IMPACT OF NEOADJUVANT CHEMOTHERAPY ON LOCALLY ADVANCED BREAST CANCERSurajit Hazarika¹, R. K. Deka², P. C. Kumar³¹Registrar, Department of Surgery, Gauhati Medical College.²Professor, Department of Surgery, Gauhati Medical College.³Associate Professor, Department of Surgery, Gauhati Medical College.**ABSTRACT****BACKGROUND**

Locally advanced breast cancer (LABC) is a common presentation in India with patients presenting with large breast masses with skin involvement or matted axillary nodes, which constitutes 40% of the clinical presentation in medical institutions. The advent of neoadjuvant chemotherapy has radically changed the management of locally advanced breast cancer and a complete response is reported to significantly improve disease free survival. In this study, an attempt was made to check impact of NACT on LABC downstaging as well as assessment of association of clinical response in ER/PR positive LABC cases.

Study Design- Case series of 50 locally advanced breast cancer cases.

MATERIALS AND METHODS

Fifty patients with locally advanced breast cancer, who were admitted in GMCH were selected for the study. True-cut biopsies were performed on all the cases to obtain hormonal receptor status and histology. All patients were put on 4AC-4T (Adriamycin, cyclophosphamide, taxen) NACT regime, at the end of 8th cycle tumour status were evaluated. Post-operative pathological staging obtained were compared with pre-NACT clinical staging. Statistical analysis were done using SPSS version 16.0. An association was found between clinical complete response and hormone receptor positive breast cancer with 'p' value of 0.0013 (p < .05).

RESULTS

All the LABC cases studied in this series were in stage IIIA (72%) and stage IIIB (28%). Majority of cases 26 (52%) showed ER-/PR-receptor status and 10 (20%) cases showed ER+/PR+ receptor status. In the present series seven cases (14%) showed complete response, 26 (52%) cases showed partial response and 17 (34%) cases showed no response. All the cases showed downstaging with two complete pathological response. Out of 36 stage IIIA, 16 cases fell to stage IIB, 18 cases fell to stage IIA and 2 dropped to zero and out of 14 stage IIIB, 8 cases fell to stage IIIA, 5 cases fell to stage IIB and 1 case dropped to stage IIA following NACT.

CONCLUSION

Hormone receptor positive LABC cases responding well to the NACT and a poor response was noticed in stage IIIB disease.

KEYWORDS

NACT, LABC, ER, PR.

HOW TO CITE THIS ARTICLE: Hazarika S, Deka RK, Kumar PC. Impact of neoadjuvant chemotherapy on locally advanced breast cancer. J. Evolution Med. Dent. Sci. 2017;6(69):4961-4965, DOI: 10.14260/jemds/2017/1076

BACKGROUND

Breast cancer is by far the most frequent cancer among women with an estimated 1.7 million new cancer cases diagnosed in 2012 (23% of all cancers) and ranks second overall (11.9% of all cancers), while mortality has increased by 14%. It is now the most common cancer both in developed and developing regions. Breast cancer ranks as the fifth cause of death from cancer overall. Overall risk of breast cancer doubles each decade until the menopause, when the increase slows down or remains stable. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk assume the rate in the host country within one or two generations.

This shows that environmental factors are important in the progression of the disease. According to Globocan (WHO) for the year 2012, India recorded 70,218 deaths due to breast cancer more than any other country in the world (second: China- 47,984 deaths and third: US - 43,909 deaths).¹

The scenario of breast cancer in Assam is almost similar to the national standard. The total number of cases reported in Guwahati and Dibrugarh are 4679 (with relative risk 14.4%) and 2276 (with relative risk 14.8%) respectively in the year of 2007 - 2011, HBCR report. The 5-year relative proportion shows peak incidence in Guwahati between 45 - 49 years, where in Dibrugarh the peak is seen in 10 years younger age group, i.e. 35 - 39 years. The proportion of breast cancer presenting with localised is 1% in Dibrugarh, 7.2% in Guwahati, whereas regional spread is presented with 87.9% in Dibrugarh and 74.2% in Guwahati.

Clinically, when breast cancer has advanced locoregionally but has not yet spread outside of the breast and regional lymph nodes, it is considered locally advanced breast cancer (LABC). In addition, LABC includes breast cancers that have evidence of a large mass, involve the skin of the breast or the underlying muscles of the chest wall and cancers that have infiltrated into the local lymph nodes. In terms of the American Joint Committee on Cancer- "TNM

Financial or Other, Competing Interest: None.

Submission 19-04-2017, Peer Review 15-08-2017,

Acceptance 21-08-2017, Published 28-08-2017.

Corresponding Author:

R. K. Deka,

Professor,

Department of Surgery,

Gauhati Medical College.

E-mail: drranjit_deka@hotmail.com

DOI: 10.14260/jemds/2017/1076

staging system," LABC is defined as stage III disease and is represented by stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), stage IIIB (T4N0-2M0) and stage IIIC (TanyN3M0).

Locally advanced breast cancer (LABC) is a common presentation in India with patients presenting with large breast masses with skin involvement or matted axillary nodes, which constitutes 40% of the clinical presentation in medical institutions,² while LABC accounts for 10% - 20% in the West.³

The diagnosis is made by combination of clinical assessment, radiological imaging and cytological or histological examination.

Women with locally advanced disease require multimodal therapy and coordinated treatment planning among the medical oncologist, surgical oncologist and radiation oncologist is necessary to optimise patient care. The use of chemotherapy, radiotherapy and hormone therapy have made a huge difference in the management of breast cancer. The present standard of treatment for LABC is still evolving. In the past decade anthracycline-based chemotherapy in the neoadjuvant setting followed by surgery and locoregional radiotherapy followed by hormonal therapy in hormone receptor positive patients has been the standard. Taxanes are under intense investigation. Combined or sequential use of anthracyclines and taxanes are both acceptable.³

MATERIALS AND METHODS

In the present series 50 cases of locally advanced breast cancer, admitted and treated in the six surgical units of Gauhati Medical College, Guwahati, during the period from July 2014 to June 2015, are included. The cases are selected on the basis of history, clinical examination, radiological and pathological findings.

Statistical Analysis were done using SPSS Version 16.0

Clinical Complete Response and Positive Hormonal Receptor Status Association

ER+/PR+		Complete	Partial	No Resp.	Total
Yes	No	6	2	2	10
	%	85.70%	6.50%	16.70%	20.00%
No	No	1	29	10	40
	%	14.30%	93.50%	83.30%	80.00%
Total	No	7	31	12	50
	%	100.00%	100.00%	100.00%	100.00%

**ER+/PR+ Breast Cancers
and Clinical Response Cross-Tabulation**

The 'p' value calculated from above table is less than .05 ($p < .05$) and the association is statistically significant, i.e. both hormones receptor positive LABC's were more sensitive than the rest.

Clinical Response and LABC Staging Association

Stage		Complete	Partial	No Resp.	Total
IIIA	N	6	30	0	36
	%	85.70%	96.80%	0.00%	72.00%
IIIB	N	1	1	12	14
	%	14.30%	3.20%	100.00%	28.00%
Total	N	7	31	12	50
	%	100.00%	100.00%	100.00%	100.00%

**Clinical Stage and Clinical
Response Cross Tabulation**

'P' value calculated from the above table is less than .05 ($p < .05$) and the association is statistically significant, i.e. stage IIIA LABC's were more sensitive to neoadjuvant chemotherapy.

Inclusion Criteria

Cases with locally advanced disease (stage IIIA, IIIB, IIIC) are included in the study.

Stage IIIA T0 N2 M0.
T1a N2 M0.
T2 N2 M0.
T3 N1 M0.
T3 N2 M0.

Stage IIIB T4 N0 M0.
T4 N1 M0.
T4 N2 M0.

Stage IIIC Any T N3 M0.

Exclusion Criteria

Early breast cancer, metastatic and recurrent diseases are excluded from the study.

After complete history taking clinical examination, baseline investigations were done along with tru-cut biopsy and mammography.

Management of Locally Advanced Breast Cancer in this Study

All the patients were treated as follows-

- Neoadjuvant chemotherapy.
- Surgery.
- Radiotherapy.
- Hormonal Therapy (ER, PR Positive cases).

Neoadjuvant Chemotherapy

After complete workout, body surface area was calculated from height and weight of the patient and patients were put on chemotherapy cycles. All the patients were treated with 4 cycles of Adriamycin (60 mg/m², On Day 1); Cyclophosphamide (500 mg/m² on Day 1) followed by 4 cycles of Taxol (paclitaxel, 175 mg/m²) every 3 weekly.

A support of oral APREPITANT capsule was given to prevent chemotherapy induced vomiting.

Another support of PEGYLATED FILGRASTRIM was given to prevent chemotherapy-induced neutropenia.

During the chemotherapy period 2 weekly monitoring of TC, DLC, Hb%, Platelet Count and LFT's were done.

Response Assessment after Neoadjuvant Chemotherapy

- Clinical complete response: Disappearance of all known disease at primary sites and nodes.
- Partial response: At least a 50% reduction in bi-dimensional tumour size of all lesions added together with no appearance of new lesions.
- Stable disease: If any composite lesion increased by lesser than 25% and no new lesion appeared.
- Pathological complete response: If the mastectomy specimen did not reveal any histological evidence of invasive carcinoma in the breast or axilla.

Surgery

All the patients underwent modified radical mastectomy with 7 cases of primary skin grafting; 100% graft acceptance was seen.

Radiotherapy

Radiotherapy was given to all the patients irrespective of axillary lymph nodes status using Cobalt 60.

The dose of radiation is 50 Gy/ 5 wks. including chest wall, internal mammary, supraclavicular, infraclavicular and axillary nodes. Radiation can be given by telecobalt, low or high-energy accelerators and photon beam.

Hormonal Therapy

Patient with positive hormonal receptors were treated with 20 mg Tamoxifen daily for 5 years.

Staging

Following MRM specimen sent for HPE, pathological staging obtained were compared.

RESULTS

The present study has been carried out in the Department of Surgery, Gauhati Medical College and Hospital, Guwahati for a period of one year from July 2014 to June 2015. It comprises of a series of 50 cases of locally advanced breast cancer, all females.

Incidence

Total CA breast cases admitted in the study period were 178. Out of 178 cases, 63 cases in LABC category with incidence rate of 35.39% and 50 cases were considered for study.

Age

Age in Years	Number of Patients	Percentage (%)
21-30	0	0
31-40	16	32%
41-50	25	50%
51-60	7	14%
61-70	2	2%

Table 1. The Incidences of Locally Advanced Breast Cancer in Relation to the various Age Groups were as Follows

Religion

Religion	No. of Patients	Percentage
Hindu	38	76%
Islam	12	24%

Table 2. The Religions in the Present Series of Forty Five Patients were as Follows

Age of Menarche

All patients attained menarche by the age of 15 years, 39 (78%) patients had attained menarche before the age of thirteen years, remaining 11 (22%) attained menarche between 13 and 15 years.

Menopausal Status

Out of 50 female patients 30 had attained menopause, i.e. 60%; and the remaining 20 were premenopausal i.e. 40%.

Parity

Parity (p)	No. of Patients	Percentage (%)
P ₀	3	6%
P ₁	6	12%
P ₂	19	38%
P ₃	16	32%
P ₄	4	8%
P ₅	2	4%

Table 3. The Relationship of Parity to the Incidence of Breast Cancer as seen in this Series of Patients are as Follows

Age at First Pregnancy

Age in Years	No. of Patients	Percentage
Nulliparous	03	6%
16-20	07	14%
21-25	20	40%
26-30	17	34%
31-35	03	6%

Table 4. The following Table shows the Number of Breast Cancer Patients and their Age at First Pregnancy

Side

Side	No. of Patients	Percentage
Right	29	58%
Left	21	42%

Table 5. Side wise distribution of all breast cancers in this study as follows

Presenting Complaints

Lump in the breast was the main complaint in the present series of study 66%; next common was lump in the breast with skin changes- skin changes like fixity, peau d'orange and cutaneous nodules 28%.

Complaints	No. of Cases	Percentage
Painless Lump	33	66%
Lump with skin changes	14	28%
Lump with pain	2	4%
Lump with nipple retraction	1	2%

Table 6

Site within the Breast

The breast was assessed to know the exact site of tumour. Though majority of the tumours had extension to more than one quadrant, the quadrant which was filled totally with the tumour was taken as the site of tumour. Majority of the tumours were seen in upper outer quadrant 60% and least in the lower inner quadrant with 4%.

Axillary Lymph Nodes

In the present series, 46 (92%) patients had palpable axillary lymph nodes. In 43 cases only single mobile axillary lymph node (N1) was palpable and in 3 cases matted lymph nodes (N2) were palpable.

Clinical Staging

All the LABC cases studied in this series were in stage IIIA (72%) and stage IIIB (28%). N3 category disease was absent in the studying series, so no cases in stage IIIC.

Majority of cases 26 (52%) showed ER-/PR- receptor status and 10 (20%) cases showed ER+/PR+ receptor status. Out of all LABC cases, 12 (24%) showed HER-2/neu+ status

and 38 (76%) showed HER-2/neu- status and 7 (14%) found to be triple negative.

Receptor Status	No. of Patients	Percentage
ER+/PR+	10	20%
ER+/PR-	13	26%
ER-/PR+	01	02%
ER-/PR-	26	52%
TOTAL	50	100%
HER2neu+	12	24%
HER2neu-	38	76%
ER-/PR-/Her2neu-(Triple Negative)	07	14%

Table 7. Tru-Cut Biopsy (ER, PR, HER-2/Neu Receptor Status)

Clinical Response following Neoadjuvant Chemotherapy

Seven cases (14%) in the present series showed complete response, i.e. complete disappearance of the tumour on palpation. Majority of the cases 26 (52%) showed partial response, i.e. more than 50% reduction in size of the tumour and 17 (34%) cases showed no response, i.e. less than 50% reduction in size of the tumour.

Histological Type 10

The following table shows the incidence of histological types of breast cancer as seen in the present series of fifty cases.

Histological Type	No. of Patients	Percentage
Infiltrating ductal carcinoma	45	90%
Lobular carcinoma	03	06%
Medullary carcinoma	01	02%
Mucinous carcinoma	01	02%

Table 8

Post-MRM Specimen Pathological Staging

Following MRM, specimen sent for HPE, pathological staging obtained were compared with pre-NACT clinical staging. All the cases showed down staging with two complete pathological response (nodular sclerosing). Out of 36 stage IIIA 16 cases fell to stage IIB, 18 cases fell to stage IIA and 2 dropped to zero, and out of 14 stage IIIB 8 cases fell to stage IIIA, 5 cases fell to stage IIB and 1 case dropped to stage IIA following NACT.

Diagnostic Workout

In the present series, mammography was done in 50 cases; 41 cases in BIRADS category 5 and 9 cases in BIRADS category 4. Ultrasonography diagnosed breast cancer in 42 patients with sensitivity of 84% and 08 patients it was inconclusive. Baseline investigation showed anaemia in seven patients, cardiomegaly in 3 cases. Eight cases had hypoproteinaemia and 2 cases had marginally high liver enzymes.

Management

All the patients were treated in the Department of General Surgery in Gauhati Medical College and Hospital, Guwahati. The management protocols followed in the cases in this series of fifty cases are as follows-

- All the patients received eight cycles of chemotherapy of (4AC-4T) regime. At the end of 8th cycle, clinical response was evaluated.

- All the patients underwent Modified radical mastectomy with 7 cases of primary skin grafting; 100% graft acceptance was seen.

5 cases reported of wound infection and treated with local dressing and oral antibiotics. Seroma formation was reported in 6 cases and were treated with keeping suction drainage catheter for 3 weeks. Dog ear incision was found in 4 cases.

- Radiotherapy was given to all the patients irrespective of axillary lymph node status in B. Borooah Cancer Institute, Guwahati, 3 km away from GMCH.
- All the hormonal receptor positive cases are treated with 10 mg Tamoxifen oral tablet twice daily.

Followup

The patients were followed up monthly for first 3 months and after that every 3 months up to 1 year postoperatively. Then, the patients were advised to come for check-up six monthly and finally once a year for 5 years. No signs of local recurrence and signs of distant metastasis were noted in the followed up cases; 2 cases reported arm oedema at 1st month of followup. Only 7 cases could be followed up at 6th month, post-MRM mammography done at 6th month found to be normal for the contralateral breast. All the cases could not be followed up, as the study duration was only 1 year.

DISCUSSION

The present study comprised of 50 cases of locally advanced breast cancer, admitted into the surgical wards of Gauhati Medical College and Hospital, Guwahati, over a period of 1 year from July 2014 to June 2015. The results and observations of the present series were analysed and compared with available data from different authors.

They were evaluated from the view point of aetiopathology, clinical presentation, diagnosis and treatment. The incidence rate of LABC among all cases of carcinoma breast in this study was 35.39%; V Raina et al reported incidence rate of LABC in his study 26.24%, 2011. Majority of patients in our study were between 41 - 50 yrs. of age with average age of 44.2 yrs., youngest was 33 years old and oldest was 65 years of age. M. Naeem, N. Khan et al (2008) in a series of 46 cases of locally advanced breast cancer found that incidence was highest in the age group of 41 - 50 years.

No male LABC patient was found in the present series. In the present series 38 patients (76%) were Hindus, 12 patients (24%) were Muslims. This however does not reflect an increased propensity of the disease in Hindus, but probably reflects the population ratio religion wise in the area under study.

Majority of the patients, i.e. 39 (78%) attained menarche before 13 years; 30 (60%) patients presented at post-menopausal state. Earlier age at menarche is high risk factor with relative risk of 1 - 2 according to study by Barbara S Hulka.⁴

Most of the patients were multiparous and only 3 patients (6%) were nulliparous. The incidence of the disease was highest among the women who had their first pregnancy between 21 and 35 and women with 2 full-term pregnancies (i.e. parity 2) accounted for the highest incidence, i.e. 19

patients (38%). The mean age at first pregnancy was found to be 24.6 years. All parous women breast fed their babies. None of the patients had suggestive family history of breast cancer.

S. Saxena, B. Rekhi et al (2005) in the series of 569 cases of breast cancer found that 10 (1.75%) cases were nulliparous.

S. K. A. Saad et al (2006) in their study of 52 patients, 10 (19.2%) cases were nulliparous.⁵

The duration of symptoms ranges from 1 month to 2 years and majority of cases (60%) reported in the first 6 months. Painless breast lump was the commonest presentation (66%) followed by 28% patients with breast lump with skin changes, nipple retraction was seen in 15% of the cases. Right breast (58%) was more commonly affected and no bilateral involvement was seen. In most of the cases (60%) upper and outer quadrant of the breast was affected. Axillary lymph nodes were palpable in 46 patients and out of these in 43 patients axillary lymph node was mobile and 3 patients presented with matted lymph node. V. Deo et al (2009) reported 62% in outer quadrant followed by 26% in inner quadrant and 12% in central quadrant.

All the cases reported belonged to stage IIIA (72%) and IIIB (28%). No case was seen in stage IIIC as N3 disease was absent in the study. Swarup Kumar et al 2014 (37 cases),⁶ reported 62.1% in stage IIIA followed by 29.7% in stage IIIB. The commonest histological type was invasive ductal carcinoma, which was present in 43 (86%) cases followed by lobular carcinoma 3 (6%) cases, 1 (2%) of each of medullary and mucinous carcinoma. M. Naeem and N. Khan et al (2008) reported, 82.6% of invasive ductal carcinoma in his study.

Majority of cases 26 (52%) showed ER-/PR- receptor status and 10 (20%) cases showed ER+/PR+ receptor status. Out of all LABC cases, 12 (24%) showed HER-2/neu+ status and 38 (76%) showed HER-2/neu- status and 7 (14%) found to be triple negative. Z. Nahleh et al 2008⁷ reported 53% ER-/PR- status and 18% ER+/PR+ status, and 27% HER-2/neu+ and 73% HER-2/neu-.

Following neoadjuvant chemotherapy, 7 (14%) cases showed complete clinical response; 26 (52%) cases showed partial response; 17 (34%) cases showed no response. Out of 7 complete clinical response, 2 cases showed complete pathological response.

Swarup Kumar et al 2014 (37 cases)⁶ reported 15% clinical response followed by 55% partial response, 10% no response and 20% progressive disease.

The introduction of neoadjuvant chemotherapy has tremendous role in downstaging the disease, thus improving operability rate, locoregional recurrence as well as overall survival rate. In the present study, all the cases showed response to the NACT with two cases showing complete pathological response. An association has been established that impact of NACT on hormone positive breast cancer is more effective than rest of the cases ($p < .05$).

All the patients were treated by neoadjuvant chemotherapy followed by modified radical mastectomy. Radiotherapy was given in all cases. Hormone receptor positive breast cancers were treated with Tamoxifen 10 mg tablet for 5 years.

The patients were followed up monthly for first 3 months and after that every 3 months up to 1 year postoperatively. Then the patients were advised to come for check-ups six monthly and finally once a year for 5 years. No signs of local recurrence and signs of distant metastasis were noted in the followed up cases; 2 cases reported arm oedema at 1st month of followup. Only 7 cases could be followed up at 6 months; post-MRM mammography done at 6th month was found to be normal for the contralateral breast. All the cases could not be followed up as the study duration was only 1 year.

CONCLUSION

NACT was the appropriate treatment for patients with locally advanced stage-III and is worthy of consideration in females with stage-IIIA or IIIB irrespective of tumour size. Response was better in hormone positive breast cancers. Combined modality therapy based on the NACT represents the standard of care for patients with LABC. NACT contributes to improved operability and enhanced local control.

REFERENCES

- [1] Donepudi MS, Kandapalli K, Amos SJ, et al. Breast cancer statistics and markers. *J Can Res Ther* 2014;10(3):506-11.
- [2] Goel AK, Seenu V, Sukla NK, et al. Breast cancer presentation at a regional cancer center. *National Medical Journal of India* 1995;8:6-9.
- [3] Raina V, Kunjahari M, Shukla NS, et al. Outcome of combined modality treatment including neoadjuvant chemotherapy of 128 cases of locally advanced breast cancer: data from a tertiary cancer center in northern India. *Indian J Cancer* 2011;48(1):80-5.
- [4] Poller DN, Snead DR, Roberts EC, et al. Oestrogen receptor expression in ductal carcinoma in situ of the breast: relationship to flow cytometric analysis of DNA and expression of the c-erbB-2 oncoprotein. *Cancer* 1993;68(1):156-61.
- [5] Silverstein MJ, Cohan BF, Gierson ED, et al. Duct carcinoma in situ: 227 cases without microinvasion. *Eur J Cancer* 1992;28(2-3):630-4.
- [6] Breasted JH. *The Edwin Smith surgical papyrus*. Classics of Medicine Library 1930;3:pp 405.
- [7] Moore CH. On the influence of inadequate operations on the theory of cancer. *Med Chir Trans* 1867;50:245-80.