outcome. Long term DFS, OS and PFS are under assessment.

Images Showing Pathological Response To Neoadjuvant In Cancer Breast



Fig.-1 Hematoxylin and Eosin Stain image showing dense inflammatory infiltrates.



Fig.-2 Hematoxylin and Eosin Stain image showing fibrosis.

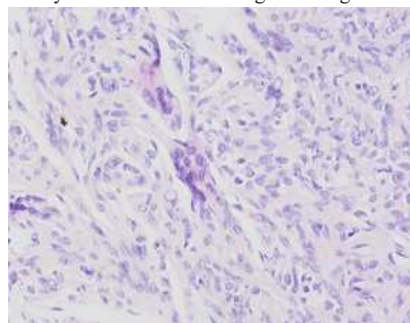


Fig.-3 Hematoxylin and Eosin Stain showing Giant cells.

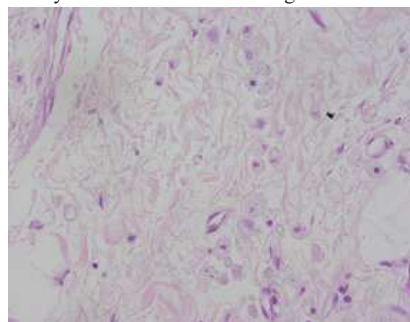


Fig.-4 Hematoxylin and Eosin Stain showing foamy macrophages.

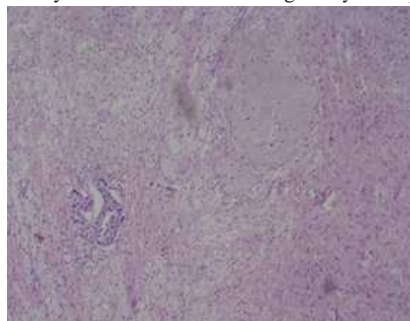


Fig.-5 Hematoxylin and Eosin Stain showing tiny tumor focus.

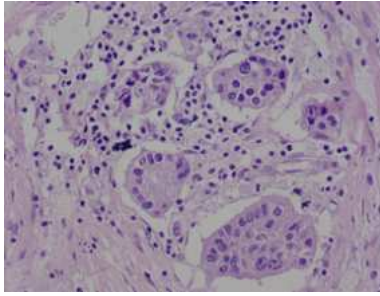


Fig.-6 Hematoxylin and Eosin Stain showing tiny tumor focus.

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