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ORIGINAL ARTICLE

Impact of Surgery in De Novo Metastatic Breast Cancer after Systemic Disease Control

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ABSTRACT

Background: Systemic chemotherapy is the standard of care for patients with metastatic breast cancer, with an undecided role in surgery. Limited data is available for the role of surgery on the overall survival of stage 4 breast cancer in regards to luminal subtypes of patients. This is a retrospective data analysis comparing overall survival benefit and disease-free survival in stage IV breast cancer after systemic treatment and systemic disease control concerning luminal classification in the last five years.

Method: Patients who had surgery and no surgery after systemic treatment and disease control were compared for 5 years overall survival as the primary endpoint and disease-free survival as the secondary endpoint. The survival benefit was also compared in regards to tumor biology (ER/PR, HER2 status)

Results: Data included 430 patients, 244 in surgery and 186 in no surgery group. At one year survival for surgery performed and not performed was not significant. Five-year overall survival for surgery performed and not performed was 84.4% and 74.6%. A statistically highly significant difference in survival rates was observed ($p<0.0001$). The mortality rate was 15.6% in surgery performed and 25.4% in the no-surgery group which showed a significant difference among the two study groups ($p=0.011$). We found statistically significant differences in luminal B ($p=0.01$) and triple-negative breast cancer patients ($p=0.001$) for survival rates in surgery performed and not performed groups.

Conclusion: Surgery has a positive impact on overall survival in Stage 4 patients with systemic disease control even in high-risk luminal B, Her 2 Positive, and triple-negative breast cancer patients. There was no significant difference observed in disease-free survival who were operated on or not. However, there was no local recurrence in the operated group.

Keywords: Metastatic breast cancer: Neoadjuvant chemotherapy, local breast surgery, Luminal sub-types

INTRODUCTION

6-10% of all breast cancer patients have de novo metastatic stage 4 breast cancer[1,2] and has been considered as an incurable disease[3] Management of this (MBC) is meant for disease control, potentially prolonging life, relieving symptoms, or putting off time that symptoms develop; in nutshell improving quality of life[4].

Although incurable, progress in adjuvant treatment options and a better knowledge of tumor biology appear to have upgraded patient survival from months to years with a decent quality of life in recent years[5].

Systemic therapy (ST) is currently a cornerstone for the control of disease whereas the Role of local treatment in metastatic breast cancer i.e. surgery is controversial. Usually, locoregional treatment (surgery or radiation) has been used only for palliation, i.e. ulceration and bleeding.

In medical research, local tumor resection in the case of stage IV breast cancer with regards to survival benefit is debated. Opponents of surgery in stage IV patients proposed that tumor excision can cause distant tumor seedling, increase circulatory tumor cell adhesion, immunosuppression, and could potentially increase the metastatic spread[6]. Whereas improved immunomodulation through decreased tumor load of breast cancer stem cells and removal of the root of new metastases increased chemotherapeutic efficacy and decreased development of potentially resistant cell lines[7,8]

Research work done for the role of locoregional treatment in metastatic breast cancer has the typical limitations of retrospective data, selection, and performance bias.

Our data was encouraged by several retrospective analyses that have shown survival benefits from local treatment patients with metastatic breast cancer.

Stage IV breast cancer patients now have increased life expectancy with the increase in survival rate at five years from 10% in 1970 to about 40% in women treated after 1995 (Giordano)[9]. With new treatment modalities patients with metastatic breast cancer treated between 1995 and 2002 had an 18% lower risk of death than women treated earlier between 1985 and 1994 (Ernst)[10]. Median overall survival improved from 20 months (1988 to 1991) to 26 months (2007 to 2011) in other series (Thomas)[11].

There have been studies to see survival differences in patients who go for upfront surgery or no surgery with varying results. The criticism is that there can be selection bias and one may try to operate younger patients, smaller tumor size, and less systemic burden of disease. Once the systemic disease is under control this eliminates the bias and one can assess the impact of local control in a better way. This also allows seeing if treatment response and overall survival are any different in luminal subtypes. We tried to find survival benefits in patients who were stage IV on presentation and locoregional treatment was done once the systemic disease was controlled after neoadjuvant systemic treatment. We compared survival benefits and disease-free survival on 1, 2, and 5 years and also compared overall survival with luminal subtypes of breast cancer.

METHOD

Study design and participants: This is a retrospective comparative study of 430 stage IV metastatic breast cancer patients from 2010 to 2020, in the Breast Unit of the General Surgery. Data were collected from the hospital tumor registry and patient electronic records. All patients with biopsy-proven breast cancer with distant metastasis evident on a radiological assessment like CT scan chest and liver and Bone scan received neoadjuvant systemic therapy were selected. After completion of chemotherapy, those who had no evidence of residual systemic disease on post neoadjuvant imaging were offered local breast surgery. All of these patients who received the surgical intervention had an R0 resection with histologically negative margins. Chemotherapy was given according to NCCN guidelines (Anthracycline and Texans). Anti HER2 treatment was given depending upon tumor biology in patients with financial affordability. Adjuvant radiotherapy & hormonal therapy was given as per NCCN recommendations[21]. Patients who did not respond to chemotherapy, residual locally advanced breast cancer, and persistent distant systemic disease after neoadjuvant chemotherapy were not operated upon were excluded from the study. Comparative analysis was done among patients who underwent surgery and who had no surgery after systemic therapy.

Data was entered and analyzed using SPSS version 21. Mean and the standard deviation was calculated for numerical

variables. Frequencies and percentages were computed for qualitative variables. Chi-square/Fisher exact test was applied to compare the characteristics among the two groups. The log-rank test was applied to compare survival rates among the two groups with Surgery and without and Kaplan-Meier curves were also plotted. P-value ≤0.05 was considered statistically significant.

RESULTS

Four hundred and thirty-three (430) patients of Stage 4 are included in our study. 244 patients in the surgery group and 186 patients in the No surgery group. The mean age of all patients was 48.96±12.17 years. Most of them presented with grade II 150(34.6%). There were 342(79%) who had single organ metastasis and 91(21%) had more than 1 site tumor metastasis. The most common sites of metastasis were bone 192(44.3%) and lung 189(43.6%). Out of 244(56.4%) patients in the surgery group, 173(70.9%) underwent a mastectomy and 70(29%) had breast conservation. Axillary treatment was done depending upon radiological nodal status and sentinel node biopsy. Axillary clearance was done when proved to have metastatic disease in the axilla 5(1.2%) had luminal A, 154(35.6%) had luminal B, 61(14.1%) hormone receptor and Her 2 positive, 54(12.5%) only Her2 positive and 85(19.6%) had triple-negative disease. The detailed frequency distribution of all patients is presented in Table-1

Table 1: Clinical details of the patients with Stage 4

	n(%)
Age	48.96±12.17
Grade	
I	11(2.5)
II	150(34.6)
III	91(21)
T-Stage	
0	53(12.2)
1	11(2.5)
2	88(20.3)
3	62(14.3)
4	203(46.9)
Organ	
Single	342(79)
Multiple	91(21)
Sites of Mets	
Bone	192(44.3)
Pulmonary	189(43.6)
Hepatic	117(27)
Brain	12(2.8)
Nodal Axillary	10(2.3)
Adrenal	9(2.1)
Abdominal	2(0.5)
Others	11(2.5)
Surgery performed	
Yes	244(56.4)
No	189(43.6)
Axillary clearance (n=244)	
Yes	176(72.1)
No	68(27.9)
Procedure	
Mastectomy	173(40)
Conservation	70(16.2)
Luminal Type	
A	5(1.2)
B	154(35.6)
HR/Her 2 Positive	61(14.1)
Her2 Positive	54(12.5)
Triple Negative	85(19.6)
Chemotherapy	
Given	368(85)
Not given	65(15)
Radiotherapy	
Given	185(42.7)
Not given	248(57.3)
Hormonal given	
Given	184(42.5)
Not given	249(57.5)
Recurrence	
Yes	17(3.9)
No	416(96.1)
Status	
Alive	347(80.1)
Expired	86(19.9)

Five-year overall survival for surgery performed and not performed was 84.4% and 74.6% respectively. A statistically highly significant difference in survival rates of the two groups was observed (p<0.0001). The detailed survival analysis is presented in Table-2 and Fig: 1

Table 2: Overall survival rates among patients with and without surgery performed

Survival time	Surgery		p-value
	Performed (%)	Not Performed (%)	
1-year overall survival	82.1	72.4	0.283
2 years overall survival	85.7	75.7	0.027*
5 years overall survival	84.4	74.6	<0.0001*
Log Rank Test is applied.			
*Significant at p≤0.05			

DISCUSSION

There has been a lot of debate about the advantage of doing local surgery in stage 4 breast cancer patients. Initially, the only reason was to palliate the local symptoms like bleeding and ulceration. But recent evidence suggests that local surgery may improve survival in this group of patients[12,13]including various meta-analyses that showed the survival benefit in surgery.[14,15] The reported mortality reduction has ranged from 18 to 37%.

Since all evidence was from retrospective studies and there can be selection bias in terms of maybe selecting younger patients with the limited locoregional disease and minimal systemic disease burden.

Our study was retrospective, but surgery was done when there was no evidence of radiological systemic disease, so this would avoid selection bias. Like in other cancer surgeries we expect the outcome to be better when the resection is done with tumor-free margins[16]and all our patients had negative margins. Our results also showed a statistically improved survival benefit in the surgery group.

To further see the impact of surgery prospective studies were done. Turkish study showed survival advantage[17], Indian study could not[18]. The possible reason could be that there was no standardize chemotherapy regimen given and this emphasizes the value of optimal systemic therapy.

Breast cancer is now accepted as a group of diseases rather than a single entity because of the heterogeneous clinical behavior of disease and greater consideration on the molecular basis of breast cancer[19]. In recent medical advances, tumor biology is a cornerstone for the treatment of breast cancer. With the invention of targeted therapy, immunotherapy, and other novel therapies against molecular targets, molecular phenotype has improved survival[20]. Patient factors such as comorbidities, performance status, social and psychological circumstances allow us to move for individualized cancer treatment.

CONCLUSION:

Metastatic breast cancer should be treated actively and many patients will survive with good quality of life for months and often years. A multimodal treatment approach should be adopted. Surgery has a positive impact on overall survival in Stage 4 patients with systemic disease control even in high-risk luminal B, Her 2 Positive, and triple-negative breast cancer patients.

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