Original Article

Surgical Outcome after Downstaging in Locally Advanced Breast Carcinoma-A Clinical Study of 50 Cases

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Abstract

Background: *The number of deaths related to breast cancer are increasing at an alarming pace worldwide. In Bangladesh incidence rate of breast cancer was about 22.5 per 100000 females. Almost everyone has a palpable lump, and 40% of them have locally advanced breast cancer. The typical treatment for the patients with Locally Advanced Breast Carcinoma (LABC) is neoadjuvant chemotherapy followed by surgery.*

Objective: *To Identify the Surgical Outcome after Downstaging in Locally Advanced Breast Carcinoma*

Materials and Methods: *From January 2018 to December 2020, 50 newly diagnosed locally advanced breast cancer (LABC) patients were enrolled in this prospective study at the Bangladesh Medical College Hospital, Dhaka; to assess the clinical and pathological response of the disease after chemotherapy and surgery. The size of the primary tumor and the size of the axillary nodes were measured and compared to the previous record. The patients had a surgery and axillary excision after three to six weeks of neoadjuvant treatment. The pathological response of the primary tumor and axillary node was examined using histopathology. Other biological markers were tested, including the estrogen receptor (ER), progesterone receptor (PR) and Human epidermal growth factor receptor (Her-2).*

Results: *44 patients (88.0%) responded clinically after four cycles of neoadjuvant chemotherapy, with 7 patients (14.0%) showing complete clinical response (cCR) and 41 patients (82.0%) showing partial response (pCR). In 22 individuals, surgical specimens revealed complete pathological response (cPR) (10 percent).*

Conclusions: *The neoadjuvant chemotherapy schedule for locally advanced breast cancer has good surgical outcome.*

Key words: *Breast cancer, Clinical response, Neoadjuvant chemotherapy.*

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Introduction

Breast Cancer is a type of cancer originating from breast commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk.[1] Breast cancer is the commonest malignant disease among women in the Western world accounting for 1/5th (18%) of all cancer in women. Every year about one million women are diagnosed with breast cancer worldwide and approximately 60,000 die from it.[2] It is also rapidly emerging as a very common cancer in the developing countries as well. In Bangladesh, 16% of the total cancer affected women are victim of breast cancer. WHO also ranked Bangladesh 2nd in terms of mortality rate of women in the country from breast cancer.[3]

Advanced breast cancer is either locally advanced or metastatic disease. Locally advanced breast cancer (LABC) is characterized by varying clinical presentations such as presence of a large primary tumor (>5 cm) associated with or without skin or chest-wall involvement or with fixed (matted) axillary lymph nodes or with disease spread to the ipsilateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastases.[4] These cancers are classified as stage IIB, IIIA, IIIB & IV breast cancer according to the American Joint Committee for Cancer Staging and End Results Reporting (AJCC, 1997). Locally advanced breast cancer is a very common clinical scenario especially in developing countries (30-60%) possibly due to various factors like lack of education and poor socio-economic status (Desai). With this wide spectrum of presentation, management of LABC is a challenge for the oncologist. Treatment of LABC has evolved from single modality treatment consisting of radical mutilating surgery or higher doses of radiotherapy in inoperable disease to multimodality management consisting of surgery, radiation therapy (RT), chemotherapy with or without hormonal therapy.

Breast cancer is categorized into operable and advanced breast

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cancer for the management purpose. After achieving reasonable local control with a combination of surgery and radiation therapy, the overall survival of LABC still remained dismal, as distant metastasis appear in majority of patients within 24 months.[5] Therefore, addressing the systemic component of the disease was considered important with an aim to achieve good Survival in these women. Adjuvant chemotherapy over the last 3-4 decades established a firm place in the management of operable and advanced breast cancer. The use of neoadjuvant chemotherapy (NACT) in LABC was based on the rationale that these patients present with a relatively high burden of micro-metastasis and therefore makes sense to initiate systemic therapy upfront at the earliest.[6] Further studies also showed that response to NACT could be considered as a short-term surrogate marker for long-term outcome and therefore act as an in-vivo marker for tumor response to chemotherapy, especially in the primary tumour.[5] There is however a debate in the application of this strategy. While the use of NACT certainly allows an early initiation of systemic treatment, inhibition of post-surgical growth spurt, delivery of chemotherapy through intact tumor vasculature, in vivo assessment of response and downstaging of primary tumor and lymph node metastases, it facilitates less radical loco-regional therapy. The local treatment for non-responders becomes delayed with risk of drug resistance, chemotherapy having to act on a larger tumor burden, inaccurate pathological staging and a possible increase in the risk of surgery and radiotherapy related complications. With the increasing usage of NACT, an interesting spin off was noted. Since a number of patients achieved significant reduction in their tumor and nodal masses, it became apparent that breast conservation therapy (BCT) could even be respond in these patients, a possibility which is almost unimaginable in the conventional management paradigm.

Surgery has been the oldest treatment for breast cancer, yet its enthusiasm has waxed and waned over a period of time. Different surgeries have been devised, discarded, rediscovered, changed and abandoned again in seemingly endless fashion as physicians sought to employ the science and technology of their own times. William Halsted towards the nineteenth century (1882) described surgical technique for removal of the entire breast and en bloc removal of all axillary lymphatics, the chest wall muscles and at times a part of chest wall with the majority of cases being locally advanced in that era. With the success of Halstedian mastectomy, this surgery became a standard in the management of breast cancer. However, the long- term results were poor with survival ranging from 13-20% at 5 years.[7] The pioneering work by Mc Whirter et al. in the mid-20th century (1949) showed that less mutilating surgery produced results equal to that of radical mastectomy (RM).[8] The switch from RM to less mutilating surgery came when it was largely recognized that treatment failure from breast cancer was largely due to systemic dissemination prior to surgery.[9] A number of prospective randomized trials comparing RM with modified radical mastectomy (MRM) confirmed the evidence.[10] The failure of Halstedian principle of enbloc extirpation of breast and draining lymph nodes to cure many patients of breast cancer, frequent identification of small breast cancer by mammography and success of moderate doses of RT in eliminating sub-clinical foci of breast cancer led to the development of MRM. MRM is the term used to describe a variety of surgical procedures, but all involve complete removal of the breast and some of the axillary lymph nodes. Although it may not seem to differ significantly, it seemed to represent a major departure from Halstedian mastectomy. Considering the above evidence, MRM became the standard of care as compared to RM (Special report: Treatment of primary breast cancer, 1989). In this study we discuss the evolution of the management of LABC and attempt to provide guidelines for current practice.

Materials and Methods

This prospective study was done involving 50 newly diagnosed locally advanced breast cancer (LABC) patients from January 2018 to December 2020 in the Bangladesh Medical College Hospital, Dhaka to observe the clinical and pathological response of locally advanced breast cancer after neoadjuvant chemotherapy and surgery. In the TNM staging classification, LABC is represented by stage IIIA (T0N2, T1N2, T2N2, T3N1, and T3N2), stage IIIB (T4N0, T4N1, T4N2) and stage IIIC disease (any T, N3). Old age (>70 years), distant metastasis, vital functions severely compromised (ASA grade III & IV) & patients who did not receive NACT as per schedule were excluded. Before going to neoadjuvant chemotherapy each patient was evaluated clinically, radiologically; by routine blood test, biochemical test for liver function, kidney function and cardiac function test by ECG and Echocardiogram. Diagnosis was confirmed by FNAC and Core cut biopsy. Baseline patient and tumor characteristics were recorded including age, tumor size, nodal stage, tumor grade, estrogen receptor (ER) status and progesterone receptor (PR) status. Clinical response was assessed after first two cycle of chemotherapy and after completion of four cycles. Surgery was done 4-6 weeks after last cycle of chemotherapy.

Responses were recorded according to Union for International Cancer control (UICC) criteria. A complete clinical response (CCR) was considered if original mass became impalpable, partial response (CPR) if there was 50% or greater reduction in bi-dimensional tumor measurements and progressive disease (CPD) if bi-dimensional measurements increased by 20% or more. Pathological response was assessed at definitive surgery on completion of neoadjuvant chemotherapy. A pathological complete response (PCR) was considered if there was no evidence of residual tumor on histological examination of the surgical specimen. The PCR rate was compared by response category after four cycles of chemotherapy. The observations and results were stated with 95% confidence interval. An appropriate method for small samples was applied to the percentages and p values were determined by chi square test using SPSS version 16.1. Informed written consent was obtained from each patient.

Results

Table I: Clinical Response of Axillary Lymph nodes to Neoadjuvant chemotherapy (n=50).

Clinical Response of Axillary Lymph nodes	n	%
Complete response	11	22.0%
Incomplete or no response	39	78.0%

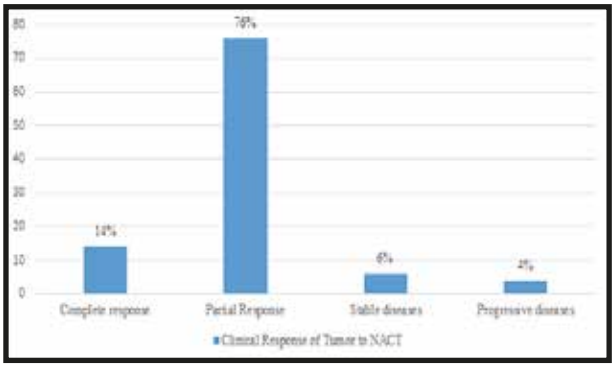

Figure 1: Neoadjuvant chemotherapy response (n=50)

The results were prepared on fifty patients. The median age of the patients at the time of diagnosis was (36±5.9) years (range: 25–70). In terms of menopausal status, 68.0% patients were pre-menopausal while 30% were post-menopausal.

According to histological classification 80.45% were classified as invasive ductal carcinoma (IDC), 15 as invasive lobular carcinoma (ILC) (13.64%) and 7 as other types (5.91%), including mixed invasive patterns. Malignancy grading was also done: 2(4.0%) were grade I, 44 (20%) were grade II and 37 (74.0%) were grade III. Among them her2 receptors were found overexpressed in 33 cases (66.0%) The mean tumor diameter measured in the surgical sample after neoadjuvant chemotherapy was 2.8 cm (range 0–12 cm). Twenty-nine patients (13.18%) had a clinical complete response (CCR), 83 had a partial response (75%), 14 had stable disease (6.36%) and 6 had progressive disease (5.45%) (Figure-I).

Table I shows that clinical examination of the axilla revealed a complete response in 11 (22%) and an incomplete or no response in 39 (78%).

Figure 2: Pathological Response of Tumor to Neoadjuvant chemotherapy (n=50).

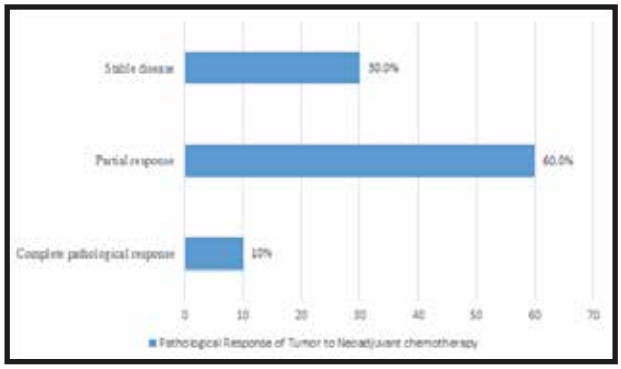

Figure 2 shows that the patients receiving neoadjuvant chemotherapy, underwent modified radical mastectomy. About 10.58% attained complete pathological response (PCR), 60.0% demonstrated partial response, while the rest 30.0% showed pathological stable disease. There was no significant difference in the response rates based on the stage of the disease.

Table-II: Correlation between the histological type of tumors and clinical response (n= 50).

		Complete	Partial	Stable disease	Progressiv disease	
Histologic type	Ductal	7	30	2	0	39
	Lobular	1	2	2	1	6
	Medullar	0	3	0	0	3
	Tubular	0	2	0	0	2
Total		8	37	4	1	50

Basic correlation between histological type of tumors and clinical response showed that 39(78.63%) ductal carcinoma patients showed good response to therapy whereas all progression of tumor observed in 1(2%) patients were lobular type of carcinoma. (Table-II).

Table-III: Baseline patient and tumour characteristics and the distribution of the characteristics by clinical response after four cycles of chemotherapy, (n=50).

Parameter	**Total population N (%)**		**Responders after four cycles**		**Non-responders after Four cycles**		**P value**
	n	%	n	%	n	%	
Tumor Stage							
III a	8	16	7	14	1	17	<0.00001 S
III b	40	80	36	72	4	67	
III c	2	4	1	2	1	17	
Nodal stage							
N 0	3	6	2	4	0	0	
N 1	11	22	10	20	1	17	<0.00001 S
N 2	32	64	31	62	1	17	
N 3	4	8	1	2	4	67	
Tumor grade							
G1	2	4	2	5	0	0	NS 0.114
G2	10	20	8	18	2	33	
G3	38	76	34	77	4	67	

8 patients (16%) had Stage III a disease, 40(80%) had Stage III b disease and 2(4%) had Stage III c disease. Axillary nodal status was N0 in 3 patients (6%), N1 in 11 patients (22%), N2 in 32 patients (64%) and N3 in 4 patients (8%). The tumor grade was G1 in 2(4%) patients, G2 in 10(20%) and G3 in 38(76%). (Table-III)

Estrogen Receptor Status was positive in 35(70%) cases and negative in 15(30%) cases. Progesterone Receptor Status was positive in 28(56%) cases and negative in 22(44%) cases and Her 2 Receptor Status positive in 18(36%) cases and negative in 32(64%) cases.

Table IV: Receptor status of the study patients, (n=50).

Receptor Status	Total population N (%)		Responders after Four cycles		Non responders After four cycles		P value
	N	%	N	%	N	%	
Estrogen Receptor Status							
ER +ve	35	70	32	70	3	75	0.851 NS
ER -ve	15	30	14	30	1	25	
Progesterone Receptor Status							
PR +ve	28	56	25	50	3	6	0.862 NS
PR - ve	22	44	20	40	2	4	
Her 2 Receptor Status							
Her2 +ve	18	36	17	34	1	2	0.895 NS
Her2-ve	32	64	30	60	2	4	

Discussion

A proper evaluation of the tumor to evaluate how it responds to NACT is extremely beneficial for later surgical planning.[11] In our study, neoadjuvant chemotherapy was found to be helpful in cases with locally advanced breast cancer. The clinical response of LABC after employing NACT was observed in 44 patients, with an 88.0 percent success rate. Our findings were comparable with the National Surgical Adjuvant Breast and Bowel Project B-18, which found that 80 percent of 40 patients had an objective response.[12] Patients who obtained full clinical remission may yet have residual tumor histologically.[13,14] In our study, 7 individuals (14.0 percent) achieved complete clinical response, 11 had complete pathological remission, and the remaining 4 had histologically residual illness. Measurement of the tumor's maximal diameter, mammography, or ultrasonography, depending on the patient's age, may offer further information on tumor size following NACT.[15] Although it is unclear if Magnetic Resonance Imaging (MRI) can provide a stronger connection with pathogenic size, first results look encouraging.[16,17] Clouth et al demonstrated that the reduction in tumor enhancement on an MRI scan coincides with the degree of the illness as determined by pathology.[18] However, none of our patients had MRI for this assessment following NACT since the imaging procedure is prohibitively costly in our opinion. Several studies have advocated breast sparing radiation for individuals who have achieved complete clinical response.[19] The ability to correctly evaluate tumor size before neoadjuvant chemotherapy is critical for determining the type and extent of surgery to be undertaken.[20,21] In this study, the patients who exhibited clinical response 76% of them had Grade 3 tumors during diagnosis, which is reliable with numerous studies which proved stronger responses might be achieved in fast proliferating tumors along with a higher grade.[22-24] 70% of the respondents had estrogen receptor positive tumors, which is quite adjacent to the data reported by Raina et al., who found that about 50.5 percent of Indian patients had estrogen receptor positive tumors.[21] In 1992, Redkar et al found 43.9 percent estrogen receptor positive. ER positive was found in 60–80% of individuals in Western studies. Disparities in ER status between Indian and Caucasian patients might be attributed to a lower average age at presentation or ethnic differences.[22] In consistency with previous studies, the presents study found that NACT responders were also had positive estrogen receptors. Besides, a higher objective response rate was observed (cCR+ pCR) in patients with ER-positive in comparison with ER-negative patients (p=0.886). But, the results were not seen statistically significant. Moreover, the patients who attained PCR were ER-positive as well. This finding contradicts the finding of the study of Danishad et al. who reported that ER negative tumors respond better after chemotherapy.[25] Brifford et al reported a highly significant clinical response in patients with invasive ductal carcinoma (IDC).[22] The study of Mathieu et al. and Newman et al. claimed that invasive lobular carcinoma (ILC) is an independent predictor of ineligibility for BCS after neoadjuvant chemotherapy in comparison with IDC.[26] Despite, all these studies demonstrated that ILC patients had less chance to achieve BCS after neoadjuvant chemotherapy, whether the use of neoadjuvant chemotherapy improves the baseline BCS rates for ILC patients was not mentioned there.[27] In this study, 39 patients out of 50 patients diagnosed as invasive ductal carcinoma showed clinical response (complete or partial) to NACT. A complete pathological response was not seen in any lobular carcinomas to NACT in this study. After evaluating all these findings, this study suggests that histological type in breast carcinoma may help in predicting the degree of tissue response and pathologic response to NACT.

Conclusion

Patients with LABC who were admitted to our hospital and treated, excellent response was observed in terms of tumor size, axillary lymph nodes, and pathological response. As a consequence, we may conclude that conventional neoadjuvant chemotherapy is effective in our perspective.

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