Frontline primary tumor resection followed by systemic therapy in metastatic breast cancer patients may be non-inferior to systemic treatment alone: A retrospective study.

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Abstract

Background: Primary tumor resection in metastatic breast cancer (MBC) remains a palliative procedure. Its impact as an upfront option on survival is debatable. No data from our locality addressed this issue

Key words: Breast cancer, Surgery, Systemic treatment.

Introduction:

About one tenth of breast cancer patients have distant metastases at initial presentation. 20 % of them live for 5 years [1]. De novo MBC had a longer survival than those with relapsed disease [2]. New treatments modalities had led to improved prognosis of MBC patients over time [3-5]. Treatment directed to the primary tumor in MBC patients is limited to palliative intention and systemic therapy (ST) still the current standard of care. Removal of primary tumor reduced the overall tumor burden and this led to improvement of survival in other metastatic cancers like ovarian, renal, colorectal and gastric cancer. [6–15]

For such reasons, several retrospective and small prospective studies conducted to explore primary tumor resection and its impact on survival in MBC. However, its impact remains controversial. Some retrospective studies and meta-analyses suggested that surgery in appropriately selected MBC patients improves loco-regional progression and prolongs disease-free and overall survival (OS). [16-32] Despite these retrospective studies results; two randomized controlled trials did not show improvement of survival in patients with stage IV breast cancer treated by local tumor resection. [33, 34]

A Turkish prospective trial showed that initial improvement in 3-ys survival was not met with frontline surgery for MBC patients. However with longer follow-up; statistically significant improvement in median survival has been observed but age, performance status, co-morbidities, tumor type, and metastatic disease burden should be taken into consideration. [35]

This retrospective work conducted to investigate the survival benefit (progression and overall) of upfront primary tumor resection in MBC patients at our centers.

Patients and Methods:

Data for analysis collected retrospectively from medical reports at Sohag University and Sohag Cancer Center after Ethical Committee approval from both centers. Data used between January 2010 through December 2015 from Sohag Cancer Institute (SCC) and Sohag University Hospital (SUH), Egypt. Patients considered eligible if they had a metastatic breast cancer diagnosis at presentation and whether they received surgery prior to any systemic therapy or received systemic therapy only. Both groups were matched as regards age at diagnosis, tumor subtypes, ER, PR, site and number of metastatic lesions, systemic therapy (any chemotherapy, any hormonal), radiotherapy type and outcome (progression, PFS and OS). Patients with HER2 positive status were excluded from analysis as anti-HER2 treatment was not available for all patients due to limited resources.

Statistical analysis:

Kaplan-Meier estimates of median survival and descriptive statistics were used to compare patient and tumor characteristics between both groups. Data was analyzed using STATA intercooled version 12.1. Quantitative data was represented as mean, standard

deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally distributed; Mann-Whitney test was used to compare two groups. Qualitative data was presented as number and percentage and compared using either Chi square test or fisher exact test. Survival time was defined as the period between the date of diagnosis and the date of death or end of 2015. Crude survival rates were calculated using the life-table method. The log-rank test was performed to evaluate significant differences between survival curves of surgically and non-surgically treated patients in univariate analyses. Hazard ratios (HR) with 95% confidence intervals (CI) and P values were estimated with respect to the reference category for each co-variate. Graphs were produced by using Excel or STATA program. P value was considered significant if it was less than 0.05.

Results:

Four hundred patients recruited between January 2010 and December 2015, of them only 332 patients were eligible for analysis. 68 cases were HER2 positive and as anti-HER2 treatment was not easily available for these patients due to lack of resources; inclusion of these cases without proper treatment would affect overall outcome in both groups, so, they were excluded from the study. After matching; patient and tumor characteristics were presented in Table 1. Surgical group patients were 188 and ST group were 144 patients. No significant differences were found between both groups in terms of progression rate, time to progression and death events. There were 44 (30%) and 32 (17%) death events in ST and surgery group respectively. Median age for was 53 and 51 years for ST and surgery group respectively. Patients in surgery group found to be younger (surgery: 82.9 % < 60 years, ST: 72.2 % < 60 years). [Table 1]

Both groups were homogeneous as regards the pathological type and it was predominantly invasive adenocarcinoma (91 % for both). Median tumor size was 5 cm and 4 cm for ST and surgery group respectively. ER and PR status were evenly distributed with no significant difference but triple negative cases (TNBC) were 50% in ST and 35% in surgery group. ST group were more likely to receive more than one line of chemotherapy (69 % and 48 % for ST and surgery group, respectively). Radical radiotherapy frequency was higher in surgery group (25 % and 2 % for surgery and ST, respectively), while palliative radiation was more in ST group. ST group were more likely to have higher disease volume as 50% had more than one distant metastatic site compared to 17 % in surgery group (p-value= 0.001); also, visceral metastases were significantly higher in ST group (75 % in ST and 51 % in surgery; p-value= 0.03). [Table 1]

There were 32 (17%) deaths in the surgery group and 44 (30%) in ST group with no significant difference (p-value=0.15). Kaplan–Meier estimates of median survival showed no significant difference with median OS time 4.77 years and >5 years for ST and surgery groups respectively (p value=0.11). [Fig. 1]

On univariate analysis, survival was prolonged in younger patients, endocrine sensitive tumor, receipt of hormonal treatment, less chemotherapy and fewer progressions, however on multivariate analysis, only hormonal treatment recipients and less progressive disease sustained significant association with better OS. [Table 2]

ST had slightly more progressive pattern (38%) compared to surgery group (29%) but with no statistically significant difference (p= 0.39) with a median progression time 1.75 years for ST and 2.41 years for surgery group (p-value= 0.36). [Fig. 2] On univariate analysis, ER/PR-positive status (P = 0.002; 0.001), fewer metastatic sites (P= 0.04), non-visceral metastases (P= 0.006), use of endocrine therapy (P = 0.0001), and less chemotherapy (P = 0.001) were associated with longer PFS on univariate analysis, however, no specific clinical factor among them had significant association on multivariate analysis. [Table 3]

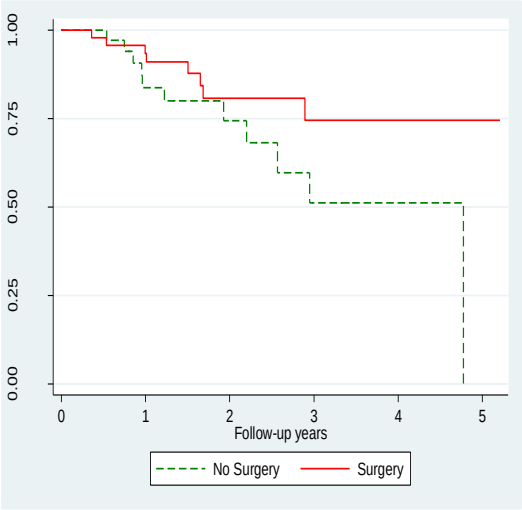

Figure 1: Relative survival of patients according to surgery (Log-rank test for equality of survivor functions showed p value=0.11)

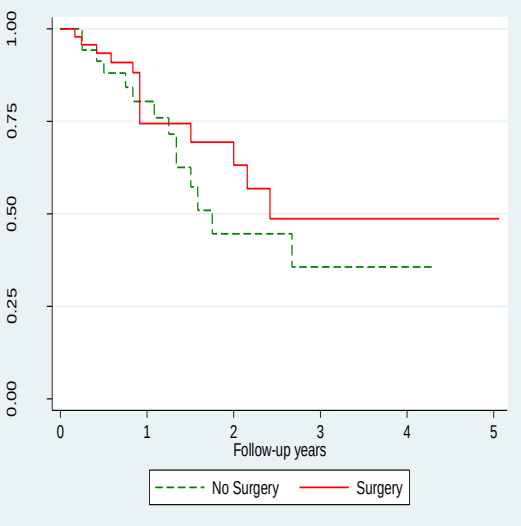

Figure 2: Relative progression free survival of patients according to surgery (Log-rank test for equality of survivor functions showed p value=0.36)

Table 1: Comparison of characteristics of surgically versus non-surgically treated patients

Variable	No surgery group N=144	Surgical group N=188	P value
Age			
Median (range)	53.5 (28-85)	51 (30-75)	0.34
Age group			
<60	104 (72.22%)	156 (82.98%)	0.50
60-69	20 (13.89%)	16 (8.51%)	
≥70	20 (13.89%)	16 (8.51%)	
Pathology			
IDC	132 (91.67%)	172 (91.49%)	0.91
ILC	8(5.56%)	8 (4.26%)	
Mixed	4 (2.78%)	8 (4.26%)	
Size(cm)			
Median	5	4	0.13
No. of metastasis			
1	64 (44.44%)	156 (82.98%)	
2	52 (36.11%)	32 (17.02%)	0.001
3	20 (13.89%)	0	
4	8 (5.56%)	0	
Visceral metastasis			
No	36 (25.00%)	92 (48.94%)	0.03
Yes	108 (75.00%)	96 (51.06%)	
Estrogen receptors			
Negative	68 (47.22%)	68 (36.17%)	0.31
Positive	76 (52.78%)	120 (63.83%)	
Progesterone receptors			0.38
Negative	72 (50.00%)	76 (40.43%)	
Positive	72 (50.00%)	112 (59.57%)	
ER/PR both negative	72 (50%)	66(35.1%)	0.9
Chemotherapy			
0	8 (5.56%)	8 (4.26%)	0.21
1	36 (25.00%)	88 (46.81%)	
2	52 (36.11%)	64 (34.04%)	
3	24 (16.67%)	16 (8.51%)	
4	24 (16.67%)	12 (6.38%)	
Hormonal therapy			
0	76 (52.78%)	68 (36.17%)	0.31
1	56 (38.89%)	96 (51.06%)	
2	12 (8.33%)	24 (12.77%)	
Radio therapy			
No	68 (47.22%)	52 (27.66%)	0.01
Palliative	72 (50.00%)	88 (46.81%)	
Radical	4 (2.78%)	48 (25.53%)	
Progression			
No	88 (61.11%)	132 (70.21%)	0.36
Yes	56 (38.89%)	56 (29.79%)	
Death			
No	100 (69.44%)	156 (82.98%)	0.11
Yes	44 (30.56%)	32 (17.02%)	

Table 2: Univariate and multivariate Cox' regression analysis predicting deaths in patients

Variable	Hazards ratio (95% confidence interval)	P value
Univariate Cox' regression analysis		
Estrogen receptors		
Negative	1 (Ref)	
Positive	0.24 (0.09-0.65)	0.005
Progesterone receptors		
Negative	1 (Ref)	
Positive	0.27 (0.10-0.72)	0.009
Chemotherapy		
0 -1	1 (Ref)	
2+	3.26 (1.07-9.85)	0.04
Hormonal therapy		
0	1 (Ref)	
1	0.09 (0.02-0.38)	0.001
2	0.17 (0.05-0.99)	0.05
Progression		
No	1 (Ref)	
Yes	4.65 (1.67-12.95)	0.003
Multivariate Cox' regression analysis		
Hormonal therapy		
0	1 (Ref)	
1	0.10 (0.01-0.93)	0.04
2	0.16 (0.01-1.68)	0.13
Progression		
No	1 (Ref)	
Yes	4.63 (1.15-18.62)	0.03

Table 3: Univariate and multivariate Cox' regression analysis predicting progression in patients

Variable	Hazards ratio (95% confidence interval)	P value
Univariate Cox' regression analysis		
No. of metastasis		
1	1 (Ref)	
2+	2.14 (1.00-4.55)	0.049
Visceral metastasis		
No	1 (Ref)	
Yes	3.49 (1.44-8.48)	0.006
Estrogen receptors		
Negative	1 (Ref)	
Positive	0.29 (0.14-0.63)	0.002
Progesterone receptors		
Negative	1 (Ref)	
Positive	0.36 (0.17-0.79)	0.01
Chemotherapy		
0 -1	1 (Ref)	
2+	5.47 (2.01-14.90)	0.001
Hormonal therapy		
0	1 (Ref)	
1	0.12 (0.05-0.34)	<0.00
2	0.41 (0.15-1.12)	01
		0.08
Multivariate Cox' regression analysis		
No. of metastasis		
1	1 (Ref)	
2+	0.86 (0.26-2.77)	0.80
Visceral metastasis		
No	1 (Ref)	
Yes	0.84 (0.21-3.38)	0.84
Estrogen receptors		
Negative	1 (Ref)	
Positive	1.07 (0.18-6.21)	0.94
Progesterone receptors		
Negative	1 (Ref)	
Positive	1.34 (0.29-6.31)	0.71
Chemotherapy		
0 -1	1 (Ref)	
2+	1.87 (0.41-8.56)	0.42
Hormonal therapy		
0	1 (Ref)	
1	0.18 (0.03-1.21)	0.08
2	0.60 (0.07-5.46)	0.65

Discussion:

MBC patients traditionally subject to systemic treatment and surgery directed to the primary site is reserved for palliative purposes, however, primary tumor resection in MBC attained a great controversy as several retrospective studies and meta-analyses of and population databases have demonstrated improved survival in women with stage IV disease who undergo surgery for an intact primary tumor [16-32]

The present retrospective study showed that women with MBC who had upfront resection of the primary tumor followed by systemic therapy lived longer than their counterparts who received standard therapy alone with a median OS more than 5 years compared to 4.7 years in ST group, despite that, these findings did not reach a statistical significance (p= 0.11). [Table 1; Fig. 1] These results coincide with some of the former retrospective studies [16-32]; nearly 83% of the women who received surgery lived for 5 years after diagnosis, compared with 69% of the women who did not receive surgery. These results are in match with Alexandra Thomas, et al [36] in retrospective analysis using data from Surveillance, Epidemiology, and End Results (SEER) program, who found an improvement of the median survival from 20 months (1988-1991) to 26 months (2007-2011) in patients received surgery.

Also, a systematic review and meta-Analysis of 30 observational studies done by Weikai Xiao, et al[37] showed significant OS improvement in MBC who had local tumor resection (HR = 0.65; , P < 0.001).

The underlying study showed that ST group had slightly more progressive pattern (38%) compared to surgery group (29%) with a median PFS of 1.67 years for ST and 2.42 years for surgery group but with no statistically significant difference (p-value= 0.36). [Fig. 2]This coincides with Weikai Xiao, et al [37] who showed that primary tumor resection was associated with better distant progression-free survival but did not impact PFS.

On univariate analysis, survival was prolonged in younger patients, endocrine sensitive tumor, receipt of hormonal treatment, less chemotherapy and fewer progressions, however on multivariate analysis, only hormonal treatment recipients and less progressive disease sustained significant association with better OS. [Table 2] These results are similar to findings observed in a previous retrospective studies [17, 23, 24, 28, 30, 31, 36, 38- 44] highlighted that positive ER status; a younger age; a smaller primary tumour are positive prognostic factors in terms of OS in the course of univariate analysis.

In univariate analysis, ER/PR-positive status (P = 0.002; 0.001), fewer metastatic sites (P= 0.04), non-visceral metastases (P= 0.006), use of endocrine therapy (P = 0.0001), and less chemotherapy (P = 0.001) were associated with longer PFS on univariate analysis, however, no specific clinical factor among them had significant association on multivariate analysis. [Table 3]

These findings are not in match with results from previous retrospective studies. [38]

Limitations and interpretation

There were several limitations in this study. The main limitation of our study, is its retrospective nature, so, surgery was not assigned by randomization. A subset of this study cohort had surgery without full staging workup and upstaged after surgery. In such case, these patients decided to have surgery based on an assumption of a lower stage. It was not registered if palliative primary tumor resection was done as mandatory initial treatment decision, this added to higher rate of upfront surgery for this group. Surgery group found to be younger (surgery: 82.9 % < 60 years,

ST: 72.2 % < 60 years) [Table 1] so, they were less likely to have comorbidity which would affect better survival results.

Also, triple negative cases (TNBC) were 50% in ST and 35% in surgery group. ST group were more likely to receive more than one line of chemotherapy (69 % and 48 % for ST and surgery group, respectively); ST group were more likely to have higher disease volume as 50% had more than one distant metastatic site compared to 17 % in surgery group (p-value= 0.001); finally, visceral metastases were significantly higher in ST group (75 % in ST and 51 % in surgery; p-value= 0.03). [Table 1]

These results are difficult to extrapolate to general population of MBC and this mandates large population-based randomized controlled study to confirm them.

Conclusion:

Primary tumor resection followed by systemic treatment was similar to systemic treatment alone as regards overall mortality and risk of progression in MBC. So, primary breast tumor resection in MBC should not be routinely used as frontline therapy but it may be considered in selected cases.

List of abbreviations

MBC= metastatic breast cancer
SUH= Sohag University Hospital
SCC = Sohag Cancer Center
ST= systemic therapy
ER= estrogen receptor
PR= progesterone receptor
HER2= human epidermal growth factor receptor-2
OS= overall survival
PFS= progression free survival
HR= hazards ratio
CI= confidence interval
TNBC = triple negative breast cancer

Competing interest

Authors have no financial competing interests to disclose.

Author's contributions

All authors carried out study design, data collection, analysis, interpretation of data, manuscript editing, the sequence alignment, and in the decision to submit the manuscript for publication. All authors read and approved the final manuscript.

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