Could Local Surgery Improve Survival in Stage IV Breast Cancer?

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Abstract:

Background: Metastatic breast cancer (Stage IV) accounts for 3% of all newly diagnosed patients with breast cancer in Japan, which is not different from that of USA (6%) reported according to the Surveillance, Epidemiology and End Results data. The treatment of Stage IV breast cancer has traditionally been palliative care with chemotherapy, hormonal therapy and/or radiation therapy. Young patients with limited metastatic (oligometastatic) disease and an excellent performance status tend to be long-term survivors. Combined treatment for such patients including surgery, provide better chance for long-term progression-free survival than systemic therapy alone.

Objective: Evaluating overall survival and progression free survival for metastatic breast cancer patients underwent mastectomy plus systemic therapy versus that on systemic therapy alone.

Patients and methods: This randomized study was conducted in surgical oncology department, medical oncology department, South Egypt Cancer Institute, Assiut University. We prospectively review and compare women presented with metastatic breast cancer between from January 2014 and December 2020, who received primary tumor resection (group A) and women treated non-operatively (group B).

Results: This study was conducted in surgical oncology department, medical oncology department -South Egypt Cancer Institute, Assiut University. we retrospectively and prospectively review and compare women (200 patients) presented with metastatic breast cancer between January 2014 and December 2019, who received surgery to the breast and women treated non-operatively. The study includes 67 patients who underwent surgery (42 patients underwent primary surgery then systemic treatment the others 25 patients received 1ry systemic treatment then underwent surgery) and 133 patients received only systemic treatment. Overall survival and progression free survival was 63.0% and 58.5% respectively, mean time of OS was28.1100 ± 1.3012 with range of 6 – 60 months and mean time of PFS was 26.0700 ± 1.3110 with range of 5 – 57 months.

Conclusion: Historically the standard treatment for metastatic breast cancer was systemic therapy and surgical resection of primary tumor was specified for palliation but with advanced understanding of tumor microbiology and animal module studies extent of surgery in advanced breast cancer increases.

Keywords: Metastatic breast cancer, Stage IV breast cancer, Overall Survival, Progression Free Survival and Surgical and non-surgical.

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Introduction:

Metastatic breast cancer (Stage IV) accounts for 3% of all newly diagnosed patients with breast cancer in Japan, which is not different from that of USA (6%) reported according to the Surveillance, Epidemiology and End Results data. The treatment of Stage IV breast cancer has traditionally been palliative care with chemotherapy, hormonal therapy and/or radiation therapy [1,2]

Metastatic breast cancer is unlikely to be cured. Systemic chemotherapy uncommonly causes complete remissions and long period of progression- free happened only in a fraction of complete responders. Patients with stage IV breast cancer has median survival

of 18 to 24 months with the range extends from few months to many years [3-5].

Common approach of treatment is to perform biopsy of the tumor to confirm diagnosis and give systemic therapy. Most oncologists consider that there is no survival benefit of aggressive local therapy in metastatic breast cancer. However, resection of the primary tumor can provide palliation of ulceration, bleeding or infection [6].

There is percent of metastatic breast cancer patients who have biologically indolent disease and limited systemic tumor burden. Two to five percent of patients with stage IV disease become long-term survivors and 5 to 10 percent survive five or more years [7,8]. Young patients with limited metastatic (oligometastatic) disease and an excellent performance status tend to be long-term survivors. Combined treatment for such patients, including surgery, provide better chance for long-term progression-free survival than systemic therapy alone [9].

Aim of the study

Evaluating overall survival and progression free survival for metastatic breast cancer patients underwent mastectomy plus systemic therapy versus that on systemic therapy alone.

Patients and Methods:

This randomized study was conducted in surgical oncology department, medical oncology department, South Egypt Cancer Institute, Assiut University.

we prospectively review and compare women presented with metastatic breast cancer between from January 2014 and December 2020, who received primary tumor resection (group A) and women treated non-operatively (group B).

Study design

Included in this study; Primary untreated patients with histologically confirmed invasive breast cancer, diagnosed as metastatic disease other than axillary lymph nodes by radiological examination, had three or less affected organs. All patients received primary systemic therapy either chemotherapy, hormonal and/or target therapy according to the estrogen and progesterone and human epidermal growth factor receptors type-2 status of the primary breast cancer. After 3 months, the patients with stationary or regression course were randomized to the primary tumor resection plus systemic therapy arm or the systemic therapy alone arm. Patients underwent primary resection of the tumor (modified radical or conservative mastectomy) then diagnosed as metastatic disease before start of systemic therapy were included in the study. Patients who underwent palliative mastectomy with or without lymph node evaluation were included in the surgery group. Patients had brain metastasis or progressive course on primary systemic therapy were excluded from the study. Patients unfit or refusing surgery were excluded from surgical arm and putted in non-surgical one.

Demographic information included patient's age, comorbidities and performance were collected. The American Joint Committee on Cancer (AJCC) 6th edition on tumor staging system was used to describe tumor size and lymph node involvement. Other tumor characteristics collected included presence of Her2Neu overexpression, pathologic type, hormone receptor status and information on the number and type of metastases and the use of adjuvant therapy including chemotherapy, target therapy, radiation therapy and endocrine therapy were recorded.

Overall survival and progression free survival (Progression of metastasis was defined as either clinical or radiographic evidence of a new site of metastatic disease, increasing tumor burden or recurrence at a previously treated known metastatic site) of the enrolled patients were measured from start till the end of the study. Survival will be calculated in days from day of cancer diagnosis to last documented clinic visit or day of death. Patients with missed follow up will be considered deaths.

Ethical considerations

Approval for this study was obtained from our Ethical Committee. Informed consent was taken from the patients.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS®) version 16.0 (SPSS, Inc. Chicago, IL, United States).

Results:

This study was conducted in surgical oncology department and medical oncology department, South Egypt Cancer Institute, Assiut University. We retrospectively review and compare women (200 patients) presented with metastatic breast cancer between January 2014 and December 2019, who received surgery to the breast and women treated non-operatively.

Patients demographic data

In table 1 we declare patients demographic data; the mean age of patients in the study was 55.41 ± 11.139 yrs. with range of 22 – 76 yrs. and mean BMI was 29.6544 ± 5.56155 with range of 22 - 43. The study includes 67 patients who underwent surgery (42 patients underwent primary surgery then systemic treatment the others 25 patients received 1ry systemic treatment then underwent surgery) and 133 patients received only systemic treatment. 47.0% of patients were healthy while 53% were diseased (D.M 11.5%, hypertension 16.5%, cardiac 5.5%, hepatic 4.5%, renal 3.5% and multiple 11.5%). According to performance 66.5% of patients have zero performance, 23.5% and 10% have one and two performance respectively. 141(70.5%) patients were postmenopausal and 59(29.5%) were not. 24(35.8%) patients had radical surgery, 29(43.3%) simple and 14(20.9%) partial surgery. 31(46.3%) patients underwent complete axillary dissection,

19(28.4%) sampling and 17(25.4%) had no dissection. Surgery was diagnostic, therapeutic, palliative and post-chemotherapy in 5, 18, 19 and 25 patients respectively.

Tumor characters and hormonal status

Table 2 viewing tumor characters and hormonal status where number of patients with tumor size ≤2cm was 84(42.0%) and patients with size >2cm were 116(58.0%), patients with IDC were 151(75.5%) then ILC 38(19.0%) and other pathology 11(5.5%). Patients having grade 1 tumor were 72(36.0%), grade 2 tumors 85(42.5%) and grade 3 tumors 43(21.5%). Breast cancer was at right site in 57(28.5%) patients, left in 120(60.0%) patients and bilateral in 23(11.5%) patients. Patients having more than one site of metastasis were 64(32.0%). Mean number of metastasis was 2.3050

± 1.46722, mean number of dissected L.Ns was 17.7612 ± 15.40768 and mean number of +ve L.Ns was 9.3284±7.76431. According site of metastasis; patients with bone metastasis were 141(70.5%), lung 28(14.0%), hepatic 19(9.5%) and others 12(6.0%). When reviewing hormonal status of the tumor patients having +ve progesterone were 140(70.0%), +ve estrogen 135(67.5%) and -ve Her2neu 169(84.5%).

Overall survival and Progression Free Survival

In table 3; overall survival and progression free survival was 63.0% and 58.5% respectively, mean time of OS was 28.1100 ± 1.3012 with range of 6 – 60 months and mean time of PFS was 26.0700 ± 1.3110 with range of 5 – 57 months. In table 4 we correlated clinic-pathological factors with OS and PFS using Chi-square test where age, BMI, associated diseases, tumor size, pathological type, grade, reason of surgery, laterality, no. of dissected L.Ns, no. of ± ve L.Ns, menopausal status and Her2neu had no significant correlation with OS (P value was 0.535, 0.289, 0.452, 0.155, 0.296, 0.375,0.642, 0.749, 0.245, 0.077, 0.295 and 0.205 respectively but performance, surgery, type of surgery, site of metastasis, more than one site of metastasis, no. of metastasis, axillary dissection, progesterone and estrogen had significant correlation with OS where living patients had good performance, more radical surgery, more in bone metastasis, lesser number of metastatic sites, lesser number of metastasis, more complete axillary dissection and had more positive progesterone and estrogen receptors(P value was 0.006, 0.024, 0.026, 0.000, 0.000, 0.000, 0.010, 0.046 and 0.000 respectively). While PFS had no significant correlation with age, BMI, associated diseases, type of treatment (surgical or non-surgical). tumor size, pathological type, type of surgery, reason of surgery, laterality, no. of metastasis, axillary dissection, no. of dissected L.Ns and no. of ±ve L.Ns(P value was 0.542, 0.205, 0.291, 0.464, 0.221, 0.655, 0.642, 0.749, 0.141, 0.355, 0.449 and 0.416 respectively) but it had significant correlation with performance, grade, metastatic site, more than one site of metastasis, menopausal status, progesterone, estrogen and Her2neu where PFS had tendency toward good performance, low grade tumor, more bone metastasis, lesser number of metastatic sites, more postmenopausal cases and high number of positive progesterone, estrogen and Her2neu receptors(P value was 0.008, 0.000, 0.004, 0.034, 0.000, 0.040, 0.002 and 0.034 respectively).

Comparison between surgical & non-surgical group

In table 5 we compared between surgical and non-surgical in clinic- pathological factors; where there were no significant difference between the two groups in age, associated diseases, performance, histology, grade, laterality, site of metastasis, number of metastatic sites, number of metastasis, menopausal status, progesterone, estrogen, PFS, time of OS and time of PFS (P value was 0.770, 0.730, 0.493, 0.395, 0.370, 0.499, 0.220, 0.268, 0.516, 0.061, 0.425, 0.467, 0.464, 0.484 and 0.192 respectively), the only significant difference was in BMI (patients in surgical group had larger mean BMI than non-surgical 30.0130±5.8350 vs 29.4737±5.4322 respectively [P=0.014]), tumor size (surgical group had more larger tumor 67.2% vs 53.4% for non-surgical group [P=0.043]), Her2neu -ve in non-surgical group more than surgical group 88.0% vs 77.6% (P=0.046) and overall survival was higher in surgical group compared to non-surgical one 73.1% vs 57.9% (P= 0.024).

Multivariate analysis

Multivariate analysis is presented in table 6 where age, associated diseases, grade, histology, type of surgery, performance, progesterone, estrogen, Her2neu, menopausal status, axillary dissection, laterality and reason of surgery had no significant relation with overall survival (P value was 0.810, 0.555, 0.619, 0.844, 0.302, 0.051, 0.148, 0.760, 0.232, 0.791 and 0.900 respectively) but BMI, tumor size, surgery (surgical & non-surgical), metastatic site, more than one metastatic site, no. of metastasis, no. of dissected L.NS and no. of +ve L.Ns independent factors had significant relations with OS (P value was 0.042, 0.032, 0.000, 0.004, 0.008, 0.000 and 0.000 respectively). While PFS had only significant relation with grade (P value was 0.018).

Surgical and Non-surgical group OS & PFS

By using Kaplan Meier test to evaluate OS and PFS we found that surgical group had significant effect on overall survival (mean OS for surgical group was 47.666 Lower Bound 42.921 and Upper Bound 52.411 where that for non-surgical group was34.751 Lower Bound 31.800 and Upper Bound 37.702 at 95% Confidence Interval) (Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware significance was 0.006, 0.014 and 0.009 respectively) (fig 1) but there was significant difference between the 2 groups in progression free survival (mean PFS for surgical group was 40.284 Lower Bound 35.431 and Upper Bound 45.136 where that for non-surgical group was 33.734 Lower Bound 30.652 and Upper Bound 36.816 at 95% Confidence Interval) (Log Rank (Mantel- Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware significance was 0.223, 0.342 and 0.275 respectively) (fig 2).

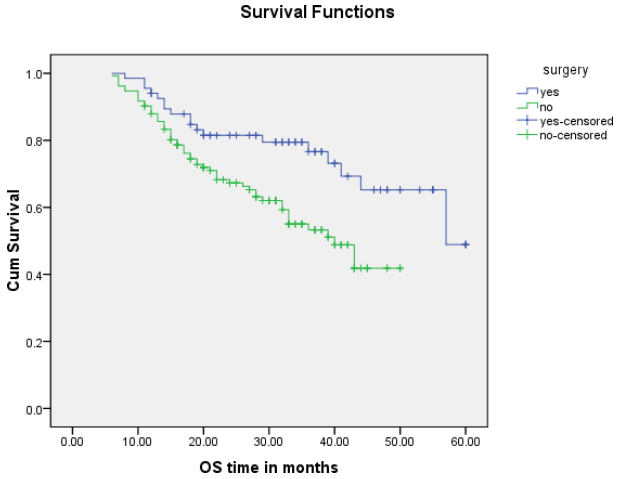

Figure 1: Showing OS of the groups

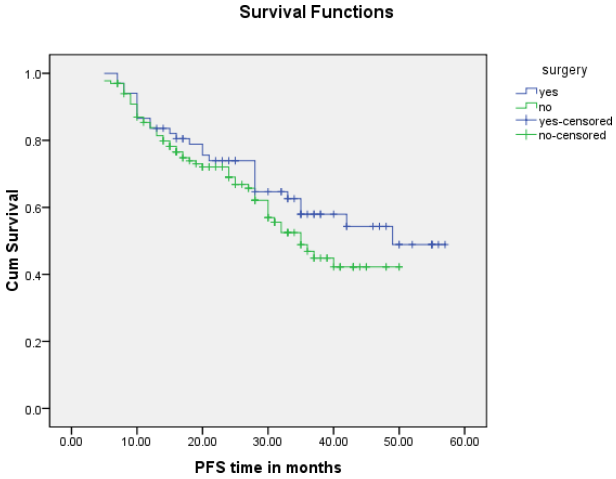

Figure 2: Showing overall survival of the groups

Table 1: Patient characters and treatment

	Number	Percent
Age		
- **Mean ± SD**		55.41 ± 11.139 yrs.
- **Range**		22 – 76 yrs.
BMI		
- **Mean ± SD**		29.6544 ± 5.56155
- **Range**		22 - 43
Associated diseases		
- **Healthy**	94	47.0%
- **D.M**	23	11.5%
- **Hypertension**	33	16.5%
- **Cardiac**	11	5.5%
- **Hepatic**	9	4.5%
- **Renal**	7	3.5%
- **Multiple**	23	11.5%
Performance		
- **0**	133	66.5%
- **1**	47	23.5%
- **2**	20	10.0%
Postmenopausal status		
- **Yes**	141	70.5%
- **No**	59	29.5%
Surgery		
- **Yes**	67	33.5%
- **No**	133	66.5%
Type of surgery		
- **Radical**	24	35.8%
- **Simple**	29	43.3%
- **Partial**	14	20.9%
Axillary dissection		
- **Complete**	31	46.3%
- **Sampling**	19	28.4%
- **Non**	17	25.4%
Reason of surgery		
- **Diagnosis**	5	7.5%
- **Treatment**	18	26.9%
- **Palliative**	19	28.4%
- **Post- chemotherapy**	25	37.3%

Table 2: Tumor clinic-pathological characters and hormonal status

	Number	Percent
Tumor size		
- **≤2cm**	84	42.0%
- **>2cm**	116	58.0%
Histology		
- **IDC**	151	75.5%
- **ILC**	38	19.0%
- **Others**	11	5.5%
Grade		
- **grade 1**	72	36.0%
- **grade 2**	85	42.5%
- **grade 3**	43	21.5%
Laterality		
- **Rt**	57	28.5%
- **Lt**	120	60.0%
- **Bilateral**	23	11.5%
More than one met. site		
- **yes**	64	32.0%
- **no**	126	68.0%
No. of metastasis		
- **Mean ± SD**	2.3050 ±1.46722	
- **Range**	1 - 7	
No. of dissected L.Ns		
- **Mean ± SD**	17.7612 ±15.40768	
- **Range**	0 - 50	
No. of + ve L.Ns		
- **Mean ± SD**	9.3284±7.76431	
- **Range**	0 - 30	
Site of metastasis		
- **Bone**	141	70.5%
- **Lung**	28	14.0%
- **Liver**	19	9.5%
- **Others**	12	6.0%
Progesterone		
- **+ ve**	140	70.0%
- **- ve**	60	30.0%
Estrogen		
- **+ ve**	135	67.5%
- **- ve**	65	32.5%
Her2neu		
- **+ ve**	169	84.5%
- **- ve**	31	15.5%

Table 3: Overall Survival and Progression Free Survival

	Number	Percent
Overall survival (OS)		
- **Dead**	74	37.0%
- **Living**	126	63.0%
Progression free survival (PFS)		
- **Progress**	83	41.5%
- **Free**	117	58.5%
Time of OS		
- **Mean ± SD**	28.1100 ± 1.3012	
- **Range**	6 – 60 months	
Time of PFS		
- **Mean ± SD**	26.0700 ± 1.3110	
- **Range**	5 – 57 months	

Table 4: Correlation between clinicopathological factors with OS and PFS.

	Overall survival		Chi-square P value	PFS		Chi-square P value
	Dead (74)	**Living (126)**		**Progress (61)**	**Free (86)**	
Age	54.73±	55.80±		52.52±	57.45±	
Mean ± SD	11.482	10.959	0.535	12.734	9.382	0.542
Range	22 - 76	28 - 75		22 - 76	35 -74	
BMI	30.1662±	29.3537±		29.0434±	30.0878±	
Mean ± SD	6.11677	5.21013	0.289	5.23225	5.76659	0.205
range	20 - 43	20 - 42		20 - 43	20 - 42	
Associated diseases						
- **Healthy**	33(44.6%)	61(48.4%)		44(53.0%)	50(42.7%)	
- **D.M**	10(13.5%)	13(10.3%)		13(15.7%)	10(8.5%)	
- **Hypertension**	12(16.2%)	21(16.7%)		11(13.3%)	22(18.8%)	
- **Cardiac**	6(8.1%)	5(4.0%)	0.452	3(3.6%)	8(6.8%)	0.291
- **Hepatic**	4(5.4%)	5(4.0%)		2(2.4%)	7(6.0%)	
- **Renal**	4(5.4%)	3(2.4%)		2(2.4%)	5(4.3%)	
- **Multiple**	5(6.8%)	18(14.3%)		8(9.6%)	15(12.8%)	
Performance						
- **0**	44(59.5%)	89(70.6%)		45(54.2%)	88(75.2%)	
- **1**	16(21.6%)	31(24.6%)	0.006	26(31.3%)	21(17.9%)	0.008
- **2**	14(18.9%)	6(4.8%)		12(14.5%)	8(6.8%)	
Surgery						
- **Yes**	18(24.3%)	49(38.9%)	0.024	27(32.5%)	40(34.2%)	0.464
- **No**	56(75.7%)	77(61.1%)		56(67.5%)	77(65.8%)	
Tumor size						
- **≤ 2cm**	35(47.3%)	49(38.9%)	0.155	38(45.8%)	46(39.3%)	0.221
- **>2cm**	39(52.7%)	77(61.1%)		45(54.2%)	71(60.7%)	
Histology						
- **IDC**	53(71.6%)	98(39.45%)		62(74.7%)	89(76.1%)	
- **ILC**	18(24.3%)	20(15.9%)	0.296	15(18.1%)	23(19.7%)	0.655
- **Others**	3(4.1%)	8(6.3%)		6(7.2%)	5(4.3%)	
Grade						
- **grade 1**	28(37.8%)	44(34.9%)		21(25.3%)	51(43.6%)	
- **grade 2**	34(45.9%)	51(40.5%)	0.375	33(39.8%)	52(44.4%)	0.000
- **grade 3**	12(16.2%)	31(24.6%)		29(34.9%)	14(12.0%)	

Type of surgery						
- **Radical**	2(11.1%)	22(44.9%)		9(33.3%)	15(37.5%)	
- **Simple**	12(66.7%)	17(34.7%)	0.026	13(48.1%)	16(40.0%)	0.655
- **Partial**	4(22.2%)	10(20.4%)		5(18.5%)	9(22.5%)	
Reason of surgery						
- **Diagnosis**	3(11.1%)	2(5.0%)		3(11.1%)	2(5.0%)	
- **Treatment**	8(29.6%)	10(25.0%)	0.642	8(29.6%)	10(25.0%)	0.642
- **Palliative**	8(29.6%)	11(27.5%)		8(29.6%)	11(27.5%)	
- **Post- chemotherapy**	8(29.6%)	17(42.5%)		8(29.6%)	17(42.5%)	
Laterality						
- **Rt**	22(26.5%)	35(29.9%)	0.749	22(26.5%)	35(29.9%)	
- **Lt**	50(60.2%)	70(59.8%)		50(60.2%)	70(59.8%)	0.749
- **Bilateral**	11(13.3%)	12(10.3%)		11(13.3%)	12(10.3%)	
Site of metastasis						
- **Bone**	27(36.5%)	114(90.5%)		48(57.8%)	93(79.5%)	
- **Lung**	20(27.0%)	8(6.3%)	0.000	14(16.9%)	14(12.0%)	0.004
- **Liver**	17(23.0%)	2(1.6%)		14(16.9%)	5(4.3%)	
- **Others**	10(13.5%)	2(1.6%)		7(8.4%)	5(4.3%)	
More than one met.site						
- **Yes**	50(67.6%)	14(11.1%)	0.000	33(39.8%)	31(26.5%)	0.034
- **No**	24(32.4%)	112(88.9%)		50(60.2%)	86(73.5%)	
No. of metastasis						
- **Mean ± SD**	3.5270± 1.59814	1.6190± .78849	0.000	2.5783± 1.57821	2.1453± 1.37881	0.141
- **Range**	1 - 7	1 - 5		1 - 7	1 - 6	
Axillary dissection						
- **Complete**	6(33.3%)	25(51.0%)		12(44.4%)	19(47.5%)	
- **Sampling**	10(55.6%)	9(18.4%)	0.010	10(37.0%)	9(22.5%)	0.355
- **Non**	2(11.1%)	15(30.6%)		5(18.5%)	12(30.0%)	
No. of dissected L.Ns	16.2778±	18.3061±	0.245	17.8148±	17.7250±	0.449
Mean ± SD	12.48908	16.43320		14.15583	16.37538	
Range	0 - 42	0 - 50		0 - 44	0 - 50	
Number of + ve nodes	12.8333±	8.0408±	0.077	9.2963±	9.3500±	0.416
Mean ± SD	8.28358	7.23118		6.39600	8.64559	
Range	0 - 30	0 - 22		0 - 22	0 - 30	
Postmenopausalstatus						
- **Yes**	50(67.6%)	91(72.2%)	0.295	47(56.6%)	94(80.3%)	0.000
- **No**	24(32.4%)	35(27.8%)		36(43.4%)	23(19.7%)	
Progesterone						
- **+ ve**	46(62.2%)	94(74.6%)	0.046	52(62.7%)	88(75.2%)	0.040
- **- ve**	28(37.8%)	32(25.4%)		31(37.3%)	29(24.8%)	
Estrogen						
- **+ ve**	25(33.8%)	110(87.3%)	0.000	46(55.4%)	89(76.1%)	0.002
- **- ve**	49(66.2%)	16(12.7%)		37(44.6%)	28(23.9%)	
Her2neu						
- **- ve**	60(81.1%)	109(86.5%)	0.205	65(78.3%)	104(88.9%)	0.034
- **+ ve**	14(18.9%)	17(13.5%)		18(21.7%)	13(11.1%)	

Table 5: Correlation between surgery and clinicopathological factors.

	Surgical (67)	Non-surgical (133)	Chi-square P value
Age			
- Mean ± SD	53.43±12.309	56.40±10.408	0.770
- Range	22 - 75	25 -76	
BMI			
- Mean ± SD	30.0130±5.8350	29.4737±5.4322	0.014
- range	22 - 43	20 - 42	
Associated diseases			
- Healthy	35(52.2%)	59(44.4%)	
- D.M	7(10.4%)	16(12.0%)	
- Hypertension	12(17.9%)	21(15.8%)	0.730
- Cardiac	4(6.0%)	7(5.3%)	
- Hepatic	3(4.5%)	6(4.5.0%)	
- Renal	2(3.0%)	5(3.8%)	
- Multiple	4(6.0%)	19(14.3%)	
Performance			
- 0	42(62.7%)	91(68.4%)	
- 1	16(23.9%)	31(23.9%)	0.493
- 2	9(13.4%)	11(8.3%)	
Histology			
- IDC	54(80.6%)	97(72.9%)	
- ILC	11(16.4%)	227(20.3%)	0.395
- Others	2(3.0%)	9(6.8%)	
Grade			
- grade 1	24(35.8%)	48(36.1%)	
- grade 2	25(37.3%)	60(45.1%)	0.370
- grade 3	18(26.9%)	25(18.8%)	
Laterality			
- Rt	16(23.9%)	41(30.8%)	
- Lt	44(65.7%)	76(57.1%)	0.499
- Bilateral	7(10.4%)	16(12.0%)	

Site of metastasis			
- Bone	44(65.7%)	97(72.9%)	0.610
- Lung	12(17.9%)	16(12.0%)	
- Liver	6(9.0%)	13(9.8%)	
- Others	5(7.5%)	7(5.3%)	
More than one met. site			
- Yes	19(28.4%)	45(33.8%)	0.268
- No	48(71.6%)	88(66.2%)	
No. of metastasis			
- Mean ± SD	2.4627±1.40700	2.2556±1.51084	0.516
- Range	1 - 6	1 - 7	
Postmenopausal status			
- Yes	42(62.7%)	99(74.4%)	0.061
- No	25(37.3%)	34(25.6%)	
Progesterone			
- + ve	48(71.6%)	92(69.2%)	0.425
- - ve	19(28.4%)	41(30.8%)	
Estrogen			
- + ve	46(68.7%)	89(66.9%)	0.467
- - ve	31(31.3%)	44(33.1%)	
Her2neu			
- - ve	52(77.6%)	117(88.0%)	0.046
- + ve	15(22.4%)	16(12.0%)	
Overall survival			
- Dead	18(26.9%)	56(42.1%)	0.024
- Living	49(73.1%)	77(57.9%)	
Progression free survival			
- Progress	27(40.3%)	56(42.1%)	0.464
- Free	40(59.7%)	77(57.9%)	
Time of OS			
- Mean ± SD	32.5821± 1.4440	25.8571±1.1650	0.484
- Range	8 - 60	6 – 50	
Time of PFS			
- Mean ± SD	29.9552±1.4673	24.0902±1.1850	0.192
- Range	7 -57	5 – 50	

Table 6: Multivariate analysis of clinicopathological factors Correlation with overall survival and DFS.

Variables	**OS & PFS**	Sig.
Age	survival	0.810
	Progression free survival	0.564
BMI	survival	0.042
	Progression free survival	0.918
Associated diseases	survival	0.555
	Progression free survival	0.500
Tumor size	survival	0.032
	Progression free survival	0.843
Surgery	survival	0.000
	Progression free survival	0.249
Grade	survival	0.619
	Progression free survival	0.018
Histology	survival	0.844
	Progression free survival	0.590
Type of surgery	survival	0.302
	Progression free survival	0.170
Performance	survival	0.228
	Progression free survival	0.065
Progesterone	survival	0.051
	Progression free survival	0.798
Estrogen	survival	0.148
	Progression free survival	0.465
Her2neu	survival	0.298
	Progression free survival	0.666
Postmenopausal	survival	0.760
	Progression free survival	0.753
Metastatic site	survival	0.004
	Progression free survival	0.168
More than one	survival	0.008
metastatic site	Progression free survival	0.254
No. of metastasis	survival	0.000
	Progression free survival	0.184
Axillary dissection	survival	0.232
	Progression free survival	0.066
No. of dissected L.Ns	survival	0.000
	Progression free survival	0.662
Laterality	survival	0.791
	Progression free survival	0.060
No. of +ve L.Ns	survival	0.000
	Progression free survival	0.167
Reason of surgery	survival	0.900
	Progression free survival	0.089

Discussion:

Conventional approach to metastatic breast cancer was limited to resections of the primary tumor that aim to control ulceration, infection, bleeding or fungation that are resistant to non-operative measures. Recently it is challenging because of rational of potential therapeutic effect by removing source of tumor seeding and minimizing the total body tumor burden. Also advancement in systemic therapies for breast cancer had improved survival of metastatic breast cancer in the last few decades. From these studies; Khan et al, 2002, this retrospective study was done on 16,203 patients with stage IV disease in the period from 1990 to 1993, where 57.2% underwent complete or partial mastectomy, reported that 3-year survival was improved from 26% to 35% in complete mastectomy compared to partial mastectomy with a hazard ratio of 0.61 (95% confidence interval [CI] 0.581–0.646). In their multivariate analysis; extent of primary tumor resection, site of metastasis and number of metastatic sites were significant independent covariates, thus calling into question the historical solely palliative role of mastectomy in stage IV breast cancer.[10]

Two retrospective studies reviewed in 2006. One of these studies was done on 224 patients with stage four breast cancer in the period from 1997 to 2002, 142 of them did not surgery while 82 treated with mastectomy. This study reported significant improvement in disease-free survival (p=0.007) and trend toward improvement in overall survival (p=0.12).[11] The other paper reviewed 300 patients with metastatic breast cancer between 1977 and 1996, 173 of them did not receive surgery while 127 underwent mastectomy. The study reported that mastectomy improves survival in metastatic breast cancer especially in patients with only bone metastasis where there was 40% reduced risk of death (p=0.49).[12]

Another two more studies published in 2007 supporting role of mastectomy in metastatic breast cancer. The first study reported 409 patients between 1996 and 2005, 187 of them had treated surgically and reported overall survival improvement from15.4 months to 31.9 months (p<0.0001), even after controlling of other factors.[13]

The second study, Gnerlich et al reported 9,734 patients in the period from 1988 to 2003in (SEER) program, 47% of these patients had received surgical treatment and reported that even after controlling of covariates there was improved overall survival 36 months compared to 21 months (p<0.001).[14]

In 2008, A study published by Blanchard et al involving 295 patients with stage IV cancer breast, in the period from 1973 to 1991, 153 did not have surgery while 142 were treated surgically. The study reported that even after multivariate analysis, overall survival was 16.8 months for non- surgical vs 27.1 months for surgical group. (p<0.0001).[15]

Also Rao et al. published study in the same containing 224 patients metastatic breast cancer from 1997 to 2002, 142 of them did not have surgery compared to 82 who had surgical treatment. The study showed that patients, who had synchronous resection of distant disease, complete resection, Caucasian race and only one site of metastasis, had improved PFS.[16]

In conversely to the previous rational, others have suggested that resection of the primary tumor may disrupt the immunologic balance which happened in the small fraction of patients with metastatic disease that remains indolent for long time and there was selection bias in the previous studies and covariates may explain the positive results. From these conflicting studies, a study done by Cady et al published in 2008 including 622metastaic breast cancer patients from 1970 to 2002, 38% had complete surgical resection and 62% had no surgical treatment. The study firstly showed improved survival in surgical group but in case matching there was reduced or eliminated survival benefit in surgical group and reported that improvement due to selection bias.[17]

In 2009 two studies were published eliminating role of surgery in improving survival in metastatic cancer breast. First study included 147 patients between 1998 and 2005, 58.5% did not have surgery and 41.5% underwent operation and reported survival benefit in the surgical group, which was disrupted by stage migration.[18]

The second study reviewed 204 patients between 1990 and 2000, 52 of them had received surgery compared to 152 had not. The study reported survival benefit in chemotherapy but not from surgery.[19]

However, in 2009 a study of 581 patients between 1980 and 2004, comparing survival in patients received systemic therapy alone (261 patients) vs patients received locoregional treatment 320 (13% surgery, 78% radiotherapy and 9% both). The authors found improved 3-year survival in local therapy group even after multivariate analysis (43.4% for locoregional group vs. 26.7% systemic therapy alone group, p=0.00002). They suggested that radiotherapy may be an alternative to surgical treatment in these patients.[20]

In addition, in 2010 Neuman et al reviewed in the period from 2000 to 2004, 186 patients with stage IV breast cancer of them 117 did not have surgery and 69 patients underwent surgical treatment and 117 who did not. They reported that improved survival in surgical group was only in patients with positive receptors (p=0.004).[21]

In 2013 an animal study was conducted through orthotropic implantation of adenocarcinoma cells in murine mammary gland to evaluate effect of mastectomy on metastatic breast cancer (comparing between mastectomy and observation alone), after a while the authors found that early after tumor resection there was transiently proliferation of metastatic lesions but after follow up there was significant improvement in overall survival in mastectomy group vs observational group so they emphasize that primary tumor resection reduce overall tumor burden which is the important factor determining survival.[22]

Our study includes 200 female patients with stage IV breast cancer, 67 patients who underwent surgery (42 patients underwent primary surgery then systemic treatment the others 25 patients received 1ry systemic

treatment then underwent surgery) and 133 patients received only systemic treatment.

In our study, we analyzed many clinicopathological variables which may affect overall survival and progression free survival like age, BMI, associated diseases, performance, side and size of the tumor, histopathology, grade, type of treatment, hormonal receptors, postmenopausal status, site of metastasis, No of metastatic sites and No of metastasis. Also in surgical group we analyzed No of dissected L.Ns and No of positive L.Ns. In our study overall survival and progression free survival was 63.0% and 58.5% respectively, mean time of OS was 28.1100 ± 1.3012 months and mean time of PFS was 26.0700 ± 1.3110 months. During comparison between surgical and non-surgical group we found the only significant difference was in BMI (P=0.014), tumor size (P=0.043), Her2neu (P=0.046) and overall survival (P= 0.024) towards surgical group. In multivariate analysis BMI, tumor size, surgery (surgical & non-surgical), metastatic site, more than one metastatic site, no. of metastasis, no. of dissected L.Ns and no. of +ve L.Ns independent factors had significant relations with OS (P value was 0.042, 0.032, 0.000, 0.004, 0.008, 0.000 and 0.000 respectively). While PFS had only significant relation with grade (P value was 0.018). Our study reported that even after multivariate analysis, mean time of overall survival was 24.1 months for non-surgical vs 30 months for surgical group. (p=0.000).

Conclusion:

Historically the standard treatment for metastatic breast cancer was systemic therapy and surgical resection of primary tumor was specified for palliation but with advanced understanding of tumor microbiology and animal module studies extent of surgery in advanced breast cancer increases. Our study and many other single and meta-analysis retrospective studies of stage IV breast cancer reported higher survival rate in surgical group than nonsurgical group. So we recommend mastectomy in appropriately selected patients. Our recommendation for stage IV breast cancer is to start with systemic therapy at first then evaluating the patients if there is regressive or stationary course and the patients have the same finding after stoppage of treatment for six months patients may have surgical resection of primary tumor. We may recommend primary resection of the tumor with safety margin if the tumor size, breast size, general conditions of the patients and non-aggressive distant metastasis as patient may have psychological benefit that she had get rid of the tumor which may improve immune system also decreased tumor bulk may improve response to systemic therapy.

Limitations

We may have selection bias in the 25 patients whom started with systemic therapy first and after response we proceed to surgery.

Conflict of interest

None of the authors have a conflict of interest to declare.

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