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Original Research Article

Clinical, radiological and pathological evaluation of residual disease in women receiving neoadjuvant chemotherapy for locally advance carcinoma breast

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ABSTRACT

Background: Egyptians were first to note this disease, 3,500 years ago and described fairly accurately in George Ebers papyri. This disease occurs almost entirely in women, but men can get it, too. Breast cancer is most common among women worldwide. In India, its second after cancer cervix. Its incidence outranks all other cancers in women >35 years of age. Age adjusted incidence rates vary from 9.7- 28.2/100,000. The treatment of locally advanced breast cancer has considerably changed and now includes a multidisciplinary approach, which is directed both to locoregional control and destruction of distant micro-metastasis. Neoadjuvant therapy causes a reduction in size of primary tumor allowing more conservative surgical approach without any increase in locoregional recurrence rate. Limitations of clinical methods for assessment of response to neoadjuvant chemotherapy have now incorporated by imaging and pathological method.
Methods: In present study author assess LABC clinically, radiologically and pathologically by mammography USG, FNAC and histopathologic examination, pre- and post-neoadjuvant chemotherapy and evaluate response to chemotherapy, reduction of tumor volume and prior assessment of the patient's prognosis.
Results: Present study shown USG is more accurate in assessing residual disease in post neoadjuvant chemotherapy in defining the real extent of residual disease and also superior in term of detecting complete pathological response.
Conclusions: A multimodal assessment of response of neoadjuvant chemotherapy is needed to direct optimal surgical treatment with acceptable cosmesis.

Keywords: LABC, Chemotherapy, Clinical, Evaluation, Pathological, Radiological

INTRODUCTION

LABC generally defined as bulky primary chest wall tumor and extensive adenopathy. This includes patients with T3 (>5cm) or T4 tumors (chest wall fixation or skin ulceration and/ or satellitosis) and N2/N3 disease (matted axillary and/ or internal mammary metastasis).[1] Olivitto, Brito et al, demonstrate that prolonged survival can be achieved when metastatic disease limited to be supraclavicular nodes after appropriate multimodality breast cancer treatment.[2] As a result, AJCC staging system now includes isolated supraclavicular metastases in the stage III/LABC disease category.[3]

Diagnosis of LABC

There is grave clinical presentation like skin ulceration, skin edema, tumor fixation to the chest wall, large and /or

fixed axillary lymph nodes than 2.5cm. Satellite skin nodules and infraclavicular, internal mammary and supraclavicular adenopathy. Shannon M. et al, said LABC includes bulky primary breast tumors (large tumor or those involving the skin or chest wall) and breast cancers with extensive lymphadenopathy.[4] Katia HK et al, studied that tumor locally advanced and non-metastatic involve: tumors with a diameter >5cm, large lymph node involvement, direct involvement of the chest wall or skin, and inflammatory carcinoma.[5]

Evolution of treatment of LABC

Surgeons historically have at forefront of investigating LABC treatment. Haagensen and Stout provided early data suggest of radical mastectomy alone as treatment for LABC over 60 years ago, reporting 5-years local recurrence and survival rates of 46% and 6% respectively.[6] This experience led to the definition of inoperable LABC when patients presented with extensive breast skin edema or satellitosis, intercostals/parasternal nodules, arm edema, supraclavicular metastases, or inflammatory breast cancer. McCready et al, confirmed the prognostic value of axillary staging in LABC patients that have received neoadjuvant chemotherapy followed by axillary lymph node dissection.[7]

Neoadjuvant systemic therapy

Neoadjuvant therapy has become a valuable strategy in multidisciplinary treatment approach to breast cancer. Some clinical data suggest early introduction of systemic therapy improve survival, enable direct assessment of response to systemic treatment, and lead to identification of a subgroup for whom the intensification of treatment has potential to treat micro-metastasis more effectively.

Indications for neoadjuvant chemotherapy

Cristofanilli, studied neoadjuvant chemotherapy for was management of LABC and inflammatory breast cancer, as a strategy for improving local control of these high-risk cases by transforming inoperable disease into amenable to resectable one. Use of neoadjuvant chemotherapy has recently been extended to women who have early-stage breast cancer to improve eligibility for BCS among women presenting with tumors that are bulky in proportion. So, patient expected to require postoperative chemotherapy may be an appropriate candidate for neoadjuvant chemotherapy, regardless of tumor size.[8]

Table 1: Breast response according to RECIST criteria.

Best response	WHO change in sum of products	RECIST change in sum longest diameter
Complete response	Disappearance of all target lesions without any residual lesion; confirmed at 4 weeks	Disappearance of all target lesions; confirmed at 4 weeks
Partial response	50% or more decrease in target lesions, without a 25% increase in any one target lesion; confirmed at 4 weeks	At least 30% reduction in the sum of longest diameter of target lesions, taking as reference baseline study; confirmed at 4 weeks
Stable disease	Neither PR or PD criteria are met	Neither PR or PD criteria are met, taking as reference smallest sum of longest diameter recorded since treatment started
Progressive disease (PD)	25% or more increase in size of measurable lesion or appearance of new lesions	At least 20% increase in sum of longest diameter of target lesions, taking as reference smallest sum longest diameter recorded since treatment stared or appearance of new lesions

Response evaluation criteria in solid tumors (RECIST)

The RESIST introduced by WHO to unify response assessment criteria, to define how to choose evaluable lesions and to enable use of new imaging technologies.[9]

Mammography

Conventional imaging still has an important place in evaluation of breast cancers treated by neoadjuvant chemotherapy, because it gives an accurate determination of tumor size depends on lesion type, contrast between lesion and normal tissue. Vinicombe et al, observed a mammographic response in 82% of cases; seven times mass disappeared, but with a persistence of macrocalcifications; 46 times mass decrease in size, but not in density, 11 times in density but not in size. Architectural distortions were not modified in most cases.[10]

Ultrasound

Breast ultrasound is method of choice for determination of solid and cystic lesions.

Apparently showing a more effective method in determination of tumor measurements. Ultrasound is an alternative method for assessing tumor may predict response to systemic treatment via use of primary colour Doppler.

MRI

Fischer U, MRI is most sensitive and reliable modality for this local assessment. In such patients, a multidisciplinary approach is required, and it is important to emphasize that evaluation of residual disease is still difficult to some of these patients.[11] Greenstein O, studied that MR imaging allows morphological analysis of tumors and kinetic study of their contrast enhancement via neoangiogenesis and found an excellent correlation between histological and MR tumor sizes after neoadjuvant chemotherapy with correlation coefficients ranging from 0.75 to 0.89.[12]

Position emission tomography and molecular imaging

Quon A, and Gambhir SS, as changes in tumor metabolism precede reduction in tumor size, metabolic imaging modalities are promising techniques for monitoring response to neoadjuvant chemotherapy. FDG-PET has a high sensitivity in detection of therapy-induced glucose metabolic rate changes.[13] Tools are needed to increase speed and efficiency of drug development for cancer like targets for drug development include specific kinases, cellular receptors (estrogen receptors) and signaling molecules (Erb/HER receptor tyrosine kinases) for measuring fundamental properties of cancer such as proliferation, apoptosis, angiogenesis and hypoxia.

Pathological response

Waljee JF, studied that diagnosis was typically done by FNAC. Therefore, pathologic information about the carcinoma and information for staging was limited. The combination of image guided biopsies has substantially increased ability to accurately classify and stage carcinoma before surgical excision. Thus, increasing numbers of women with earlier stage operable breast cancers are now being treated with chemotherapy or hormonal therapy before surgery.[14]

Pathological changes occurring in LABC after neoadjuvant chemotherapy

Although there are many different combinations of agents used for neoadjuvant chemotherapy, typical changes are seen in most carcinomas with any type of treatment. The following changes are commonly observed after neoadjuvant therapy.

Neoadjuvant therapy reduces the size of the primary tumor for most patients. Size can usually determine by clinically in minimal treatment response. However, tumor that have undergone a marked response are more difficult to palpate, due to marked softening of the tumour stroma.

Fisher ER, said that most carcinomas do not change in appearance after treatment, except loss of cellularity. However, some tumor may appear to be higher grade, and in rare instances may be lower grade because of cytomorphologic changes seen in residual tumor cells from treatment effect. A change in tumor grade can only be assessed by comparing post treatment tumor to pretreatment biopsy before attributing to cellular pleomorphism to treatment effect.[15]

Arens N, said in general, tumor markers remain same before and after treatment. Changes in Ki-67 (MIB-1) have been suggested as a means to measure response to therapy, particularly with hormonal therapy where inhibition of proliferation is the primary goal, studied that HER2/neu expression rarely change after chemotherapy, but may be diminished in a subset of carcinomas after treatment with trastuzumab.

It is unknown if this change is due to downregulation or selection of tumor cells not expressing HER2/neu.[16]

METHODS

The study was conducted in Department of surgery, Radiodiagnosis, Radiotherapy and Pathology of HIMS, Varanasi. The study included a total of 60 patients presenting to surgery OPD of HIMS Hospital Varanasi, between June 2016 to August 2017.

Inclusion criteria

All female patients LABC undergoing neoadjuvant chemotherapy were included.

Exclusion criteria

Patients who have not undergoing neoadjuvant chemotherapy, post-operative cases of carcinoma of breast, having distant metastasis and whom neoadjuvant chemotherapy was contraindicated.

Clinical assessment

Clinical assessment of disease was done by TNM classification. Measurements were repeated before and after neoadjuvant chemotherapy and response assessed with RECIST criterion.

Radiological assessment

Imaging of both the breast with mammography and ultrasonography.

Mammographic examination

In Film-screen mammography, two standard views, craniocaudal and mediolateral oblique views, of each breast were taken. All the findings including the accurate measurements were confirmed on ultrasonography. Measurements were repeated after neoadjuvant chemotherapy and response assessed with RECIST criterions.

Ultrasonographic examination

In next stage, patients sonologic examination was done. Clinical data obtained was recorded on a preprinted proforma before patient appeared before the sonologist for evaluation.

Neoadjuvant chemotherapy

All patient enrolled in the study were given four cycles of chemotherapy with 5-flourouracil, cyclophosphamide, and adriamycin after taking consent from the patient.

Monitoring

All the patients underwent routine Hemogram, biochemical and cardiological evaluation before and after two weeks of chemotherapy.

Surgical technique

All the patients enrolled in the study underwent modified radical mastectomy by autchincloss technique. Axillary dissection was done en bloc in all the patients. Specimen was tagged with different markers for assistance in orientation during pathological examination.

Pathological examination

Gross examination

Each mastectomy specimen was anatomically oriented and measured in all three dimensions. Skin, nipple and areola were examined; followed by slicing of lesion at 1cm. intervals from deep resected plane. After routine histological processing sections taken were processed in a histokinette.

Statistical Analysis

Data was expressed as mean±SD and as percentage. Student's t-test was used to compare between ordinal data. P value <0.05 was considered to be statistically significant.

RESULTS

Table 2: Age distribution at presentation of LABC.

Age (yrs)	No. of cases	Percentage
≤35	25	41.66%
36-45	16	26.66%
46-55	12	20%
>55	7	11.66%

The age of patients of LABC ranged from 30 to 62 years. The peak incidence of the cases was seen in patients below 35 years of age constituting 41.66% of all enrolled cases. The mean age of presentation was 42.08years with left to right preprodence in ratio 3:1. 70% cases were of premenopausal and 30% cases were of post-menopausal (Table 2).

Table 3: Clinical, mammographic and USG wise size distribution before neoadjuvant chemotherapy.

	Clinical		Mammography		USG	
Size (cm)	No. of cases	%	No. of cases	%	No. of cases	%
<5	7	11.66	42	70	39	65
5-8	44	73.33	18	30	21	35
>8	9	15	0	0	0	0

In present study clinical size of lesion in 11.66% cases were of size <5cm, in73.33% cases were of size 5-8cm and in15% were of size >8cm respectively before neoadjuvant chemotherapy (mean value 6.28cm). So, the peak incidence of the cases before neoadjuvant chemotherapy between 5-8cm (73.33%) of clinical size. 100% LABC had clinically palpable axillary lymph nodes. In present study of 60 LABC patient, 70% were T4bN1M0 stage,20% were T3N1M0 stage, 5% cases presented with T3N2M0 stage and 5% cases presented with T4bN2M0 stage respectively (Table 7). Before neoadjuvant chemotherapy 70% cases had lump of size <5cm and 30% cases had lump of size 5-8cm (mean value 4.23cm). So maximum number of cases before neoadjuvant chemotherapy were <5cm of mammographic size. In USG evaluation before neoadjuvant chemotherapy, 65% cases were of size <5cm and 35% cases were of size 5-8cm (mean 4.56cm). So, maximum number of cases before neoadjuvant chemotherapy was <5cm in USG evaluation also (Table 3).

Table 4: Status of estrogen receptor (ER), progesterone receptor (PR), and HER2 neu.

	ER	PR	HER2 NEU
Positive	0	3	42
Negative	60	57	18

In present study none of patients included in the study expressed estrogen receptor ,5% patients expressed progesterone receptor. HER2 was expressed by 70% (Table 4).

Table 5: Comparison of clinical, mammographic and USG size before and after chemotherapy.

Size (cm)	Pre-chemotherapy (mean)	Post-chemotherapy (mean)	P value
Clinical	6.3±1.4	5.2±1.9	<0.001
Mammographic	4.2±1.5	3.6±1.8	<0.01
USG	4.57±1.06	3.74±1.64	<0.01

Pre-chemotherapy Mean clinical size was 6.3cm with standard deviation of ±1.4cm. Post chemotherapy mean value of clinical size was 5.2cm with standard deviation of ±1.9cm. The difference was statistically significant with p value less than 0.001. Prechemotherapy mean mammographic size was 4.2cm with a standard deviation of ±1.5cm. Post chemotherapy mean value of mammographic size was 3.6cm with a standard deviation of ±1.8cm. The difference was statistically significant with p value was equal to 0.01. Pre-chemotherapy mean value of USG size was 4.57cm with a standard deviation of ± 1.06cm. Post chemotherapy mean value of USG size was 3.74cm with a standard deviation was equal to 3.74of ±1.64cm. The differences were statistically significant with p value less than 0.01 (Table 5).

Table 6: Response to neoadjuvant chemotherapy on clinical examination, mammography and USG.

Response	Clinical examination		Mammography		USG	
	No. of case	%	No. of cases	%	No. of case	%
Complete response	0	0	0	0	3	5
Partial response	24	40	18	30	18	30
Stable disease	33	55	36	60	36	60
Progressive disease	3	5	6	10	3	5

In present study on clinical examination none of patients had a complete response. Partial response was observed in 40% of patients, stable in 55% of the patients, the disease was progressive in 5% of patients. In present study on mammography none of patients had a complete response. Partial response observed in 30% of patients, stable in 60% of patients and progressive in 10% of patients. In present study on USG three patient had a complete response (5%), Partial response was observed in 30% of patients, stable in 60% of patient and 5% patients showed progressive disease. On statistical analysis, response was classified based on above categories response was compared as assessed by clinical and imaging methods (Table 6).

On clinical examination, 40% cases were responded to chemotherapy and 60% did not respond to chemotherapy. Mammography identified response in 30% and 70% were non-responders. Likewise, USG identified response in 35% and 65% were non-responders (Table 7).

Table 7: Comparison of response by clinical and imaging methods.

Responses	Clinical examination	Mammography	USG
Responder	24	18	21
Nonresponder	36	42	39

There was no significant difference between the clinical and imaging methods. In post chemotherapy cases 46.66% were had clinical size <5cm (Mean 5.27cm) with a standard deviation of ±1.9cm cm as compare to 65% were had pathological size <5cm (Mean pathological size of 3.9cm) with a standard deviation of ±1.7cm. This difference was statistically significant with p value less than 0.001. The mean size of tumour was 35% larger on clinical examination as compared to mean on pathological examination. In the same way, in comparison of mammographic versus pathologic examination; 75% were had mammographic size <5cm (Mean 3.6cm) with a standard deviation of ±1.8cm as compare to 65% were had pathological size <5cm (Mean value 3.9cm) with a standard deviation 1.7cm. The mean size of tumor was 8% underestimated by mammography but it was statistically insignificant with p value <0.05.

If, author compare USG with pathological examination for extent of tumor 85% were had USG size <5cm (Mean 3.74cm) with a standard deviation of ±1.64cm. USG was superior to both in assessing residual tumour size and underestimated the pathological size by 4%. It was statistically insignificant with p value <0.05 (Table 8).

Table 8: Comparison of residual extent of tumour on clinical examination, mammography, USG and pathological examination.

Size(cm)	Clinical examination post-chemotherapy (no of cases)	Mammographic examination post-chemotherapy (no of cases)	USG examination post-chemotherapy (no of cases)	Pathological examination post-chemotherapy (no of cases)
<5cm	28 (45.66%)	45 (75%)	51(85%)	39 (65%)
5-8cm	27 (45%)	15 (25%)	9 (15%)	21 (35%)
>8cm	5 (8.33%)	0(0%)	0(0%)	0 (0%)

DISCUSSION

The extent of residual disease was an assessed clinical examination was significantly (p >0.05) overestimated on comparison to pathological size. The mean size of tumour was 35% larger on clinical examination as compared to mean on pathological examination.

Mammography underestimated the real extent of the tumour. The mean size of the tumour was 8%

underestimated by mammography but it was statistically insignificant (p <0.05). USG was superior to both in assessing residual tumour size and underestimated the pathological size by 4% which was statistically insignificant (p <0.01). There were three patients with pathological complete response which was rightly detected on USG, but mammography and clinical examination was unable to identify the correct response due to presence of macrocalcification and chemotherapy induced fibrosis.

The study has shown that USG is feasible method of non-invasive evaluating response to neoadjuvant chemotherapy in patients with LABC. The study has shown that USG is superior to clinical examination and mammography in defining the real extent of residual disease although it slightly underestimates the actual size on pathology which is in accordance with the results so far. USG is also superior in term of detecting complete pathological response which clinical examination and mammography are unable to identify In the series of Herrada, ultrasonography was found to be superior to clinical examination and mammography, especially when the tumor was hypoechoic.[17] In the series of Schott, the accuracy of physical examination, mammography and ultrasound in determining the pathologically complete response was 75, 89 and 82%, respectively, without significant differences.[18]

CONCLUSION

LABC may be unresectable due to its large size or local invasion. Induction chemotherapy may downstage the tumour, decrease tumour size and render tumour resectable. The major factor complicating management of this disease is lack of proven method for monitoring the response of such cancers after therapy is commenced. If effectiveness of therapy can be predicted early, selection of the most effective treatment or immediate surgery may be able to minimize associated morbidity.

Many reports indicate that histological response to chemotherapy is single most important prognostic factor in patient with locally advanced breast cancer. Imaging modalities that enable residual cancer to be accurately staged before surgery assist post chemotherapeutic operative management and help to predict prognosis. It is for this reason that, so many investigations focus on preoperative assessment of chemotherapeutic response.

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