**Research Article**

“CLINICO-PATHOLOGICAL ASSESSMENT BY TRIPLE TEST AFTER NEO-ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER PATIENTS: A SINGLE INSTITUTIONAL STUDY”

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**ABSTRACT**

**Introduction:** Breast cancer is the most common invasive cancer in women and the second leading cause of cancer death. The aim of our study is to identify response assessment by triple test after neo-adjuvant chemotherapy. **Material and Methods:** This study was conducted in the Department of Radiotherapy, Government Medical College from August 2018 to January 2020, meeting specified Inclusion and Exclusion Criteria, patients willing to participate in the study were included. Out of twenty five patients, twenty patients were selected for the study. Locally advanced breast cancer were evaluated for response before and after 3rd and 4th cycle of Neo-Adjuvant chemotherapy. Patients were followed up regularly in breast cancer clinic and any evidence of loco-regional or distant metastasis was recorded. **Results:** The overall clinical response rate of the primary tumour to the neoadjuvant chemotherapy was 95% and 5% had progressive disease. Results were compared by triple test i.e. Clinical examinations, Mammography and Ultrasonography. It is seen that triple assessment is better than any single modality of response assessment. **Conclusion:** We conclude that triple assessment is a very useful diagnostic and response assessment tool, to evaluate patients with breast lumps, and to detect patients with breast cancers, with an overall accuracy of 99.3%.

**INTRODUCTION**

Breast cancer is one of the most commonly diagnosed malignancies and the leading cause of cancer death in women over the world[1-2]. It is the leading cause of Cancer mortality among woman aged 30-50 years. Majority of patients present in early breast cancer in western countries is due to increased awareness and screening programmes, but most of the patients in our country still present with either locally advanced or metastatic breast cancer. Metastatic work up was done by Clinical examination, X-ray chest, Whole body bone scan, Mammogram & Ultrasonography of breasts and abdomen, MRI Brain. The accuracy of diagnosis of breast cancer on physical examination is only 70% even in the most experienced hands [3]. To come to a definite diagnosis, clinical judgment needs to be supported by specialized investigations. The two techniques currently available that have excellent patient tolerability are Mammography and Fine Needle Aspiration Cytology [4][3]. There are numerous reports which emphasize that if clinical examination, mammography and FNAC are combined which is known as “Triple Test”, the accuracy of diagnosis reaches 100% [6]. Response to neo-adjuvant chemotherapy were assessed by Triple Test, after 3rd cycle of chemotherapy.

**MATERIAL AND METHODS**

This study was conducted in the Department of Radiotherapy, Government Medical College from August 2018 to January 2020, informed consent was taken from all patients. Staging was done by Clinical Breast Examination involves a thorough physical examination of the whole breast area including both breasts, nipples, armpits and supra clavicular area, X-ray chest, a baseline Mammogram and Ultrasonography of breast & abdomen, Echocardiography Whole body bone scan, CT Scan/MRI brain. The results of diagnostic mammography were given as per BI –RADS grading. Tumour response assess by triple test (Clinically, Imagine and Histopathologically). The Computation of Triple Test Score C-4, M-4, U-4 were grouped together as suspicious.

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RESULTS

Mean age of the patient was 40 years with a range of 20-60 years. 10 Patients were premenopausal and 2 patients were perimenopausal and 8 patients were post menopausal.

Age:

Table 1 Clinical, Imagine and Histopathological Scoring

<table>
<thead>
<tr>
<th>Clinical Examination Score (C)</th>
<th>Imaging Score [Mammography(M), Ultrasoundography(U)]</th>
<th>Histopathology Score (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-Normal</td>
<td>M1/U1-Normal</td>
<td>P1-Normal</td>
</tr>
<tr>
<td>C2-Benign</td>
<td>M2/U2-Benign</td>
<td>P2-Benign</td>
</tr>
<tr>
<td>C3-Uncertain /likely benign</td>
<td>M3/U3-Uncertain/Likely Benign</td>
<td>P3-Uncertain</td>
</tr>
<tr>
<td>C4-Suspeicious of Malignancy</td>
<td>M4/U4-Suspeicious of Malignancy</td>
<td>P4-Suspeicious of Malignancy</td>
</tr>
<tr>
<td>C5-Malignant</td>
<td>M5/U5-Malignant</td>
<td>P5-Malignant</td>
</tr>
</tbody>
</table>

Based on preoperative assessment patients were catégorised –

a) Those who were suitable for Breast Conservation Surgery ie. WLE or quadrantectomy + Axillary clearance. b) Those who were not suitable for breast conservation. All patients joining the trial were fully informed on the objective of trial. Chemotherapy regimens used in LABC patients are FAC, CMF, AC-T and TAC regimens. A peripheral blood count was performed before each course of chemotherapy and if TLC was found less than 4000/mm³, Hb% less than 8gm%,and platelet counts less than 1 lakh chemotherapy was postponed. Injection Ondensetron 8 mg IV, Inj.Dexamethasone 16 mg IV, Inj. Pantoprazole 40 mg was given before chemotherapy. For patients with altered cardiac function, CMF regime was used ,instead of Adriamycin. All patients were advised to take light food on the day of chemotherapy. To assess tumour response, patients were assessed by triple test after 3rd cycle of chemotherapy. Patients were followed up regularly in breast cancer clinic and any evidence of loco-regional or distant metastasis was recorded.

RESULTS

Response was categorized as follows-Complete Response, Partial Response, Stable Disease and Progressive Disease. The demographic data of the patient is as follows : 

Age: Mean age of the patient was 40 years with a range of 20-60 years. 10 Patients were premenopausal and 2 patients were perimenopausal and 8 patients were post menopausal.

Neoadjuvant Chemotherapy

19 patients received FAC and 1 patient received CMF regimen. All patients received preoperative chemotherapy. 14 patients completed all 6 cycles. 5 patients took only one cycle of post operative chemotherapy.
Post Chemotherapy Evaluation

Clinical Response

The overall response rate of the primary tumour to the neoadjuvant chemotherapy was 95% (complete response 45%, partial response 50%). One patient had progression of disease and was offered surgery after two cycles. However for some personal reasons she delayed the surgery and got operated only after 4 cycles.

Table 2 Clinical response

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>9</td>
<td>45%</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>No Response (NR)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Progressive</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100%</td>
</tr>
</tbody>
</table>

Mammographic Response

18 patients underwent mammographic examination before neoadjuvant chemotherapy, while 19 patients had mammogram done following chemotherapy. In one patient mammogram did not show any measurable lesion and thus pre and post chemotherapy mammogram could be compared in 17 patients. Overall mammographic response rate was 82.2%. Responses were complete in 2 (11.7%) patients and partial in 12 (70.5%) patients. No response / or progressive in 3 (17.6%) patients.

Ultrasonographic response

17 patients underwent ultrasonographic examination of the breast before starting neoadjuvant chemotherapy while 19 patients underwent Ultrasonography, post CT. The overall objective response of primary tumour to neoadjuvant chemotherapy was above 88.1% ( complete 5.8% and partial 82.3%).

DISCUSSION

In present study the highest incidence of malignancy was noted 45 % in 41-50 years age group (4th decade) followed by 25% in 31-40 years age group (3rd decade). This is in accordance to other reports published from Indian subcontinent which show that Breast carcinoma in Indian population occurs a decade earlier than western group [7,8].

Neo-adjuvant chemotherapy is being used increasingly in the treatment of patients with large operable locally advanced breast cancer. This is done with the aim of reducing the size of the primary tumour and eliminating the micro metastasis , in order to improve prognosis[9,10,11]. It has been confirmed that patient with pathological complete response (p-CR) to neo-adjuvant treatment have better disease free survival and overall survival.

A wide variety of regimen have been used as neo-adjuvant chemotherapy. These regimens produce a complete pathological remission ranging from 3-18%. Buzdar et al[12] It is anticipated that patients treated with two alternate therapies (Paclitaxel-T followed by FAC) may have better outcome compared with patients continued on the same therapy.

We used FAC in nineteen patients while one patient received CMF. There are no randomized trials comparing FAC with CMF in the setting of neo-adjuvant chemotherapy. In a previous trial reported from AIIMS New Delhi , significantly better response rates were seen with FAC regimen as compared to CMF[13]. Two trials have suggested that response rates are lower with CMF[13]. Therefore we prefer FAC in neo-adjuvant setting and use CMF only if there is any
contraindication to use FAC and with cardiologically compromised patient. There is no apparent trend towards better response among various doxorubicin containing regimens[10]. Singletary et al [14] used three cycles of vincristine, doxorubicin, cyclophosphamide and prednisolone (VACP) at 21 days intervals and found 16% complete clinical response and 84% partial clinical response of which 23% became potential candidate of breast conservation surgery.

In our study, nineteen of our patients (95%) showed some degree of tumour reduction. Nine patients (45%) had complete clinical response, while 10 patients showed partial response (50%). Only one patient had progression of disease on clinical examination. These response rates are similar to those reported in literature using different regimens [15]. The regimen used, resulted in excellent patient compliance and low incidents of minor toxicities, like nausea, vomiting, anorexia, constipation, superficial thrombophlebitis etc. Only one patient develop severe neutropenia for which she was hospitalized and treated. She subsequently received schedules for preoperative chemotherapy. All other patients completed scheduled chemotherapy.

Clinical response rates are believed to be important because this may correlate to patient survival and also help in deciding the further surgical treatment. However it is found that response to chemotherapy is over estimated with clinical examination[16]. As many as one third of the patient thought to be in complete remission on clinical grounds, many may have residual disease on pathological examination [17]. On the other hand persistence of residual abnormalities on physical examination or mammography does not always mean persistence of pathological disease [18].

In our study, 9 patient had clinically CR (45%) but only 5 patient had pathological CR(25%), 3 out of 9 patient who have clinical CR, pathologically they have complete response. On the other hand, 2 patients, those who had partial response clinically, were found in complete remission pathologically.

Assessment of response of therapy by imaging modalities is important because this is crucial in choosing optimal surgical therapy and also because clinical examination often over estimates in tumour size [18]. Herrada et al [19] demonstrated that physical examination correlated best with pathological findings in the measurement of primary tumour.

In our study, the response to neo-adjuvant chemotherapy was assessed by mammographic response in seventeen(17) cases and by ultrasonography in sixteen(16) cases. Mammography response was seen in 82% cases. When we compared clinical CR to clinical nodal status at presentation, it was found that 11 out of 20 lymph node positive patients (55%) had clinical CR as compared to 9 out of 20 node negative patients (45%). This is also consistent with the findings of Fisher et al [11] who found that C-CR rates were nearly similar in patients with ≥ 5 cm tumours regardless of their nodal status of presentation. In contrast only 1 out of 9 clinically nodes negative patient (11%) showed pathological CR as compared to 4 out of 11 node positive patients (37%).

CONCLUSION

Use of triple test, patients with breast cancers with an overall accuracy of 99.3%. On correlating pre and post chemotherapy evaluation by clinical method, mammography and USG, with histopathology, it was found that mammography was the most sensitive (100%) followed by ultrasonography (93.7%) and clinical examination (60%). Thus we conclude that clinical assessment is not sufficient for assessment of chemotherapeutic response and should be supplemented by triple test.

References

7. Sandhu DS, Sandhu S, Karwasara RK, Marwah S. Profile of breast cancer patients at a tertiary care hospital in North India. Indian J Cancer.( 2010);47:16–122.


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