ROLE OF LOCOREGIONAL TREATMENT IN THE MANAGEMENT OF METASTATIC BREAST CANCER

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ABSTRACT

BACKGROUND

The treatment of metastatic breast cancer depends on the individual patient and receptor status and general condition of the patient. Even with newer systemic and locoregional treatment, metastatic breast cancer cannot be cured completely at present. In few patients with good prognostic factor, these treatment modalities increase the progression-free survival which in turn may significantly affect the overall survival. Many patients with metastases may live several years with modern locoregional treatment and systemic chemotherapy. The aim of the treatment of metastatic breast cancer should be towards increasing the symptom-free survival and quality of life. At the same time the side effects of the treatment should be minimised.

The objective of the study is to evaluate the role of locoregional treatment such as local radiotherapy and surgery in the management of patients with metastatic breast cancer.

MATERIALS AND METHODS

This is a retrospective observational study. One hundred and Ninety-five patients with metastatic breast cancer between the years 2003 to 2008 were taken for this retrospective ongoing study. Among these, seventy-five patients did not receive locoregional treatment, and the remaining one hundred and twenty patients received locoregional treatment to the primary. Locoregional treatment included radiotherapy and surgery.

RESULTS

Patient's survival was analysed at the end of 1 year, 3 years, 5 years, and at the end of 10 years. It was found that, in patients receiving concurrent chemoradiation, survival rates at the end of 1, 3, 5 and 10 years were 89%, 58%, 46% and 42% respectively. Similarly, in patients receiving concurrent chemoradiation followed by surgery, survival was 97%, 80%, 71% and 70% respectively. Further, survival for chemotherapy was 60%, 5%, 2% and 0% respectively. Again, for the arm including only radiotherapy, survival was around 67%, 33%, 33% and 33% respectively. Those patients who receive only hormonal therapy had 50%, 13%, 13% and 13% overall survival at the end of 1, 3, 5 and 10 years.

CONCLUSION

The data reported in this retrospective study confirmed that chemoradiation improved overall survival and symptomatic local control, demonstrated in locoregionally treated patients with metastatic breast cancer.

KEYWORDS

Breast Cancer, Metastatic, Multimodality Treatment.

HOW TO CITE THIS ARTICLE: Balaji S, Kumar SDJ, Selvaluxmy G. Role of locoregional treatment in the management of metastatic breast cancer. J. Evolution Med. Dent. Sci. 2018;7(01):76-81, DOI: 10.14260/jemds/2018/18

BACKGROUND

Carcinoma breast is the most commonly diagnosed cancer in women all over the world, affecting nearly 21% of all cancers diagnosed in females, a with high ratios in North America, Western Europe, intermediate rates in South America and Eastern Europe and low rates in Asia. 10 percent of newly diagnosed breast cancer patients have metastatic breast cancer. After all treatments, nearly one third of patients will have progressive disease. Metastatic breast cancer median survival is for 3 years.

The range is very wide with some patients having more indolent disease that they can live up to 10 – 15 years, while for others with disseminated metastatic disease, the prognosis will be in the range of months from the time of diagnosis. This will represent the disease extent and distribution of metastatic disease, and reflects the biological behaviour of carcinoma of breast, while some women have disease which shows good response to hormonal treatments, while others with triple negative breast cancer can show increased resistance to all systemic therapies.

The aim of the treatment of metastatic breast cancer should be towards increasing the symptom-free survival and quality of life. At the same time the side effect of the treatment to be minimised. The treatment of metastatic breast cancer depends on the individual patient and receptor status, general condition of the patient. Even with newer systemic and locoregional treatment, metastatic breast cancer cannot be cured at present. In few patients with good prognostic factor, these treatment modalities increase the progression-free survival which in turn may significantly affect the overall survival.^[1,2] Many patients with metastases

'Financial or Other Competing Interest': None.
Submission 04-10-2017, Peer Review 14-12-2017,
Acceptance 20-12-2017, Published 01-01-2018.

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DOI: 10.14260/jemds/2018/18

may live several years with modern locoregional treatment and systemic chemotherapy.

Incidence of stage IV disease- 5–10% of patients with breast cancer.

Survival times vary widely, with reported median survival ranging between 18 and 30 months. Systemic therapy is usually the main treatment. For palliation, the use of radical locoregional therapy, such as surgery or radiotherapy, is controversial.

A number of studies have recently demonstrated a survival benefit in stage IV breast cancer patients following surgical resection of the primary tumour.^[3] Here, we investigate the relationship between locoregional treatment and survival in patients with metastatic breast cancer and evaluate the impact of different locoregional treatments. Locoregional treatment for breast cancer patients with distant metastases at diagnosis is an important issue because of possible improvement of survival or disease-free survival. The possibility of surgery and/or radiotherapy following induction chemotherapy should be weighed and left to individual practice. Participation in randomised controlled trials should be encouraged.

MATERIALS AND METHODS

Study Design

This is a retrospective observational study. All medical records of female patients with metastatic breast cancer registered at Cancer Institute from the duration of year 2003 to 2008, which consists of 195 patients were considered conveniently in this study.

Sample Size

195 patients from 2003 to 2008 were considered in this study, conveniently.

Inclusion criteria for this study were the following.

Inclusion Criteria

In our retrospective study, we reviewed female patients with metastatic breast cancer registered at Cancer Institute from the year 2003 to 2008.

Treatment Protocol

All patients were treated with chemotherapy with or without concurrent radiotherapy. After six months of initial treatment response was assessed and decision regarding surgery was taken. Radiotherapy was given concurrently with chemotherapy. Most commonly employed dose schedule is 40-45 Gy in 22- 25 fractions at conventional 180 cGy daily for 5 weeks.

Whole Breast Irradiation

Treatment volume, the areas treated generally include the whole breast and chest wall (i.e., with or without supraclavicular, axillary regions).

Conventional field borders are used. Breast is treated using two tangential fields, medial and lateral tangents. The upper margin of the portals should be placed at the head of the clavicle to include the entire breast. The medial margin should be at or 1 cm over the midline. The lateral posterior margin should be placed 2 cm beyond all palpable breast tissue. Which is usually near the mid-axillary line. The inferior margin is drawn 2 to 3 cm below the inframammary fold. The entire ipsilateral breast should be encompassed.

Supraclavicular Field

Supraclavicular nodes are usually encompassed, with a single anterior oblique photon field angled slightly away from the spinal cord. The medial border is placed at the insertion of the clavicular head. The lateral border is placed to include approximately one-third of the humeral head. The inferior border is the inferior border of the clavicle or the superior border of the chest wall field. The superior border is set at the thyrocricoid groove. A humeral head block is added to block the humeral head and acromioclavicular joint.

To avoid the problem of hotspot while matching supraclavicular and chest wall fields following methods are used: Angling the foot of the treatment couch away from the radiation source to direct the tangential fields inferiorly so that superior edge of these beams line up perfectly with inferior border of supraclavicular field. We can also use the three-field single-isocentre technique or Hanging block technique. Half-beam block can also be used.

Internal Mammary Field

The internal mammary chain lies beside the sternum, generally in the first through the third intercostal space, although the depth may vary. Various methods of encompassing the internal mammary chain have been described, including extended tangent fields, partially wide tangent fields and matching electron and photon fields. But prophylactic internal mammary nodal irradiation is not recommended even in medial quadrant tumours.

Posterior Axillary Boost

The dose provided to the axillary nodes through the supraclavicular/axillary field can sometimes create suboptimal dose distributions to deeper lying level 3 axillary nodes. If coverage is suboptimal, the dose can be supplemented with a posterior axillary field. The field is setup opposed to the supraclavicular/axillary field. The medial border of this field is drawn to allow 1.5 to 2 cm of lung. If the inferior border is at the same level as the inferior border of the supraclavicular field, the lateral border blocks falloff across the posterior axillary fold, the superior border splits the clavicle, and the superolateral border shields or splits the humeral head.

Followup

Subsequently, patients were followed up monthly for the first year and once in three months for a period of five years from date of completion of radiotherapy, after 5 years yearly followup was done.

Assessment Tools

Medical records were reviewed for the following factors.

1. Age at diagnosis.
2. Laterality.
3. Histology of the tumour.
4. Clinical and pathologic size of the primary tumour.
5. Lymph node status.
6. Hormone receptor status.
7. HER-2 overexpression.
8. Location and number of metastases mode.
9. Date of surgical treatment, margin status,
10. Use of radiotherapy.
11. Systemic therapy.

12. The time of death.
13. The time of last review among alive patients.
14. Patients with metastatic Breast cancer excluding brain metastasis at presentation were included.
15. Patient's baseline characteristics.

Statistical Methods for Survival Analysis

The end point of the study was death due to any cause. The index date was diagnosis date and closing date was December 31, 2013. Survival time was defined as the time elapsed in months between index dates and closing date or date of death or lost to followup, whichever was earlier. OS and DFS were estimated using actuarial method. Log rank test was employed to test the differences between survival distributions. Cox PH model was utilised in univariate and multifactorial settings to elicit the independent prognostic factors for survival. SPSS software version 17.0 was used for analysis.

RESULTS

Oestrogen Receptor Status	No. of Patients
ER+ve	84
ER-ve	56
Status not known	55

Table 1. Oestrogen Receptor Status

PR Status	No. of Patients
PR+ve	66
PR-ve	66

Table 2. Progesterone Receptor Status

Graph 1. Tumour Stage of the Patients

Out of 195 patients, 118 had T3 stage and 37 had T4 stage, remaining 36 patients had T1, T2, or T0 stage disease. Most common tumour stage was T3.

Diagram 1. Nodal Stage of the Patients

24% of the patients had N3 disease and 31 had N2 stage, 36% of them had N1 and 9% had N0 disease. Most common nodal stage was N1.

Graph 2. Hormonal Receptor Status

Out of 195 patients, 86 were hormone receptor positive and in 109 patients the details of receptor status was not known.

Graph 3. HER-2/neu Status of the Patients

Diagram 2. Percentage of Patients with Left and Right-sided Tumours

- In this study, right-sided tumours were found to be more common than left-sided tumours.
- Incidence of bone metastasis.

- Out of 195 patients, 33 patients (32%) had single bone metastasis and 70 patients (68%) had multiple bone metastasis.

Diagram 3. Percentage of Patients with Single and Multiple Bone Metastasis

Site of Metastasis	No. of Patients
Liver	18
Lung	21
Both liver and lung	2

Table 3. Liver and Lung Metastasis

Out of 195 total patients, 18 patients (9%) had liver metastasis and 21 patients (11%) had lung metastasis, two patients (1%) had both liver and lung metastasis.

Diagram 4. Patients with Metastasis

Patients with Multiple Metastasis

40 patients (21%) had multiple visceral and non-visceral metastasis excluding brain which is not included in the study.

Total No. of patients	195
Multiple mets	40

Code for Various Treatment Options

- 2- Chemoirradiation (RT+CT)
- 3- Chemotherapy +surgery (CT+SX)
- 5- Chemoirradiation + Surgery (CT+RT+SX)
- 6-Chemotherapy only (CT only)

- 7- Radiotherapy only (RT only)
- 9-Chemotherapy + hormone therapy (CT+HT only)
- 10 Radiotherapy + hormone therapy (RT+HT only)
11. Chemotherapy+ radiotherapy + hormone therapy (CT+RT+HT).

Chemoirradiation and Surgery

Role of Surgery in Metastatic Breast Cancer

At present carcinoma of breast has replaced carcinoma of cervix in Indian tumour registries. Survival of these patients has increased over the years. Over the years systemic therapy is the treatment of choice and local therapy like Radiotherapy and Surgery.

The surgical management of patients involves both the primary tumour and regional lymphatics. The primary tumour may be managed by modified radical mastectomy or Breast conservative surgery. Axilla is treated by either axillary dissection or sentinel lymph node biopsy.

Chemotherapy

Scientific rationale for primary systemic chemotherapy:

The role of primary systemic chemotherapy or neoadjuvant chemotherapy was justified by several hypotheses. It indicated that non-curative reduction of tumour cell burden increased the proliferation of cells. After surgery of the primary tumour there is an increase in the proliferation of remaining tumour cells in the metastatic sites. This change occurs even after primary tumour irradiation. Removal of a primary tumour exerts its affect over the metastatic sites and causes stimulation of growth following surgical removal or reduction was due to soluble growth factor.^[4,5]

The neoadjuvant chemotherapy helps to decrease the micrometastases and prevent cancer growth. Cyclophosphamide, tamoxifen and radiotherapy prior to surgery prevent kinetic alterations, suppresses tumour growth which in turn may increase the survival.

Chemotherapy + Surgery

Out of 195 patients, 37 patients received chemoirradiation and then underwent surgery.

Chemotherapy

Out of 195 patients with Metastatic Breast Cancer, 44 patients received chemotherapy alone.

Radiotherapy (RT)

Out of 195 patients with Metastatic Breast Cancer, 3 patients received radiotherapy alone.

Chemotherapy(CT) and Surgery(Sx)

Out of 195 patients, 2 patients received chemotherapy and surgery.

Hormonal Therapy (HT)

8 patients received hormonal therapy alone.

12 patients got chemotherapy and hormonal therapy.

5 patients received radiotherapy and hormonal therapy.

6 patients received chemoirradiation and hormonal therapy.

Diagram 7. Hormonal Therapy

Diagram 8. Various Treatment Modalities

DISCUSSION

All medical records of female metastatic breast cancer patients excluding brain metastasis were reviewed and analysed with following factors such as menopausal status, hormone receptor status, HER-2/neu status, no. of metastasis (including visceral and non-visceral).

65 patients in this study were premenopausal and 112 patients belonged to postmenopausal group. 55 patients were ER negative and 84 patients were ER positive and out of 195 patients 14 patients were HER-2 positive and 31 patients were HER-2 negative and in the remaining cases status was not known.

31 patients had single bone metastasis and 68 patients had multiple bone metastasis, 18 patients had liver metastasis and 21 patients had lung metastasis, 2 patients had metastasis to liver and lung, 3 patients had supraclavicular metastasis, 7 patients had axillary metastasis.

All patients underwent various treatment modalities according to tumour board policy. 74 patients underwent chemoirradiation, 2 patients had chemotherapy followed by surgery, 37 patients got concurrent chemoirradiation followed by surgery. 44 patients received chemotherapy alone. 3 patients had only radiotherapy, 12 patients received chemotherapy and hormone therapy, 8 patients had hormone therapy only. In 5 patients radiotherapy and hormone therapy

was given, 6 patients had chemoirradiation followed by hormonal therapy.

Patients' survival rates were analysed at the end of 1, 3, 5 and 10 years.

In patients receiving CT + RT, survival rate at the end of 1 year was 89%, 3 yrs. was 58%, 5 yrs. was 46%, 10 yrs. was 42% respectively.

In patients receiving CT + RT + Surgery, survival rate at the end of 1 year was 97%, 3 yrs. was 80%, 5 yrs. was 70%, 10 yrs. was 71% respectively.

In patients receiving CT only, survival rate at the end of 1 year was 60%, 3 yrs. was 5%, 5 yrs. was 2%, 10 yrs. was 0%.

In patients receiving RT only, survival rate at the end of 1 year was 67%, 3 yrs. was 33%, 5 yrs. was 33%, 10 yrs. was 33%.

In patients receiving HT only, survival rate at the end of 1 year was 50%, 3 yrs. was 13%, 5 yrs. was 13%, 10 yrs. was 13%.

In patients receiving CT + HT, survival rate at the end of 1 year was 58%, 3 yrs. was 8%, 5 yrs. was 0%, 10 yrs. was 0%.

In patients receiving RT + HT, survival rate at the end of 1 year was 50%, 3 yrs. was 0%, 5 yrs. was 0%, 10 yrs. was 0%.

In patients receiving CT + RT + HT, survival rate at the end of 1 year was 67%, 3 yrs. was 50%, 5 yrs. was 0%, 10 yrs. was 0%.

Interestingly, chest wall control was also observed to be correlated with improved overall survival, independent of surgical resection of the primary tumour (hazard ratio [HR]: 0.42; 95% CI: 0.26–0.66; $p < 0.001$).

Theoretical Disadvantages of Locoregional Treatment by Surgery-

- A theoretical disadvantage of local therapy is based on the hypothesis that the primary local tumour can secrete substances that inhibit new blood vessels that support tumour growth.
- Removal of the primary disease can induce an angiogenic surge and promote the progression of metastases.
- Some believe that trauma induced by surgical intervention and general anaesthesia can generate cytokines that stimulate neoplastic proliferation and compromise the integrity of the immune system.

Advantages of Radiotherapy

- Non-invasive.
- Fewer morbidity.
- Can be given in patients with extensive metastatic disease visceral and multiple lesions.
- As we know skin is the best dressing, intact primary tumour will not be disturbed.

CONCLUSION

Radiation remains as most widely utilised treatment modality in the clinical management of cancer patients with locally advanced malignant tumours being treated with radiation at some point in the course of their disease (estimated 40-60% towards the therapy). Radiation therapy is a highly cost-effective modality with only 5% of the total cancer care cost. The data reported in this retrospective study confirmed that chemoirradiation improved overall survival and symptomatic local control, demonstrated in patients treated locoregionally. The optimal local management of patients with metastatic

breast cancer remains unknown. An ongoing phase III trial, E2108, has been designed to assess the effect of locoregional management in metastatic patients responding to first-line systemic therapy. Locoregional radiation can be an integral part in metastatic breast cancer treatment to improve the quality of life. If the patient did not have any metastasis at the end of one year, mastectomy can be added to improve the local control. According to this study, there is a significant overall survival and better local control with concurrent chemoradiation. Hence, Radiotherapy has an integral part in the management of metastatic breast cancer.

REFERENCES

- [1] Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery* 2002;132(4):620-6.
- [2] Bafford AC, Burstein HJ, Barkley CR, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. *Breast Cancer Res Treat* 2009;115(1):7-12.
- [3] Gnerlich J, Jeffe DB, Deshpande AD, et al. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. *Ann Surg Oncol* 2007;14(8):2187-94.
- [4] Neuman HB, Morrogh M, Gonen M, et al. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer* 2010;116(5):1226-33.
- [5] Hazard HW, Gorla SR, Scholtens D, et al. Surgical resection of the primary tumor, chest wall control and survival in women with metastatic breast cancer. *Cancer* 2008;113(8):2011-9.