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

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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 regarding 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 regarding tumor biology (ER/PR, HER2 status).
Results: Data included 421 patients, 237 in surgery and 184 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 74.5%. A statistically significant difference in survival rates was observed ($p<0.0001$). The mortality rate was 15.6% in surgery performed and

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25.5% 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=0.004) and triple-negative breast cancer patients (p=0.001) for survival rates in surgery performed and not performed groups. Disease-free survival has shown no significant difference in surgery performed and not performed group in 1, 2, and 5 years follow-up.

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.

1. 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 concerning 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.

2. METHOD

2.1 Study Design and Participants

This is a retrospective comparative study of 421 stage IV metastatic breast cancer patients from

2010 to 2020, in the Breast Unit of the General Surgery Department of Liaquat National Hospital & Medical College, Karachi Pakistan. 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 [12]. 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.

All patients had ER, PR, Her2neu status checked and patients were divided into 5 luminal groups. Luminal A, Luminal B, Luminal B with hormone receptor and her2 positive, triple-negative and only Her2 positive and ER/PR negative.

Overall Survival benefit for luminal subgroups was the primary endpoint. Overall survival, defined as the time from surgery to death from any cause.

The secondary endpoint was disease-free survival, defined as the time of disease recurrence at the local surgical site or any other site from the time of surgery.

2.2 Data Analysis

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.

3. RESULTS

Four hundred and twenty one (421) patients of Stage 4 are included in our study. 237 patients in the surgery group and 184 patients in the No surgery group. The mean age of all patients was 49.20±12.10 years. Most of them presented with grade II 146(34.7%). There were 333(79.1%) who had single organ metastasis and 88(20.9%) had more than 1 site tumor metastasis. The most common sites of metastasis were bone 191(45.4%) and lung 186(43.6%). Out of 237(56.3%) patients in the surgery group, 171(40.6%) underwent a mastectomy and 65(15) 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, 153(36.3%) had luminal B, 56(13.3%) hormone receptor and Her 2 positive, 53(12.6%) only Her2 positive and 81(19.2%) had triple-negative disease. The detailed frequency distribution of all patients is presented in Table 1.

We observed that 84(20%) patients died during five years. The mortality rate was 15.6% in surgery performed and 25.5% in the no-surgery group which showed a statistically significant difference among the two study groups. At One year survival for surgery performed and not performed was 85.2% and 72.4% respectively which was a statistically insignificant difference in survival rates of the two groups (p=0.154). Two-year Survival for surgery performed and not performed was 84.3% and 75.4% respectively which was a statistically significant difference in survival rates of the two groups (p<0.0001).

Five-year overall survival for surgery performed and not performed was 84.4% and 74.5% 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

The recurrence was observed in 16(3.8%) cases. There were 10(2.37%) patients who had a recurrence in the surgery performed group and 6(1.42%) in the not performed group. All disease recurrence was systemic, no local recurrence was observed in the surgery performed group. The one-year disease-free survival rate among

patients receiving surgery was lower than those who didn't receive it (96.3% vs. 98.3%) but no statistical significance was found (p=0.620). Two-year disease-free survival for surgery performed and not performed was 95.7% and 96% respectively. A statistically insignificant difference in survival rates of the two groups was observed (p=0.649). Five-year disease-free survival for surgery performed and not performed was 95.8% and 96.7% respectively. A statistically insignificant difference in survival rates of the two groups was observed (p=0.615). The detailed disease-free survival analysis is presented in Table 3 and Fig. 2.

Table 1. Clinical details of the patients with Stage 4

	n(%)
Age	49.20±12.10
Grade	
I	11(2.6)
II	146(34.7)
III	89(21.1)
T-Stage	
0	50(11.9)
1	10(2.4)
2	87(20.7)
3	60(14.3)
4	199(47.3)
Metastasis site	
Single	333(79.1)
Multiple	88(20.9)
Sites of Mets	
Bone	191(45.4)
Pulmonary	186(44.2)
Hepatic	116(27.6)
Nodal Axillary	9(2.1)
Adrenal	9(2.1)
Abdominal	2(0.5)
Others	11(2.6)
Surgery performed	
Yes	237(56.3)
No	184(43.7)
Procedure	
Mastectomy	171(40.6)
Conservation	65(15.4)
Luminal Type	
A	5(1.2)
B	153(36.3)
Bher2	56(13.3)
Her2	53(12.6)
Triple	81(19.2)
Chemotherapy	
Given	359(85.3)
Not given	62(14.7)
Radiotherapy	
Given	178(42.3)
Not given	243(57.7)
Hormonal given	
Given	181(43)
Not given	240(57)
Recurrence	
Yes	16(3.8)
No	405(96.2)

	n(%)
Status	
Alive	337(80)
Expired	84(20)

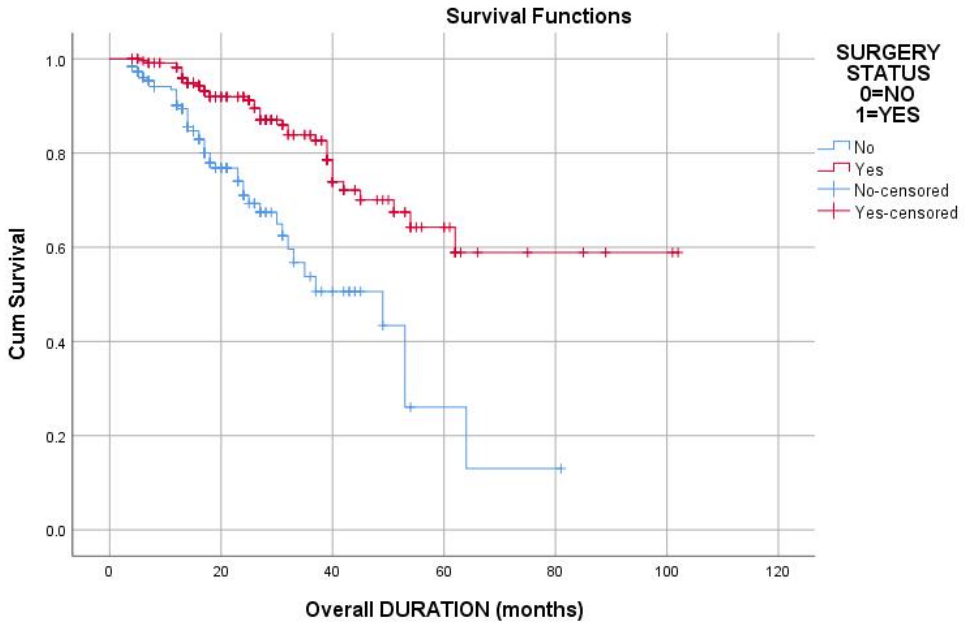

Fig. 1. Five-year overall survival among patients

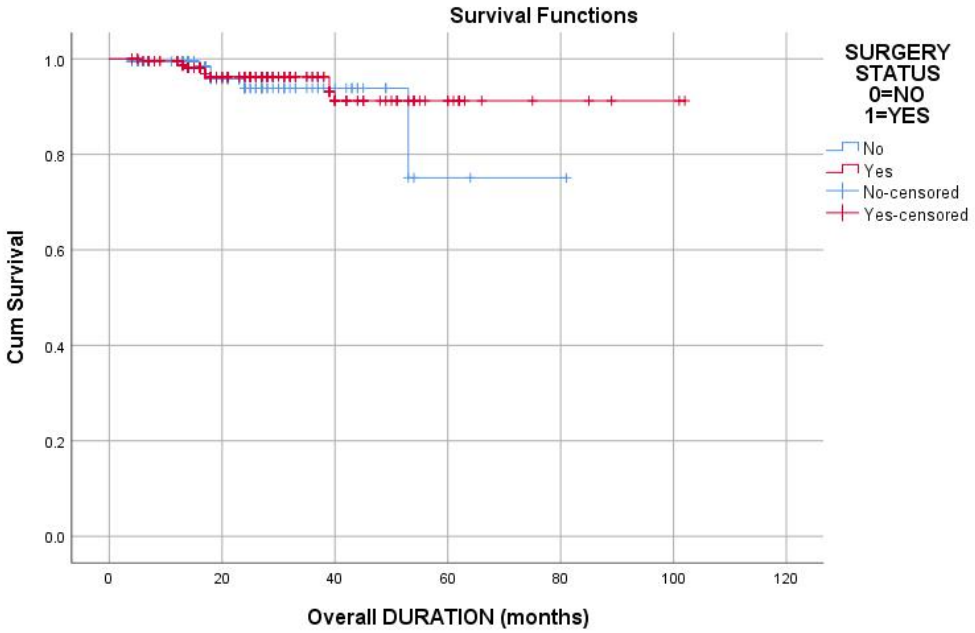

Fig. 2. 5-year disease-free survival among patients

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

	Surgery		
Survival time	**Performed (%)**	**Not Performed(%)**	**p-value**
1 years overall survival	85.2	72.4	0.154
2 years overall survival	84.3	75.4	<0.0001*
5 years overall survival	84.4	74.5	<0.0001*
Log Rank Test is applied.			
*Significant at p≤0.05			

Table 3. Disease free survival rates among patients with and without surgery performed

	Surgery		
Survival time	**Performed (%)**	**Not Performed(%)**	**p-value**
1 years disease free survival	96.3	98.3	0.620
2 years disease free survival	95.7	96	0.649
5 years disease free survival	95.8	96.7	0.615
Log Rank Test is applied.			

**Significant at p≤0.05*

Table 4. Hazard ratio among patients to identify predictors for surgery status

	Univariate analysis				Multivariate analysis			
	Hazard Ratio	**(95% CI)**		**P-value**	**Hazard Ratio**	**(95% CI)**		**P-value**
Grade								
I	0.584	0.419	0.812	0.001*	0.618	0.426	0.897	0.011*
II	0.44	0.189	1.026	0.057	0.328	0.116	0.931	0.036*
III®								
T-Stage								
0	0.998	0.682	1.461	0.994	0.960	0.365	1.453	0.848
1	2.219	1.071	4.598	0.032*	1.870	0.825	4.237	0.134
2	1.450	1.038	2.026	0.029*	1.428	0.986	2.066	0.059
3	1.333	0.898	1.979	0.154	1.401	0.900	2.181	0.135
4®								
Luminal Type								
A	1.609	0.578	4.475	0.363	0.359	1.629	0.574	0.359
B	0.677	0.479	0.956	0.027*	0.102	0.732	0.504	0.102
Her2	0.567	0.350	0.917	0.021*	0.035	0.580	0.350	0.077
BHer2	0.596	0.366	0.971	0.038*	0.077	0.628	0.376	0.035*
Triple®								

®Reference Group. Cox regression test was applied; P≤0.05 considered as significant

The overall five-year survival analysis for luminal subtype among patients who received surgery and those who didn't receive showed a survival rate of a patient with luminal A of both having surgery performed and not performed was 100%. The survival rate of a patient with luminal B for surgery performed was higher than the not performed group i.e. 91.8% and 83.6%,patient with hormone and HER2 positive for surgery performed was 80% and not performed group was 71%. And of a patient with Her2 positive group for surgery performed and not performed group was 83.3% and 81.3% respectively. The survival rate of a patient in triple-negative patients for surgery performed was higher than not performed i.e. 90% and 64.5% respectively. We found statistically significant differences in luminal B (p=0.004) and triple-negative (p=0.001) for survival rates.

The hazard ratio for the grade, T-stage, metastasis, and luminal subtype among patients who received surgery and those who didn't receive was calculated. We found overall survival of grade 2 breast cancer was significantly associated among patients who received surgery and those who didn't receive it (HR 6.396, 95% CI 2.328 –17.575; p<0·0001). T2 and T4 stage

were also significantly associated for overall survival among patients who received surgery and those who didn't receive (HR 14.611, 95% CI 3.774 – 56.565; p<0·0001), and (HR 2.770, 95% CI 1.427 – 5.377; p=0·003) respectively. Overall survival of both the single and multiple sites of metastasis was significantly associated among patients who received surgery and those who didn't receive (HR 2.983, 95% CI 1.791 – 4.969; p<0·0001) and (HR 2.809, 95% CI 1.141 – 6.917; p=0·025) respectively. The luminal type B and triple-negative was also significantly associated among patients who received surgery and those who didn't receive (HR 3.800, 95% CI 1.435 – 10.062; p=0·007), and (HR 4.866, 95% CI 1.680 – 14.090; p=0·004) respectively.

In Univariate analysis, the hazard ratio for the grade, T-stage, metastasis, and luminal subtype among patients who received surgery was calculated. We found the hazard ratio of grade I was 0.584 times lesser risk and grade II is 0.440 lesser risk as compared to grade III in patients having surgery. The hazard ratio for the T-stages showed as the patients with stage T1 have 2.219 times, stage T2 has 1.450 times, stage T3 has 1.333 times higher risk as compared to stage T4 while stage T0 has 0.998 times, lesser risk as compared to stageT4. Luminal subtype A has 1.609 times higher chances of surgery than triple-negative. Luminal B has 0.677 times lesser risk, luminal Her2 has 0.567 times lesser risk in the surgery group and luminal BHer2 Positive has 0.596 times lesser risk than triple-negative. The detailed hazard ratio for the grade, T-stage, organ, and luminal subtype among patients with surgery is presented in Table 4.

In multivariate analysis of (HR), the hazard ratio for the grade, T-stage, metastasis, and luminal subtype among patients who received surgery was also calculated. We found the overall survival hazard having grade I has 0.618 times lesser risk and grade II has 0.328 times lesser risk as compared to grade III in patients having surgery. The hazard ratio for the T-stages showed as the HR of stage T1 has 1.870, stage T2 has 1.428 times and stage T3 has 1.401 times higher chances for the surgery as compared to stage T4 while stage T0 has 0.960 times lesser chances for surgery as compared to stageT4. Luminal subtype A has 0.359 times, Luminal B has 0.102 times, the Her2 group has 0.035 times and the Hormone and Her2 positive group have 0.077 times lesser risk of surgery than the triple-negative. Single and multiple site metastases have shown no significant difference in the surgery group so no hazard ratio was calculated. The detailed hazard ratio for the grade, T-stage, organ, and luminal subtype among patients with surgery is presented in Table 4.

4. 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 [13,14] including various meta-analyses that showed the survival benefit in surgery. [15,16]. 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 [17] 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 [18], Indian study could not [19]. The possible reason could be that there was no standardized 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 [20]. 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 [21]. Patient factors such as comorbidities, performance status, social and psychological circumstances allow us to move for individualized cancer treatment.

Limited data is available in regards to surgical intervention in stage IV patients about luminal subtypes and sequence of therapy. Like Stahl K et al. [22] we also favor giving systemic therapy first and then offering surgery. Our results show significant benefit not only in high-risk Luminal B Her 2 positive but also in the triple-negative group, which was evident in years 2 and 5. This supports the role of local surgery in long run.

Secondary endpoint disease-free survival has no significant association with local surgery, but we observed no local recurrence in the surgery performed group contributed by tumor-free margins and radiation therapy.

The limitation of our study is its retrospective data, all patients with HER2 positive patients have not received anti-HER2 treatment due to financial constraints.

5. 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. There was no significant difference observed in disease-free survival who were operated or not. However, there was no local recurrence in the operated group.

DISCLAIMER

We declare that we do not have any competing interest. This research work was done purely for advancing knowledge in this much controversial topic. There was no funding from any outside source

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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