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Original research article

Observation on Modified Radical Mastectomy with Adjuvant Chemotheraphy and Hormonal Therapy in the Management of Breast Cancer

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ABSTRACT
Breast cancer is the most common cause of cancer and cancer death worldwide. Although most patients present with localized breast cancer and may be rendered disease-free with local therapy, distant recurrence is common and is the primary cause of death from the disease. Adjuvant systemic therapies are effective in reducing the risk of distant and local recurrence, including endocrine therapy, anti-HER2 therapy, and chemotherapy, even in patients at low risk of recurrence. The widespread use of adjuvant systemic therapy has contributed to reduced breast cancer mortality rates. Adjuvant cytotoxic chemotherapy regimens have evolved from single alkylating agents to polychemotherapy regimens incorporating anthracyclines and/or taxanes. This review summarizes key milestones in the evolution of adjuvant systemic therapy in general, and adjuvant chemotherapy in particular. Although adjuvant treatments are routinely guided by predictive factors for endocrine therapy (hormone receptor expression) and anti-HER2 therapy (HER2 overexpression), predicting benefit from chemotherapy has been more challenging. Randomized studies are now in progress utilizing multiparameter gene expression assays that may more accurately select patients most likely to benefit from adjuvant chemotherapy.

Keywords: Adjuvant chemotherapy, Anthracyclines, Breast cancer, Chemotherapy

INTRODUCTION
Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women, accounting for 25 % of the total cancer cases (1.68 million) and 15 % of the cancer deaths (520,000) worldwide[1,2]. In the United States, it is estimated that there will be 231,840 new cases of invasive breast cancer and 40,290 deaths from the disease in 2011, and that one in eight women will develop breast cancer during their lifetime [3]. The disease is localized to the breast at presentation in 61 % of cases, regionally advanced in 32 %, and metastatic in 7 % [4]. When localized or regionally advanced, the disease is potentially curable with local and systemic therapy. Adjuvant systemic therapies reduce the risk of distant recurrence, presumably

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by treating micro-metastatic disease that may not be clinically evident at the time of local therapy. Prognostic factors for distant recurrence irrespective of treatment include classical clinicopathologic features such as tumor size, tumor grade, and number of axillary lymph nodes with metastasis. Predictive factors that identify benefit from specific therapies include expression of the estrogen receptor (ER) and progesterone receptor (PR), which identify patients who benefit from adjuvant endocrine therapy[5], and overexpression of human epidermal growth factor receptor 2 (HER2) protein (or HER2 gene amplification)[6], which identifies patients who benefit from adjuvant HER2-directed therapy. Multiparameter gene expression assays may also provide both prognostic information and prediction of benefit from adjuvant chemotherapy in patients with ER-positive disease [7 8].

Adjuvant chemotherapy demonstrated reduction in the recurrence and of death in woman aged 70 years or younger with stage I, IIa, IIb breast cancer. It achieves 25% reduction in risk of relapse over 10-15 years. All node positive patients should receive adjuvant chemotherapy followed with tamoxifen if tumour is ER positive. Node negative patient may also benefit from adjuvant chemotherapy. NATO trial observed that node positive pre menopausal and both node positive and node negative post menopausal women were given tamoxifen 20mg daily for 2 year after mastectomy, there was reduction in recurrence rate (36%) and mortality 20% after median follow up of 66 month.

Two commonly use chemotherapeutic regimen are 6 monthly cycle of CMF (cyclophosphamide, methotrexate, 5fluorouracil) CAF (c= cyclophosphamide, A= Adriamycin, F = 5 Fluorouracil).

Complication of modified radical mastectomy include flap necrosis and sloughing, bleeding and infection in addition to the complication of axillary dissection like arm edema. The patient will be followed up every 3-4 month for 2-3 years and every 6 months for next 2-3 years. Exclusion factors for our study are male breast cancers, advanced breast cancer and women who wants breast conserving surgery.

The present work is under taken to observe the modified radical mastectomy with adjuvant chemotherapy and hormonal therapy for early breast cancer (Stage I, IIa, IIb) where limited resources and medical facilities.

MATERIAL AND METHODS

The study was conducted on female patients of breast cancer admitted in the Department of General Surgery, Darbhanga Medical College and Hospital, Laheriasarai, Bihar from 2009-2012.

METHODS:

1. History and clinical Examination:
   A detailed history was taken and salient features were noted.
2. Physical Examination:
   The points noted were-
   - i) Nipple – Position compared to ipsilateral breast and contralateral breast.
     Contour – Prominent, flat, retracted.
     Surface – Crack, eczema or fissure
     - Discharge if any.
   - ii) Areola - size
     - colour

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- surface

iii) Skin over the breast - for any redness, dimpling, retraction, pitting thicknening, puckerig, ulceration, fungation, peau 'd' orange.

iv) Breast as a whole – size, shape, position, puckering compared to contralateral breast.

v) Arm - oedema

vi) Contralateral Breast.

Palpation:

3. **Systemic Examination** :

Investigations :-

T.L.C., D.L.C., B.T., C.T., Hb%, R/E Urine.
Blood Sugar – post prandial
Chest X-ray P.A. view
U.SG. of liver (if liver enlarged)
F.N.A.C. of lump
Incisional Biopsy/Excisional Biopsy.

Selection of the Patients :-

The patients were selected for the study who fulfilled the following criteria.

a) Size of tumour less than 5 cm.
b) No fixity.
c) No peau 'de' orange.
d) Mobile lymph nodes in the axilla if axilla involved (those with fixed lymph nodes excluded).
e) C.X.R. – PA. view – W.N.L.
f) U.S.G. – N.A.D.
g) Other criteria to judge the patients fitness for Anesthesia and surgery.

Treatment :-

Surgery : Informed consent was taken and patients were subjected to modified radical mastectoymy

Chemotherapy :-

A combination chemotherapy was given to the patients starting just after removal of the stitches i.e. 10-12th day after operation as follows:

Cyclophosphamide 500mg/m^2
Methotrexate 20mg/m^2
5-Fluorouracil 500mg/m^2

The drugs were given throw slow I.V. drip on 1st and 8th day of the month, 1st dose was given on 10-12th day post operative. Guided by-T.L.C., D.L.C., S.G.P.T., Hb%
for six cycles i.e. 12 doses.

Followings were noted during the six to one year of chemotherapy.

1. General Health.
2. Any recurrence.
3. Metastasis – Liver, Lung, Bone.

4. Alopecia.
5. Myelo suppression – T.C.D.C. – Hb% - platelet count.
6. Hepatotoxicity – S.G.P.T., Serum Bilirubin.
7. Nausea vomiting, malaise.
8. Etc.

OPERATIVE PROCEDURE

1. Preoperative Management :- The patients selected were carefully examined for fitness for anaesthesia and surgery by –
   a) Looking for Hb% more than 60%, No infection – systemic or especially lung infection. Spirometry and chest physiotherapy.
   b) Patient counselling – Tactfully the patient and her attendents were explained about the disease and its probable treatment, the effort involved both in terms of time and expenses involved.
   c) Informed consent was taken duly signed by the attendents.
2. In the operation theatre the patients were put on I.V. line on the opposite upper limb to the side of affected breast and under anasthesia (Ether) skin was prepared with cetrimide and.

Sampling for Histopathological Examination :-

The Breast excised along with the tumour mass was carefully examined and tumour mass was bisected and exact measurements taken and whole of it was sent for Histopathological examination.

At the time of operation the lymph nodes removed from the different groups i.e. lateral and anterior (Level-I)- Central (Level-II) and Apical (Level -III) were counted and put in separate containers labelled respectively and were sent for Histopathological examination.

PROCEDURE FOR CHEMOTHERAPY

For administering the combination cytotoxic Chemotherpy patients were informed about the discomfort it may cause and the benefits that was intended to.

The First dose was given just after the stitches were removed and before discharging the patient.

For subsequent shots the patient was admitted for the day, fasting and with reports of Hb%, T.L.C., D.L.C., S.G.P.T. as guiding factors.

A good I.V. line was set up and Metoclopramide was injected first followed by cortisone.

Cyclophosphamide, Methotrexate and 5-Fluorouracil were injected slowly taking about 20-30 minutes time and then multivitamin was added to the drip.

The patient was kept till evening and was allowed to go home if there was no vomiting etc. and patient was comfortable.

The patients were followed up for the period of 6-12 months.

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RESULTS

Table – I

Table showing incidence of age of the patients studied

Age group in years	No. of cases	Percentage
0-10	0	0
11-20	0	0
21-30	01	03.3
31-40	04	13.33
41-50	6	20
51-60	12	40
61-70	7	23.33
Total	30	100

Table – II

Table showing the major symptoms of early carcinoma breast patients.

Symptoms	No. of cases	Percentage
Hard, mobile Breast lump (<5cm)	30	100
Nipple retraction (on the side of lump)	09	30
Nipple discharge	08	26.6
Mobile swelling in axilla	21	70

Table – III

Table showing the number of patients according to site of tumour.

Site (Quadrant)	No. of cases	Percentage
Upper outer (UO)	17	56.6
Upper inner (UI)	04	13.3
Lower outer (LO)	03	10
Lower inner (LI)	02	6.6
Central (c)	04	13.3
Total	30	100

Table – IV

Table showing size of the tumour and No. of cases.

Size of tumour (in cms)	No. of cases	Percentage
0-1.0	0	0
1.1-2.0	3	10
2.1-3.0	8	26.6
3.1-4.0	12	40
< 5.0	7	23.3
Total	30	100

Table - V

Table showing the types of nipple discharge in patients of early Breast cancer.

Type of nipple discharge	No. of cases	Percentage
Bloody	5	62.5
Watery	1	12.5
Serosanguinous	2	25
Total	8	100

Table – VI

Table showing size of tumour associated with palpable axillary L.N.

Size of tumor	No. of cases	Percentage
0-1.0	0	0
1.1-2.0	3	0
2.1-3.0	8	6
3.1-4.0	12	12
< 5.0	7	7

We found that maximum numbers of palpable axillary lymph Nodes are associated with tumour size 3-4cm.

Table – VII

Table showing day of operation during menstrual cycle in pre menopausal women

Day of operation during menstrual cycle in pre menopausal women	No. of cases	Percentage
0-5	2	11.1
6-10	10	55.5
11-15	6	33.3
16-20	0	0
21-25	0	0
26-30	0	0
Total	18	100

We found that better prognosis observed in patient operated between days 3 to 12 during menstrual cycle.

Table- VIII

Table showing the Average time taken in MRM in minutes.

Average time taken in MRM (in minutes)	No. of cases	Percentage
45-60	11	36.6
61-75	16	53.3
> 75	3	10
Total	30	100

We found that time taken in maximum cases of MRM are between 61-75 minutes.

Table – IX

Table showing histological lymph nodes sampling during MRM..

Histology		% of positive L.N
+ve L.N	-ve L.N	
0	1	0
0	2	0
2	1	66.6
4	0	100

We found that No. of lymph nodes sampling during MRM should be more than 4 to increase the positivity.

Table – X

Table showing the post operative complication of MRM

Post operative complications	No. of cases	Percentage
Hematoma	4	13.3
Infection in wound	3	10
Fever	6	20
Chest infection	6	20
Gapping	4	13.3
Sloughing	2	06.6
Pain in scar	3	10
Pain in arm	2	06.6
Oedema of arm	1	03.3
Arm movement restriction	3	10

We found that fever and chest infection are main post operative complication.

Table – XI

Table showing the days of hospital stay after MRM.

Days of hospital stay	No. of cases	Percentage
8-10	11	36.66
11-12	14	46.66
13-14	3	10
>15	2	06.66
Total	30	99.9

We found that maximum No. of cases are discharged from hospital on 11-12 days.

Table – XII

Table showing type of adjuvant therapy regimen.

Adjuvant chemotherapy	No. of cases	Percentage
CMF + Tamoxifen	25	83.33
CAF +Tamoxifen	5	16.66
Total	30	100

C- cyclophsphamide, M- methotrexate F- 5 Flurouracil, A – Adriamycin

Table – XIII

Table showing break up of patients not completing the course of combination chemotherapy

Causes of dropping	No. of cases	Percentage
Cost	7	63.63
Toxicity	3	27.22
Death	1	09.09
Total	11	100

While cause of death could not be ascertained

Table – XIV

Table showing the toxic manifestation of adjuvant chemotherapy in patients who completed the course of chemotherapy

Toxic manifestation	No. of cases	Percentage
Nausea and vomiting	15	78.94
Diarrhoea	5	26.31
Granulocytopenia	6	31.57
Thrombocytopenia	6	31.57
Anemia	8	42.10
Dermatitis	2	10.52
Alopecia	5	26.31
Neurological disorders	1	05.26
Endocrine disorders	0	0
Mortality	1	05.26

Total patient who completed the course of combination chemotherapy is 19.

Table – XV

Table showing the type of responses with combination chemotherapy.

Responses with chemotherapy	No. of cases completing the course	Percentage
Good	19	100
Bad	0	00
Total	19	100

This observation done only in patient who completed the course of chemotherapy and come in follow up. Good response means no local recurrence and systemic metastasis.

Table – XVI

Table showing prognosis of patient in follow up.

Prognosis	No. of follow up cases.	Percentage
No mortality	19	100
Mortality	0	0
Total	19	100

DISCUSSION

The present study comprises of 30 cases of early breast cancer admitted in surgical outpatient department and emergency of Darbhanga Medical College and Hospital, Laheriasarai,

Darbhanga. In this present study we have excluded the benign breast lesion and advanced breast carcinoma with our clinical examination and help of histopathologist because a significant number of female patients were presenting with symptoms of suspected breast carcinoma.

In our study, incidence of breast carcinoma was increasing with increasing age. We found 0% below age of 20 years, 3.33% between 21-30 years, 13.3% of patient between 31-40 years. 20% between 41-50 years. 40% between 51-60 years and 23.3% between 61-70 years. Similar observation was made by NCI, USA, in 1987-1988 when the incidence of carcinoma of breast is extremely rare below the age of 20 years but thereafter, the incidence steadily rises so that by the age of 90 years nearly 20% of women are affected.

This study shows that 70% of cases of breast cancers were hindus and 30% of cases were muslim. This is due to high prevalence of hindu population and higher age at marriage and at their first child in respect to muslim women. This observation was similar to those made by Kelsey JL[9].

This observation shows that 60% of women of cancer breast belongs to higher socio-economic status in comparison to 40% of low socio-economic status. This is mainly due to dietary factor particularly high fat content in diet of high socio-economic group. Blackburn GL. et al (2003)[10] found that chronic consumption of food with high fat content contributes an increased risk of breast cancer by increasing serum estrogen levels.

In this present study, as observed the percent incidence of sporadic, familial and Hereditary breast cancer, we found that (20 out of 30 66.66%) of patients are sporadic, 20% (6 out of 30) of cases are hereditary and 13.33% (4 out 30) are familial. Similar data shown by study of Martin JK, 2000[11] that sporadic cases were 65%-75% familial 20-30% and hereditary cases 5-10%.

Our study shows that almost all cases of early breast cancer were present as hard mobile breast lump with mobile swelling in axilla in 70% (21 out 30) of cases. 56.67% (17 out 30) of cases were present with nipple discharge and retraction.

This observation shows that size of tumour had a definite relation to the axillary lymph nodes. The more the size of tumour more the number of lymph nodes.

In this study most frequent quadrant of breast involved was upper outer 56.66% (17 out 30) while for the other it was 13.33% upper inner (4 out 30), 10% for lower outer, 6.6% for lower inner and 13.33% for central group. This is close to the statistics by Marshal and Higginbothom as 60% for upper outer, 12% upper inner, 10% for lower outer, 6% for lower inner and 12% for central group.

This observation shows that 62.5% (5 out 8) of patients had bloody nipple discharge, 12.5% (1 out of 8) had watery discharge and 25% had serous discharge.

In our study, the maximum number of patient were operated between 6-15 days of their menstrual cycle to get a good response ie recurrence free survival as substantiated by Hruschesky et al (1989) were observed the worst prognosis in the patient operated during 0-6 days and 21-30 days of menstrual cycle. Similar observation by Badwe et al (1991) noted a reduced overall survival and recurrence free survival in patients operated on during days 3-12 of their cycles. Sainsbury &Rounal (1992) also found a better prognosis for patients operated between days 3 and 12 of the menstrual cycle. In present study, the time taken during operation in maximum patient (53.33%) was 61-75 minutes, 45-60 minutes in 36.66% of patient and only 10% operations took more than 75 minutes. This difference in time taken during operation was due to muscular build up of patients and improper relaxation under anaesthesia.

Our study shows that 10% of post operative patient had wound infection 20% of patient had fever mostly due to chest infection. Hematoma and gapping each found in 13.33% of cases. 10%

of patient reported arm movement restriction and pain in scar. Sloughing of skin found in 6.6% patient that need delayed healing by secondary intention or later skin grafting. Only one had edema of arm.

In our observation maximum number of patient 46.66% (14 out 30) were discharged from hospital on 11-12 days, 36.66% (11 out 30) to patient between 8-10 days, 10% of cases (3 out 30) between 12-14 days. Only 6.6% of patient were discharged after move than 15 days, are those having sloughing of skin. Non of the cases had venous thrombosis.

In this present study we have started the adjuvant chemotherapy + tamoxifen to all patients before the discharge from hospital. 83.33% of patient were given the CMF (cyclophosphamide, methotrexate, 5 fluorouracil) regimen and 16.66% of patient were given CAF (cyclophosphamide, Adriamycin, 5 fluorouracil). But only19 patient out of 30 had completed their 6 cycle of monthly course. 14 out 19 had good response and 5 out 19 (26.31%) had fair response. No one had bad response. Adjuvant Hormonal therapy (tomoxifen) had given to all patient 20mg daily for 2 years. This is based on study of Novaldex adjuvant trial organization that shown highly proportional reduction in both recurrences rates (36%) and mortality (29%) in node positive premenopausal and both node positive and node negative post menopausal women (Baum M et al, 1983).

In our study 36.66% (11 out 30) were not completed the adjuvant chemotherapy regimen. 7 out 11 (63.63%) due to financial burden related to costly treatment with drugs and travels, fooding lodging expenses incurred in treatment stretching over six month. 27.22% (3 out 11) had failed to complete the chemotherapy due to toxicity and 1 had died.

The toxic manifestation of chemotherapy observed is given in the tabular from earlier. Maximum number of patients suffered a significant degree of Nausea and vomiting (78.94%).

In this present study, 63.33% have received and completed the combined adjuvant chemotherapy and tamoxifen and found to have a fair to good response in terms of local recurrence and disease free state.

CONCLUSION

On the basis of results and discussion, modified radical mastectomy with adjuvant chemotherapy and hormonal therapy is preferred treatment of early breast cancer in limited resource countries.

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