ROLE OF SURGERY IN PATIENTS WITH ADVANCED CANCER BREAST WITH OR WITHOUT INITIAL CHEMO-HORMONO-RADIOTHERAPY

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ABSTRACT

Introduction: Role of surgery has changed or changing globally in the form of down staging and surgery in locally advanced breast cancer to Modified Radical Mastectomy with axillary clearance in locally operable stage IV breast cancer with good performing status. **Aim & Objective: T**o study the role of surgery in patients with advanced cancer breast with or without initial Chemo-Hormono-Radiotherapy. **Material and methods:** The study includes 100 cases of advanced breast cancer-stage IIIb and stage IV, undergoing surgery with or without initial Chemo-Hormono-Radiotherapy. Information regarding family history of similar complaints, operative detailed history, treatment received by the patients was recorded also recorded. Postoperatively patients were followed up every monthly for completion Chemotherapy and clinical examination for first 3 months than 3 monthly interval. Patients were thoroughly examined for local site or Axillary recurrence and progress of the disease in the form of supraclavicular lymph node, opposite breast, arm edema, bony tenderness, chest infection and liver enlargement. **Result:** The highest percentage of breast cancer is reported in age group 51-60 years of age. Mean age of presentation was 52 years. The minimum age of presentation was 30 years and maximum was 80 years. Our study reported infiltrating ductal carcinoma to be the most frequent of all carcinoma of breast, comprising 95% of cases. 7% of patients underwent Palliative Mastectomy while 73% of cases underwent Modified Radical Mastectomy with Axillary clearance. Axillary clearance (level III) was done in 80 patients. While Level I axillary clearance was done in 12 patients. 7 patients underwent palliative mastectomy. Only 58 patients received Neoadjuvent Chemotherapy. 75% of patients received Radiotherapy postoperatively. **Conclusion:** Even though there is definite role of surgery in breast cancer in the early stage of breast cancer, the incidence of patients presenting with advanced breast cancer in a rural population is alarming. The treatment of stage IIIb and stage IV breast cancer is multimodal, evolving and challenging which is further complicated by resistance or refusal of Neoadjuvent Chemotherapy or Radiotherapy by the rural population.

Key words: Advanced cancer breast, Chemo-Hormono-Radiotherapy, Treatment modalities

INTRODUCTION

Breast cancer is the most common cancer in women and women living in North America have the highest rate of breast cancer in the world. The incidence of breast cancer has been steadily rising, making it one of the leading causes of cancer mortality in women worldwide [1]. Incidence of breast cancer in India found to be 20.01 per 100000 women and 0.26 per 100000 men [2].

The treatment of breast cancer is multimodal. The treatment of stage I and stage II disease is standardized in the form of surgery ± Hormonal therapy ± Adjuvant Chemotherapy or Radiotherapy.

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However management of advanced breast cancer is always evolving. New clinical questions have emerged regarding surgery of the primary site in those women with metastatic disease and a resectable intact primary tumour [3].

Surgical treatment of the intact primary in patients diagnosed with stage IIIb and IV breast cancer is generally reserved for palliative indications-bleeding, tumour ulceration, infection and hygienic considerations [4]. In 1943, Haagensen and Stout [5] published their criteria of inoperability for carcinoma of the breast, which hold true today when considering a resection for curative intent.

The criteria include tumour fixation to the chest wall, ulceration and peau d'orange, features considered to be grave prognostic signs. Surgical treatment alone is unlikely to prolong life in patients who possess these grave signs.

Various studies have been done on the role of surgery in advanced breast cancer. There have been significant

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difference in life span of patients who underwent resection of tumour as compared to those who were not operated [6-11]. On the other hand, two investigations suggested that the removal of the primary tumour might not improve survival for metastatic breast cancer [12, 13].

Aim & Objective: To study the treatment modalities in patients with advanced cancer breast (stage IIIb and stage IV) with or without initial Chemo-Hormono-Radiotherapy at Pravara Rural Hospital, Loni.

MATERIALS AND METHODS

Study design: This prospective observational study

Ethics approval: from our institutional ethical committee was obtained before initiation of the study.

Study location: The study was carried out in Pravara Rural Hospital in the Department of Surgery

Study period: May 2015 to March 2017.

Sample size: The study included 100 patients.

Inclusion criteria: All the patients with stage IIIb and stage IV Breast cancer satisfying the inclusion and exclusion criteria were included in the study. Histologically and pathologically proven carcinoma of breast with stage IIIb and IV and who underwent/undergoing surgery in stage IIIb ± initial Chemo-Hormono-Radiotherapy or who underwent/undergoing surgery (Palliative Mastectomy) ± LN dissection or MRM in stage IV ± initial Chemo-Hormono-Radiotherapy were included in the study.

Exclusion criteria: Patients of stage I, stage II and stage IIIa Breast cancer, who did not undergo surgery and those who had performance status of 3 or 4, were excluded from the study.

Methodology

Data regarding personal particular like name, age, sex, caste, education,socio-economic status, chief complaints, past medical history, menstrual history, obstetric history ,breast feeding history, were collected by interviewing patients under study and their relatives with the help of pretested and predesigned proforma.

Information regarding family history of similar complaints, operative detailed history, treatment received by the patients was recorded also recorded. Postoperatively patients were followed up every monthly for completion Chemotherapy and clinical examination for first 3 months than 3 monthly interval. Patients were thoroughly examined for local site or Axillary recurrence and progress of the disease in the form of supraclavicular lymph node, opposite breast, arm edema, bony tenderness, chest infection and liver enlargement.

RESULTS

The study included 100 patients. 90 patients were women while 10 were men. The mean age of patients was 56.8 years. Of these, 28% of patients were of 61-70 years of age, While 20% of patients were at 41-50 years of age. Most of the patients were postmenopausal ie. 78, while 12 were premenopausal. Of the 90 women, 15 were nulliparous. Out of 90 patients, 75 had history of breast feeding. All patients presented with lump in the breast while 10 patients complained of pain and 7 complained of discharge. Right, left and bilateral involvement of breast was seen in 33, 65 and 2 patients respectively. Upper and outer (72) followed by central (37) were the most common quadrants involved in the breast cancer.

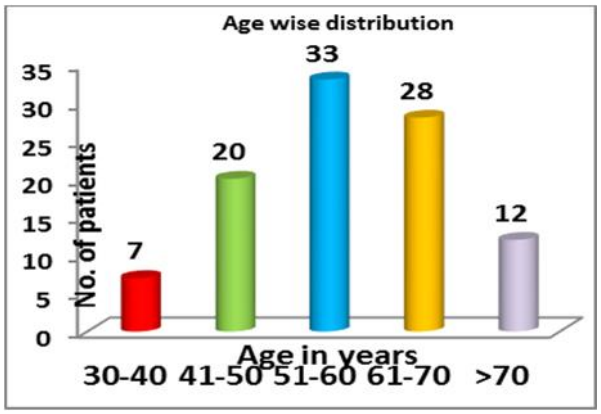

Figure 1: Age wise distribution of patients

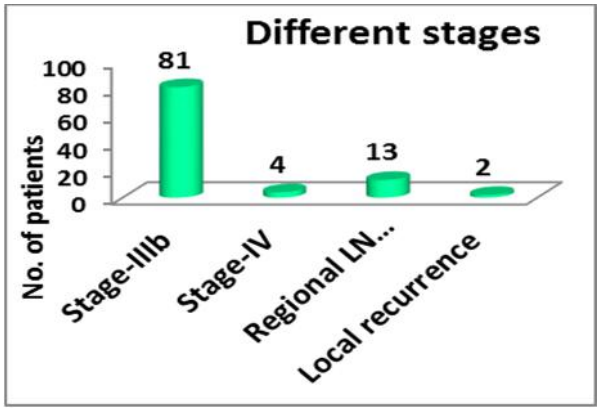

Figure 2: Stage wise distribution of patients

Patients with stage IIIb disease comprised of 80% of total cases, while stage IV patients comprise only 5%. Remaining 12% of patients were of regional LN enlargement and 3% of local recurrence. Axillary lymph nodes were clinically palpable in 82 patients. The nodal status was N_0, N_1 and N_2 in 17, 33 and 27 patients respectively. Histology of postoperative axillary lymph nodes showed that 70 out of 100 were lymph node positive.

Table 1: Axillary lymph node status by clinical examination, Histopathology and staging

	Clinically Palpable Axillary nodes	Histopathology Positive	Nodal status
Present in patients	82	70	N_0 -17, N_1 -33, N_2 -27, N_3 -23
Absent in Patients	18	30	
Total	100	100	100

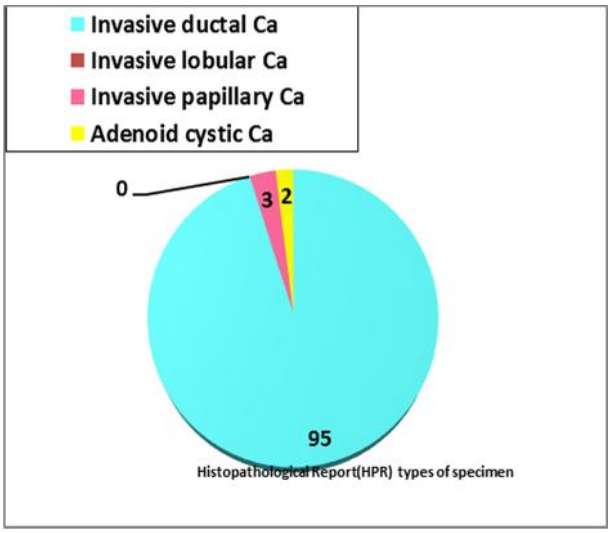

Figure 3: Histopathological Report types of specimen

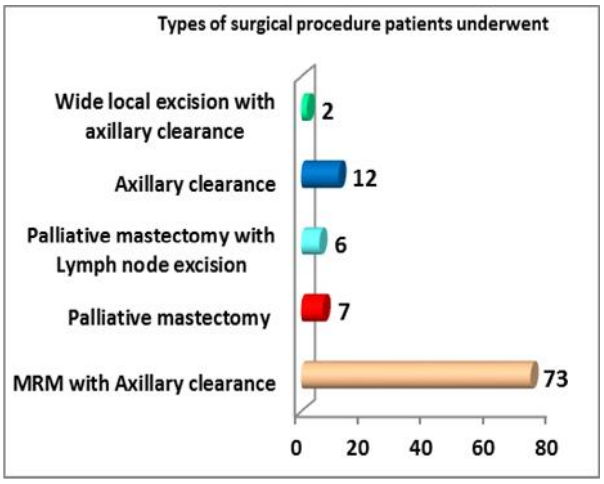

Figure 4: Surgical treatment used in patients

Five patients who underwent palliative mastectomy with/without lymph node excision includes 1 (20%) case of stage IV breast cancer with fungating mass; 3 cases(60%) who refused Neo-adjuvent Chemotherapy and later on came with local complications as fungating mass with secondary infection. One patient received Neoadjuvent Chemotherapy.

One patient with stage IV disease with fungating mass with mobile axillary lymph nodes underwent palliative mastectomy with complete axillary clearance.

Out of 5 patients who underwent palliative mastectomy, 3 patients who were presented with local complications (ulceration/ fungation/ bleeding/ infection) axillary clearance was not done.

One patient who came with local complications received Neoadjuvent chemotherapy+Radiotherapy. This patient underwent palliative mastectomy with axillary clearance upto Level I as Level II lymph nodes found to have fixed intraoperatively.

Out of 100 patients, 58 received Neoadjuvant Chemotherapy. Among the patients who did not receive Neoadjuvant Chemotherapy (42), 21 were locally operable, 15 were operated outside while 7 had local complications

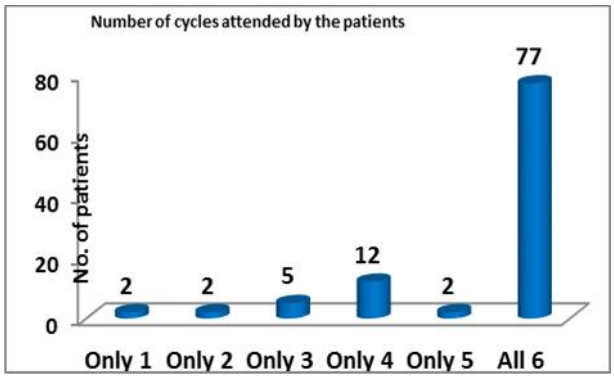

Figure 5: Distribution of patients who received Chemotherapy (CT)

77 patients completed all 6 Chemotherapy cycles.

Among the all patients, 70 received Radiotherapy.

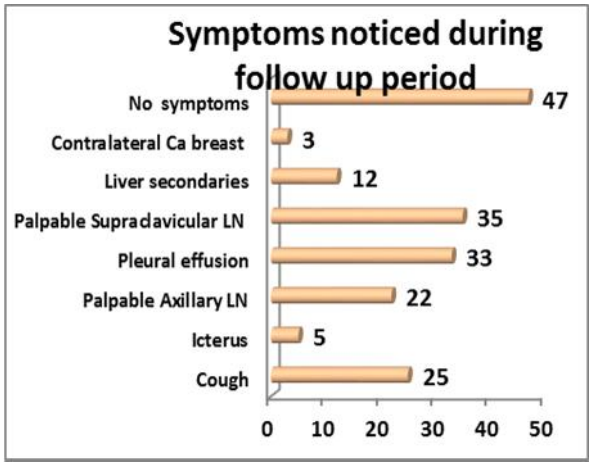

Figure 6: Post-operative complications observed in the patients.

As per our study 25% of patients developed cough progressing to the pleural effusion (33%), 22% of cases developed palpable Axillary nodes during the period of follow up, 35% developed supraclavicular lymph node enlargement. Ultrasonographically liver secondaries were found in 12% of cases while one case i.e.3 % of patients developed contralateral breast cancer for which patients underwent Modified Radical mastectomy with Axillary clearance. 47% of our patients were symptom free during the course of follow up.

Out of total patients of follow up, 10% of patients followed up for less than 6 months, 33% of patients followed up for 7-12 month interval, 40% of cases followed up for 13 to 24 months duration while 2% of cases followed up to 24-30 months duration. 6 patients died during the course of follow up i.e.15%. However this study was of short duration to comment on post-operative outcome after surgery in advanced breast cancer.

Table 2: Summary of treatment received by the patients

Type of Treatment	Neoadjuvant Chemotherapy	Surgical closure	Axillary Lymph node removal	Chemo therapy	Radio Therapy
Number of patients Treatment received	58	92	Complete clearance- **80** Clearance upto level I-**12** Total- **92**	CMF-85 CAF- 15	70
Number of patients Treatment NOT received	42	8	8	0	30
Total	**100**	**100**	**100**	**100**	**100**

DISCUSSION

Oncology has evolved in leaps and bounds and is still evolving. Carcinoma of breast is the commonest malignancy in females and that too in post-menopausal age group with rising trend of incidence almost all over the world [14].

Breast cancer is systemic disease when it is clinically palpable. Mechanism of lymphatic /local /blood born metastases was well understood today and we know how the disease spreads. Metastatic breast cancer is usually associated with the worst prognosis; an average survival of 1-2 years is expected in case of visceral metastases. This common belief has resulted in treatment regimens based on the notion that palliative management is the optional choice for stage IIIb and stage IV patients. This conventional doctrine assumes that both excision of symptomatic and asymptomatic stage IIIb and stage IV disease are unlikely to offer the patient any survival benefit [15].

According to WHO reports from the International Agency for Research on Cancer (IARC), the incidence of the disease is mainly above the age of 40 years. Similar findings have been noted by the Poona Cancer Registry showing more than 66% cases above the age of 40 years during 1981-1985 [16].

As per our study, higher incidence of breast cancer was found in age group 51-60 (32.5%) which corresponds well to the established studies. At the extremes of the age, significantly lower incidence was recorded with no patients below the age of 30 years. Bhaskar et al (1970), Lane Clyppon (1982), Jude (1912), Primorose (1912), Jussawal (1950), all have mentioned the maximum incidence of breast cancer in between 40-60 years of age [17-19].

The incidence of male breast cancer varies from 0.2 to 0.6% [20]. On the contrary our study has showed 10% incidence (10 out of 100 cases) of male breast cancer. Increased incidence of male breast cancer could be because of change in trend of carcinoma of breast, underreported female patients, smaller sample size.

During the course of our study, we came across total 60 cases of breast cancer, out of which 85 patients have stage IIIb and stage IV disease, out of 81 patients were of stage IIIb disease and 4 patients of stage IV disease.

The reasons of larger incidence of higher stage breast cancer in female population at the time of presentation can be many folds. There can be inhibition due to social customs, Unawareness of the disease or Ignorance of the disease.

Our study shows that incidence of disease is higher i.e. 78 out of 90 (86.6%) in postmenopausal women than premenopausal i.e.13.4% which corresponds well with the established studies. As per our study, 16.6% (15 out of 90) of total patients were nulliparous women, explaining it as a risk factor.

86% patients in our study had a history of breast feeding. Breast feeding has shown to have a protective influence against breast cancer [21]. Contrary to this we found increased incidence of breast cancer in breast fed women.

In our study, preponderance was seen on the left side which was involved in 65% and right side in 33% of cases. As per Paul PR, breast cancer shows a predilection for left side (52%) than right (48%) [22]. Bilateral cancer was found in 2% of cases in our study.

In our study, upper outer quadrant was the most frequent site of disease progression. Percentage wise distribution shows upper outer quadrant involvement (72%), central quadrant (37%) and upper inner and lower outer quadrant in 20% and 12% of cases respectively while lower inner quadrant and axilla showed 10% of cases each. Spratt J., Donegan W reported 48% of tumour in upper outer quadrant, 17% in central region, 15% in upper inner quadrant, 11% in lower outer quadrant and 6% in lower inner quadrant [23].

In the present study, 100% patient population presented with lump as their primary symptom, while only 10% patients had complaints of pain and 7% had complaints of discharge as associated symptoms. This is contrary to the findings of Roger G. reported presence of lump in 50% of cases and discharge in 35% of cases [24].

In our study, we found about 18% of cases in which no clinically apparent lymph node involvement was present. Histopathologically (post-operative) 30% were node negative i.e. lymph nodes in these cases not showed evidence of tumour tissue. This means that axillary lymph nodes responded very well to Neoad-

juent Chemotherapy. This results in better locoregional control with resultant good postoperative outcome.

Out of 100 patients,30 patients were clinically node negative. 33 patients were having N1 nodal status. N2 nodal status was present in 27 patients while remaining 23 patients were having N3 (along with N2) nodal status. Our clinical findings of node negative status correlates postoperatively in the form of 30 node negative patients having histopathological node negative status.

In our study, we found Invasive ductal carcinoma in 95% of cases; Invasive papillary and Adenoid cystic carcinoma were noted in 3% and 2% respectively. Medullary and Lobular carcinoma was not recorded at all.GallagerH.S. reported Infiltrating ductal carcinoma as the most frequent type of all carcinomas ofbreast , comprising nearly 75% of all cases [25].

The management of locally advanced breast cancer was a tough challenge in the past, but with the evolution of various treatment modalities it is possible to achieve a prolonged disease free survival and better quality of life. Thus over a period of time multimodality approach (including surgery ± Chemotherapy ± Radiotherapy ± Hormonal therapy) in the treatment of locally advanced breast cancer has become gold standard [26].

In our study 73 patients underwent Modified Radical Mastectomy with Axillary clearance. 7 patients underwent Palliative Mastectomy, and patients also underwent lymph node excision along with Palliative Mastectomy.

While 12 cases underwent Axillary clearance for theirregional Lymph node enlargement. Two patients who came with local recurrence underwent wide local excision with axillary clearance.

As per our study, out of 58 cases receiving Neoadjuvent Chemotherapy, 54 cases i.e.92.5% of cases showed partial response i.e. 50% or greater reduction in sum of products of the perpendicular diameters of measurable disease and no appearance of a new malignant lesion for a minimum of 4 weeks, remaining 4 cases i.e.7% of cases showed stable disease i.e. No appearance of new areas of disease or less than 50% decrease or less than 25% increase in the described measurements. None of the cases has shown complete response or progressive disease.

Good chemotherapy response of local site as well as regional site gives good locoregional control. In our study, histopathologically (post-operative) 30% were node negative i.e. lymph nodes in these cases not showed evidence of tumour tissue. This means that axillary lymph nodes responded very well to Neoadjuent Chemotherapy. This results in better loco-regional control with resultant good postoperative outcome.

In the present study, 85% of cases in our study were given CMF regimen while remaining 15% of patients were given CAF regimen. The schedules were as follows: CMF day 1 and day 8 and CAF for day 1 only and each one repeated 3 weekly. Cycles were given until response to them became static or evidence of progressive disease.

Coskun U et al evaluated locally advanced breast cancer patients who had been treated with different Neoadjuvent Chemotherapy regimens, viz. CAF (Cyclophosphamide, Doxorubicin, 5-Fluorouracil), CA (Cyclophosphamide, Doxorubicin), FEC (5-Fluorouracil, Epirubicin, Cyclophosphamide) ,CE (Cyclophosphamide, Epirubicin) and with CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil) combination in Neoadjuvent settings. In their study, overall response rates were found to be higher in Anthracyclin based combinations than CMF, but these regimens had no additional survival advantage over CMF regimen. They recommended that the long –term effects of these regimens should be investigated in further randomized trials [27].

We found the regimen CMF is cheaper (Rs 370/ cycle) and effective and hence well accepted by poor population of rural India.77 patients were able to complete all 6 Chemotherapy cycles.Remaining patients either taken only single cycle (2%) , only two cycles (2%), only three cycles (5%); some able to continue only four Chemotherapy cycles (12%) and then dropped out.

70 patients received radiotherapy in the present study. Radiotherapy as an approach in Locally advanced breast cancer has been studied by Dalena et al as early as 1978 [28] and more recently studied in the primary management of regionally confined breast cancer by Fletcher G in 1985 [29]. Grim KL studied the role of adjuvant radiotherapy followed by chemotherapy in breast cancer patients treated with mastectomy [30].

22% of cases developed palpable Axillary nodes during the period of follow up. The reasons for palpable axillary lymph node even after axillary clearance might be due to residual disease, micrometastasis, non-responders to chemo-radiotherapy, aggressive tumour or lodging of tumour cells.

Limitation of the study: Being an academic thesis, our study was carried for a period of 2 years. This is the main limitation of the study as most of the cases were still under follow up and observation.

Suggestion: During our study we noted a startling fact of higher incidence of breast cancer in multiparus and breast fed women in rural population. This is contrary to our standard learning. This particular fact needs to be studied in the context with rural population.

There is a definite role of surgery in advanced breast cancer. Hence efforts should be taken to convince the importance of not only Neoadjuvent but also post-operative therapy to the patients and their relatives thereby increasing the compliance and involvement of patient in treatment along with health education and awareness.

CONCLUSION

Problems in rural population are multifocal. 50% of our patients presented with advanced breast cancer. 15% patients ran away from the ward. 25% patients did not complete postoperative treatment (Chemo-Radiotherapy). So even though cancer treatment is a team work, general surgeon in a rural population has to shoulder the additional responsibility of an oncologists, psychologists, plastic surgeons and counselor. All this together will lead to an early and effective treatment of advanced malignancy, long disease-free interval and better quality of life in a rural population..

Conflict of interest : Nil

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