Impact of primary tumor resection on response and survival in metastatic breast cancer patients

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Abstract: About 3-10% of breast cancer patients have distant metastases at initial presentation. Patients with metastatic breast cancer have limited therapeutic options, and the mainstay of treatment remains systemic chemotherapy. Traditionally, the role of surgery has been confined strictly to palliation. However, retrospective studies have shown improved survival in patients who underwent surgery for their primary tumor. Thus, new clinical questions have emerged regarding surgery of the primary site in those women with metastatic disease and a respectable intact primary tumor. This study included 151 patients with stage IV breast cancer who divided into two groups: Group A, who underwent surgery and Group B, who did not undergo surgery. All patients then received anthracyclin based chemotherapy followed by hormonal treatment according to hormonal status. Patients were evaluated after three cycles of chemotherapy, after 6 cycles of chemotherapy, and later on every three months. Patients characteristics and survival were evaluated using univariate and multivariable analysis. 151 patients included in this analysis, Group A: 61underwent surgery for their primary tumor and Group B: 90 patients did not. There is statistically significant difference as regard the results of the first evaluation between the two groups where 3patients achieved CR (complete response), 38 patients had stable disease and16 patients achieved partial response (PR) and 3 patients in disease progression (DP) in Group A while in Group B no patient achieved CR, 66 patients achieved PR, 12 patients had stable disease and 12 patients had DP. There was statistically significant difference as regard OS between the 2 groups, the mean survival for Group A was 39.10 months and 28.04 months for Group B. Primary tumor resection increased survival in patient with metastatic breast cancer. So the role of surgery in women with stage IV breast cancer needs to be re-evaluated.
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1. Introduction

About 3–10% of all patients newly diagnosed with breast cancer show evidence of metastatic disease at the time of presentation [(1).] Despite the epidemiological burden of this condition, there are no solid guidelines on how to manage breast cancer patients presenting with systemic spread; for these patients treatment planning is essentially based on personal preferences rather than reliable clinical data[(2).]

The role of surgery in advanced breast cancer will be incomplete without consideration of the management of the intact primary in patients with metastatic disease [(3).] As systemic treatment such as chemotherapy and hormonal therapy have become ever more effective, the median survival of women with metastatic breast cancer (MBC) has continued to improve, as has the management of symptoms resulting from distant disease sites. Thus, new clinical questions have emerged regarding surgery of the primary site in those women with metastatic disease and a respectable intact primary tumor [(3).]

Traditionally the treatment for women with MBC and an intact primary tumor is systemic therapy, with surgical treatment reserved for palliation of symptoms or when the primary leads to complications (i.e. skin ulceration, infection or bleeding) [(4).] However, studies challenge this approach, suggesting that removing the primary tumor may lead to an overall improved survival [(5).]

There are several theories that are why removal of the primary tumor could potentially improve survival. First, it is known that metastatic cancer cells have numerous effects on the immune system. One of these effects is that established malignancies use induction of immune tolerance to avoid immune surveillance [(6).] Second, the breast cancer stem cell theory proposes that specialized tumor initiating cancer cells have the exclusive potential to proliferate and form new sites of tumor metastasis [(6).]

The relatively low morbidity associated with breast surgery makes this an ideal model for a prospective investigation on the surgical excision of the primary in patients with metastatic disease [(7).]

Our study aims to assess the impact of primary tumor resection on survival in stage IV breast cancer patients.

2. Material and Methods

This a comparative study included 151 breast cancer patients with stage IV breast cancer and performance status 0 to 2, who presented to Clinical Oncology Department, Menoufia University Hospital, from September 2009 to August 2011. 61 patients underwent surgery and 90 patients did not. Baseline information collected included demographics data, tumour characteristics (size, regional node status, histological characteristics, and grade), sites and number of metastases, type of operation (Excision, Breast Conservative Surgery (BCS), Modified Radical Mastectomy (MRM)) and margin status in Group A. Staging was based on TNM staging System (Edition 7 published 2009 and went into effect 2010). Based on site of Metastases patients were divided into 3 groups: patients with bone metastases, visceral metastases, and mixed metastases. All patients received Anthracyclin based chemotherapy followed by hormonal treatment according to hormonal status. An informed written consent was taken from all patients before treatment.

Data were analyzed using SPSS program (statistical package for social science) for windows version 16. Two types of statistics were done: descriptive and analytic statistics. Student's t-test, Mann-Whitney test for quantitative variables, Chi-Squared (χ^2) and Fisher's exact test for qualitative variables. Two year survival and time to progression was analyzed using the Kaplan. Meier curves.Multivariate cox regression test was done for independent prognostic factors. *P value* < *0.05* was considered statistically significant.

3. Results

Patients' characteristics for the 151 patients in the study are listed in Table 1. Within Group A, 55 patients underwent Modified Radical Mastectomy (MRM), 5 patients underwent wide local excision with axillary evacuation and only 1 patient underwent simple mastectomy.

Table (1): Patients' characteristics

	Groups				**Test**	***P* value**
	Surgery (n=61)		**No surgery (n=90)**			
	no	**%**	**no**	**%**		
Age Mean ± SD	49.63± 11.91		52.43± 12.27		T 1.38	*0.167*
Sex					Fisher's exact test	
Male	1	1.6	1	1.1	0.08	
Female	60	98.4	89	98.9		*1.0*
Menopause					χ^2	
Pre	28	46.7	40	44.4	0.03	*0.960*
Post	33	53.3	50	55.6		
Performance status						
0	38	62.3	23	25.6	χ^2	
1	20	32.8	54	60.0	**20.75**	***<0.001***
2	3	4.9	13	14.4		***(Hs)***
Complaint						
Lump	54	88.5	66	73.3		
Discharge	3	4.9	0	0.0		
Pain	2	3.3	3	3.3		
Nipple retraction	1	1.6	1	1.1	χ^2	
Bony pain	0	0.0	13	14.4	**20.59**	***0.004***
Abdominal pain	0	0.0	5	5.6		***(s)***
Dyspnea	0	0.0	2	2.2		
Bleeding per nipple	1	1.6	0	0.0		
Side						
Right	29	47.5	43	47.8	χ^2	
Left	30	49.2	42	46.7	0.45	*0.796*
Bilateral	2	3.3	5	5.6		

Site						
Axillary tail	1	1.6	6	6.7		
Upper outer	39	63.9	52	57.8		
Upper inner	5	8.2	4	4.4	χ^2	
Lower outer	3	4.9	9	10.0	4.96	*0.664*
Lower inner	3	4.9	4	4.4		
Retroareolar	7	11.5	10	11.1		
Multifocal	3	4.9	4	4.4		
Pathology						
IDC	55	90.16	81	90	FE	
ILC	5	8.2	7	7.8	0.01	*1.0*
Others	1	1.64	2	2.2		
Size						
T1-T2	42	68.9	49	54.4	χ^2	
T3-T4	19	31.1	41	45.6	3.16	*0.076*
Grade						
II	55	90.2	74	82.2	χ^2	
III	6	9.8	16	17.8	1.84	*0.175*
ER						
+ ve	45	73.8	59	65.6	χ^2	
- ve	16	26.2	31	34.4	1.14	*0.285*
PR						
+ve	44	72.1	56	62.2	χ^2	
-ve	17	27.8	34	37.8	1.59	*0.206*
Her2						
+ve	10	16.4	21	23.3	χ^2	
-ve	51	83.6	69	76.7	1.07	*0.300*
ER\ Her2						
Er+ve\Her2+ve	6	9.8	4	8.3	χ^2	
Er+ve\Her2-ve	40	65.6	24	50.0	4.58	*0.205*
Er-ve\Her2+ve	5	8.2	10	20.8		
Er-ve\Her2-ve	10	16.4	10	20.8		
CA15.3 level						*<0.001*
Elevated	18	29.5	54	60.0	χ^2	*(HS)*
Normal	43	70.5	36	40.0	13.55	
1st evaluation						
CR	3	5.0	0	0.0	χ^2	
PR	16	26.7	66	73.3	48.34	*<0.001(HS)*
Stationary	38	63.3	12	13.3		
Progression	3	5.0	12	13.3		
Cause of death	Group A Deaths (n= 18)		Group B Deaths (n= 53)		Test	*P* value
	N0	%	No	%		
Cancer related	16	88.9	52	98.1	FE	
Not cancer related	2	11.1	1	1.9	2.82	*0.156*
Cause						
Liver failure	12	66.7	25	47.2	χ^2	
Renal failure	0	0.0	1	1.9	10.19	*0.037(s)*
Respiratory failure	3	16.7	14	26.4		
Infection	1	5.6	13	24.5		
Others	2	11.1	0	0.0		

Type of surgery and pathological characteristics of the tumor are shown in table 2.

Table (2): Type of surgery and pathological characteristics of the tumor

Surgery	No (n = 61)	%
Type		
MRM	55	90.2
Simple mastectomy	1	1.6
BCS	5	8.2
Margin		
Free	50	82.0
Involved	3	4.9
Close	8	13.1
Node		
N0	2	3.3
N1	12	19.7
N2	18	29.5
N3	28	45.9
Nx	1	1.6
Multi-centric disease		
Yes	5	8.2
No	56	91.8
Lympho-vascular space invasion:		
Yes		
No	5	24.59
	46	75.41
Capsular infiltration		
Yes	16	26.23
No	45	73.77
In situ component		
Yes	20	32.79
No	41	67.21

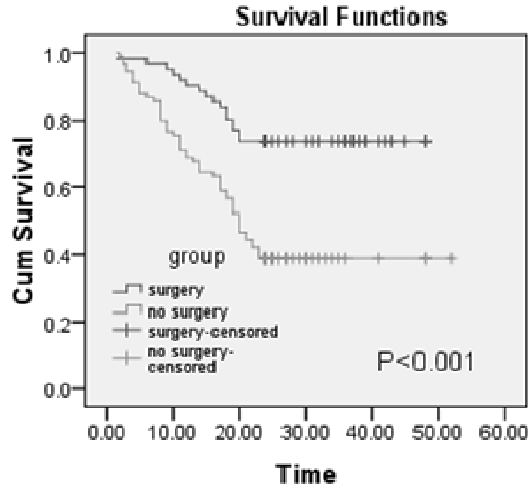
Details of metastatic sites involved, number of metastatic lesions per site and size of lesions are shown in table 3.

Table (3): Characteristics of Metastasis

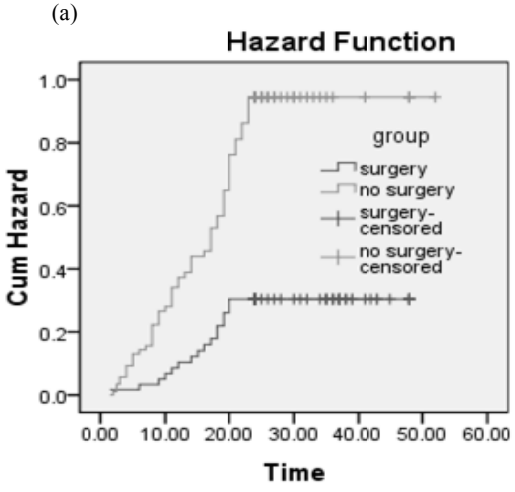
Metastasis	**Groups**				**Test**	***P* value**
	Surgery (n=61)		**No surgery (n=90)**			
	no	**%**	**no**	**%**		
Site of Metastases						
Bone	34	55.7	34	37.8	χ^2	
Visceral	18	29.5	32	35.6		*0.068*
Mixed	9	14.8	24	26.7	3.36	
Number of metastatic sites					χ^2	
1	44	72.1	59	65.6		
2	16	26.2	23	25.6	3.44	*0.179*
3	1	1.6	8	8.9		
Lung						
Yes	25	41.0	31	34.4	χ^2	*0.414*
No	36	59.0	59	65.6	0.66	
Lung						
Only	15	60.0	21	70.0	χ^2	
Lung + others	10	40.0	9	30.0	0.60	*0.437*
Liver						
Yes	7	11.5	34	37.8	**χ^2**	***<0.001***
No	54	88.5	56	62.2	**12.71**	***(HS)***
Liver						
Only	5	71.4	20	58.8	FE	
Liver + others	2	28.6	14	41.2	0.38	*0.685*
Bone						
Yes	44	72.1	59	65.6	χ^2	
No	17	27.9	31	34.4	0.72	*0.395*
Bone						
Only	12	27.3	23	39.0	χ^2	

Bone + others	32	72.7	36	61.0	1.54	*0.215*
Brain						
Yes	0	0.0	2	2.2	FE	
No	61	100.0	88	97.8	1.37	*0.515*
Brain +others	0	0.0	2	100.0	-	-
	Mean ± SD		**Mean ± SD**		**Mann-Whitney**	
Metastasis Number						
Bone	3.22 ± 2.40		4.86 ± 3.71		2.23	***0.026(S)***
Lung	3.04 ± 2.33		4.20 ± 2.79		1.58	*0.118*
Liver	3.42 ± 1.51		3.77 ± 2.64		0.06	*0.495*
Brain	-		4.50 ± 4.94		-	-
Size						
Lung	2.58 ± 0.81		2.63 ± 0.99		0.29	*0.765*
Liver	3.02 ± 0.47		3.88 ± 1.49		1.69	*0.090*
Brain	-		2.80 ± 0.28		-	-

There was statistically significant difference as regard OS between the 2 groups *(P value <0.001).* The mean survival for Group A was 39.10 months and 28.04 months for Group B (Figure 1).



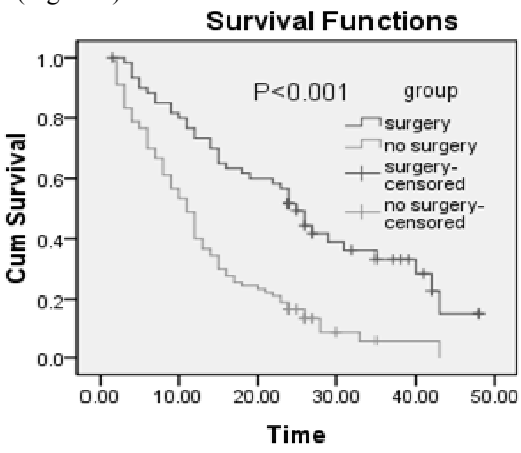
(a)



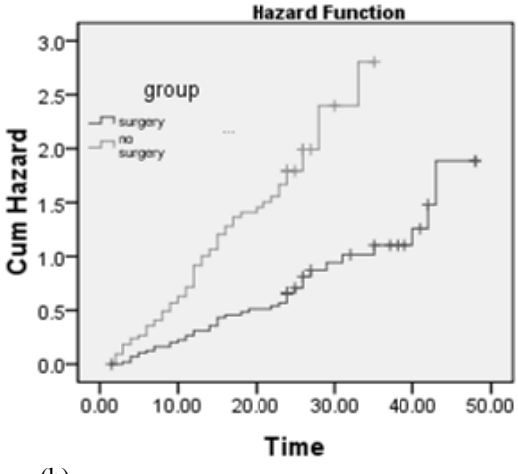
(b)

Figure (1) Kaplan-Meier overall survival curve: (a) Survival function (b) hazard function.

There was statistically significant difference in TTP between Group A and Group B *(p value <0.001),* with mean TTP 26.16 months (22.1 – 30.2) in Group A and 13.81 months (11.5 – 16.1) in Group B (Figure 2).



(a)



(b)

Figure (2) Kaplan-Meier time to progression curve: (a) Survival function (b) hazard function.

There was significant relation between site of metastases, tumor grade, estrogen receptor (ER) positivity and initial CA 15.3 tumor marker level in Group A showed in table 4**.**

Table (4): Probability of living for Group A

Surgery group		Overall survival Mean (95% CI)	SE	Log rank	*P* value
Age In years	≤50 >50	37.57 (32.0 – 43.1) 41.03 (36.1 – 45.9)	2.8 2.5	0.55	*0.457*
Menopause	Pre Post	36.80 (30.6 – 42.9) 41.06 (36.4 – 45.6)	3.1 2.3	1.08	*0.298*
PS	0 ≥1	36.0 (37.0 – 44.8) 40.9 (25.4 – 43.2)	2.5 2.8	1.74	*0.187*
Number of sites	>1 1	34.3 (35.3 – 46.4) 40.9 (32.9 – 43.0)	1.9 4.5	0.46	*0.494*
Site of Metastases	Bone Visceral Mixed	44.38 (41.0 – 47.7) 28.25 (21.1 – 35.3) 35.8 (24.5 – 47.2)	1.7 3.6 5.7	**9.95**	***0.007(s)***
Liver	+ others Only	13.3 (29.9 – 47.9) 19.0 (40.6 – 47.6)	5.0 1.0	0.33	*0.561*
Bone	+ others Only	38.9 (25.5 – 44.4) 44.1 (23.7 – 40.4)	4.5 1.8	1.26	*0.260*
Lung	+ others Only	34.9 (7.8 – 19.3) 32.1 (16.1 – 26.4)	4.8 4.2	0.01	*0.921*
Number of lesions	>5 ≤5	28.10 (20.9 – 35.3) 40.46 (36.5 – 44.4)	3.6 2.0	1.32	*0.249*
Size of lesions	>5 ≤5	33.01 (26.4 – 39.5) 33.01 (26.4 – 39.5)	3.3 3.3	-	-
Size	T1-T2 T3-T4	40.44 (35.9 – 44.8) 34.26 (27.8 – 40.6)	2.2 3.2	1.33	*0.247*
Grade	II III	40.55 (36.7 – 44.3) 25.83 (12.8 – 38.8)	1.9 6.6	**6.48**	***0.011(s)***
PR	Positive Negative	41.43 (37.5 – 45.2) 33.08 (24.3 – 41.7)	1.9 4.4	3.21	*0.071*
ER	Positive Negative	41.57 (23.1 – 41.2) 32.15 (37.8 – 45.3)	1.9 4.6	**4.09**	***0.043(s)***
HER2	Positive Negative	33.70 (24.8 – 42.5) 39.48 (35.4 – 43.5)	4.5 2.0	0.18	*0.669*
ER\ Her2	Er+ve\Her2+ve Er+ve\Her2-ve Er-ve\Her2+ve Er-ve\Her2-ve	30.66 (20.9 – 40.3) 37.63 (32.6 – 42.6) 42.40 (32.5 – 52.2) 44.80 (38.8 – 50.7)	4.9 2.5 5.0 3.0	1.89	*0.594*
Tumor marker Level	Elevated Normal	32.47 (24.2 – 40.6) 41.88 (38.0 – 45.7)	4.1 1.9	**5.25**	***0.022(S)***

Our results show that tumor grade is the independent factor affecting patients OS in Group A *(P= 0.036)* as shown in table 5.

Table (5): Multivariate Cox regression analysis for independent factors affecting patients OAS among Group A

Variable	WALD	Hazard ratio	*P* value	CI 95%	
				Lower	Upper
Tumor Grade	**4.41**	**3.57**	***0.036(S)***	1.08	11.70
ER	0.37	1.39	*0.539*	0.48	4.0
Tumor Marker Level	2.71	0.42	*0.099*	0.15	1.17
Site of Metastases	2.89	1.68	*0.089*	0.92	3.07

Probability of living in Group B showed in table 6.

Table (6): Probability of living in Group B

No Surgery group		Overall survival Mean (95% CI)	SE	Log rank	*P* value
Age In years	≤50	26.85 (21.2 – 32.4)	2.8	0.35	*0.550*
	>50	27.67 (22.3 – 33.0)	2.7		
Menopause	Pre	26.97 (20.7 – 33.1)	3.1	0.25	*0.617*
	Post	27.30 (22.4 – 21.1)	2.4		
PS	0	24.7 (16.8 – 32.6)	4.0	0.28	*0.591*
	≥1	28.6 (24.0 – 33.2)	2.3		
Site of Metastases	Bone	32.26 (25.8 – 38.6)	3.2	5.71	*0.057*
	Visceral	20.85 (17.1 – 24.5)	1.9		
	Mixed	19.81 (12.9 – 26.6)	3.4		
Number of sites	**>1**	**19.0 (13.1 – 24.9)**	**2.5**	**9.28**	***0.002***
	1	**32.3 (27.4 – 37.2)**	**2.9**		
Liver	+ others	13.6 (7.8 – 19.3)	2.9	**5.58**	***0.018***
	Only	21.2 (16.1 – 26.4)	2.6		
Bone	+ others	18.5 (11.7 – 25.2)	3.4	**7.06**	***0.008***
	Only	32.2 (25.9 – 38.4)	3.1		
Lung	+ others	20.6 (12.8 – 28.4)	3.9	**3.94**	***0.047***
	Only	23.1 (19.0 – 27.2)	2.0		
Number of lesions	>5	25.84 (20.3 – 31.1)	2.8	0.12	*0.724*
	≤5	28.60 (23.1 – 34.0)	2.7		
Size of lesions	>5	17.36 (8.9 – 25.8)	4.3	3.20	*0.073*
	≤5	26.57 (21.0 – 32.1)	2.8		
Timor Size	T1-T2	31.25 (25.6 – 36.8)	2.8	2.64	*0.104*
	T3-T4	23.03 (17.8 – 28.2)	2.6		
Tumor Grade	II	25.91 (21.9 – 29.9)	2.0	0.51	*0.476*
	III	31.12 (20.6 – 41.5)	5.3		
PR	Positive	31.97 (27.4 – 36.4)	2.3	**16.19**	***<0.001(HS)***
	Negative	18.16 (12.5 – 23.7)	2.9		
ER	Positive	31.33 (26.8 – 35.8)	2.2	**17.93**	***<0.001(HS)***
	Negative	17.90 (12.2 – 23.5)	2.8		
HER2	Positive	15.64 (11.4 – 19.7)	2.1	**6.50**	***0.011(S)***
	Negative	30.94 (26.2 – 35.6)	2.4		
ER\ Her2	Er+ve\Her2+ve	22.25 (17.5 – 26.9)	2.3	**0.18**	***0.979***
	Er+ve\Her2-ve	28.10 (21.0 – 35.1)	3.5		
	Er-ve\Her2+ve	32.20 (19.7 – 44.6)	6.3		
	Er-ve\Her2-ve	26.70 (18.7 – 34.6)	4.0		
Tumor Marker Level	Elevated	24.07 (18.9 – 29.1)	2.5	**4.86**	***0.028(S)***
	Normal	31.88 (26.1 – 37.5)	2.9		

Our results show that tumor markers *(p = 0.026)* and number of metastases sites *(p= 0.046)* are the independent factors affecting patients overall survival in Group B as shown in table 7.

Table (7): Multivariate Cox regression analysis for independent factors affecting patients OS among Group B

Variable	WALD	Hazard ratio	*P* value	CI 95%	
				Lower	Upper
PR	1.81	2.69	*0.178*	0.63	11.36
ER	0.01	0.93	*0.924*	0.21	4.04
Hers	1.73	0.66	*0.188*	0.36	1.21
Tumor Marker Level	4.96	0.52	***0.026(S)***	0.29	0.92
Number of Metastases sites	3.99	0.57	***0.046(S)***	0.32	0.98

4. Discussions

Despite the major advances in breast cancer treatment, surgery continues to play a major role in the local control of advanced breast cancer as an effective palliation for the pain, bleeding, infection and malodorous drainage that can accompany locally advanced breast cancer[8].

One of the critical issues currently impacting surgical consideration in the setting of advanced

breast cancer is the remarkable improvement in the management of patients with metastatic disease[3].

Recently, multiple studies have retrospectively sought to determine the survival impact of breast tumor resection for patients with metastatic breast cancer. Thus, new clinical questions emerged regarding surgery of the primary site in those women with metastatic disease and a resectable intact primary tumor. This retrospective study is testing this issue.

As regard demographic characteristics of the patients: There was statistically significant difference between the 2 groups as regard performance status. In Group A 38 (62.3%) patients had performance score 0, 20 (32.8%) patient had score 1and only 3(4.9%) patients with performance score 2. while in Group B 23 patients had score 0, 54 had score 1 and 13 had score 2, it is believed that this difference is related to difference in sample size and that most patient in surgery group are younger and fit where all of them were prepared to be treated on radical base as they discovered to be metastatic after surgery. Most studies for impact of primary tumor resection excluded patient with poor performance status so comparison is not possible.

There was significant difference between 2 groups in Tumor marker level which was initially elevated in 18 patients in Group A and 54 patients in Group B. Mostly this difference is due to different tumor bulk as it was measured after surgery.

There is a statistically significant difference as regard the results of the first evaluation between the two groups where 3patients achieved CR (complete response), 38 patients had stable disease and16 patients achieved partial response and 3 patients in disease progression in Group A while in Group B no patient achieved CR, 66 patients achieved partial response, 12 patients had stable disease and 12 patients had disease progression mostly due to difference in sample size and initial tumor bulk. There was statistically significant difference as regard OS between the 2 groups (P value <0.001) (Figure 1).

These results goes with the results of Babiera *et al.* [9] , who analyzed a retrospective single institution cohort of 224 patients, of which 82 had surgical resection of the primary tumor and suggested a favorable effect of surgical excision. Also these results goes with the results of Gnerlich *et al.* [10,] who retrospectively reviewed the 1988–2003 Surveillance, Epidemiology and End Results (SEER) program data identifying 9734 patients with stage IV breast cancer; 47% underwent surgery while 53% did not. Median survival was 36 versus 21months with P < 0.001.

Ruiterkamp *et al.* [2] found that the Median survival of the patients who had surgery of their primary tumor was significantly longer than for the patients who did not have surgery (31 vs. 14 months).

These all studies suggested that surgical resection of the breast primary could result in a significant survival advantage for patients with stage IV breast cancer but most of these studies did not take in consideration the effect of other treatment lines. While in our study we use the same treatment plan for all patients regardless the site of metastases to avoid bias related to type of treatment.

Leung *et al.* [6] underwent retrospective single institution study, 157 patients were included in the study founded that the median survival was 25 months for the surgery group and 13 months for the group without surgery. But after taking in consideration the impact of chemotherapy, hormonal therapy, and radiation therapy Leung *et al.* [6] in subgroup analysis concluded that hormonal therapy did not play a role in survival advantage for the surgery versus no surgery groups, and concentrated on chemotherapy, which did provide a difference in survival and when Stage IV patients received chemotherapy and there was no statistically significant survival benefit for surgery which is against our results .It is believe that this difference is due to treatment related bias which we avoided in our study by giving all patients same treatment line .

There was significant relation between the site of metastases and survival in Group A with best survival in bone only group and the worst in visceral only group (Table 3) and in Group B. These results are against Leung *et al.* [6]**,** who examined survival difference based on site of metastases and found that there was no survival difference.

On the other hand Khan *et al.* [11] showed that resection of the primary tumor provided a statistically independent survival benefit, after adjustment for the extent and type of metastatic disease and type of systemic therapy and this goes with our study.

As regard the type of surgery and margin status khan *et al.* [11], found that When there was no difference in survival time between the partial mastectomy and total mastectomy groups provided that partial mastectomy achieved negative margin. McGuire *et al.* [12], provides further evidence those women with MBC at diagnosis benefit from surgical excision of their primary tumor. Furthermore, patients who underwent total mastectomy versus partial mastectomy had a statistically significant increase in OS because that total mastectomy achieve clear margin in nearly all patients. Unfortunately this comparison is not possible in our study due to small sample size in Group A and most patients underwent MRM and achieved negative margin (Table 2) but

the median survival of the 3 patients with positive margin was 30 months and median TTP was 25 months.

Timing of surgery has been previously explored as a potential factor for survival. Rashaan *et al.* [13] , found that survival for women diagnosed with stage IV breast cancer prior to surgery was very similar to survival among the no surgery group (2.40versus 2.36 years) whereas the improved survival was only seen in women who already had surgery before the metastases were diagnosed.

Bafford *et al.* [14] subsequently assessed the effect of surgery timing in two sub-groups compared with a cohort of 86 non-operated patients. Data showed a benefit of surgery only in the "before"group (discovered accidentally as metastatic breast cancer). No significant difference was found between patients in the "after" group (after being diagnosed as metastatic breast cancer from the start) and those in the "no surgery" cohort, suggesting that the observed benefit of surgery was due to a stage migration bias.

In our study, 2 patients were excluded from Group B after they underwent surgery one due to lack of response and the other due to ulceration. The median survival of these 2 patients was 20 months and the median time to progression was 8 months much lower than that for surgery group.

There was significant relation between the site of metastases and survival in Group A with best survival in bone only group and the worst in visceral only group (Table 1). This goes with the results of Rapiti *et al.* [15], who found that surgery reduces risk of death in bone only group compared to no surgery. These results are against Leung et al [6] who Examined survival difference based on site of metastases and found that there was no survival difference.

Analyses of other factors relating to prognosis for patients with metastatic breast cancer in Group A indicated that there was significant relation between survival and type of metastases, tumor grade, estrogen receptor (ER) positivity and initial CA 15.3 tumor marker level (Table 1). However multivariate analysis revealed that tumor grade is the most independent predictive factor Table 2), while Shibasaki *et al.* [16], found that triple-negative breast cancer and metastasis to more than three sites were poor prognostic indicators this difference may be related to difference in sample size.

In summary, our results are in line with previous studies and provide additional evidence that surgical removal of the primary tumor is associated with a significantly longer survival time in patients with metastatic breast cancer at diagnosis.

The main limitations of our study are that surgery has not been assigned by randomization and relative small sample size especially in surgery group.

Conclusion:

Primary tumor resection did increase survival in metastatic breast cancer patients and increased time to progression. So, the current strategy of treatment especially the surgical role in metastatic patients should be revised**.**

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References:

1. Ernst M , Lonneke V, Fransec V, *et al.* Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002.The Breast 2007; 16, 344–351
2. Ruiterkamp J, Ernst MF, van de Poll-Franse LV, *et al.* Surgical resection of the primary tumor is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. European Journal of Surgical Oncology 2009; 35: 1146-51.
3. Alvaradoa M, Ewinga A ,Elyassniab D, *et al.* Surgery for palliation and treatment of advanced breast cancer Surgical Oncology 2007;16: 249–257
4. National Cancer Institute Surveillance Epidemiology and End Results (SEER). Cancer survival statistics. Accessed November 19: 2008.
5. Rao R, Feng L, Kuerer HM, *et al.* Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Annals of Surgical Oncology 2008;15:1696–1702
6. Leung A, Vu H, Nguyen K, *et al.* Effects of Surgical Excision on Survival of Patients with Stage IV Breast Cancer. Journal of Surgical Research 2010;161, 83–88
7. Gennari and Audisio. Surgical removal of the breast primary for patients presenting with

metastases – Where to go? Cancer Treatment Reviews 2009;35:391–396
8. Nogouchi M, Nakano Y and Kosaka T. Local Therapy and Survival in Breast Cancer with Distant Metastases. Journal of Surgical Oncology 2012; 105:104–110.
9. Babiera GV, Rao R, Feng L, *et al.* Effect of primary tumor extirpation in breast cancer patients who present with Stage IV disease and an intact primary tumor. Annals of Surgical Oncology 2006; 776: 13-82.
10. 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. Annals of Surgical Oncology2007; 14:2187–2194.
11. Khan SA, Stewart AK and Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002; 132:620-7.
12. Mc Guire KP, Eisen S, Rodriguez A, *et al.* Factors associated with improved outcome after surgery in metastatic breast cancer patients. American Journal of Surgery 2009; 198: 511-5.
13. Rashaan Z , Bastiaannet E, Portielje J, *et al.* Surgery in metastatic breast cancer: Patients with a favorable profile seem to have the most benefit from surgery .EJSO(European journal of surgical oncology 2012;38: 52-56
14. 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 Research and Treatment 2009; 115:7–12
15. Rapiti E, Verkooijen HM, Vlastos G, *et al.* Complete surgical excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. Journal of Clinical Oncology 2006; 24:2743-9.
16. Shibasaki S, Jotoku H, Watanabe K, *et al.* .Does primary tumor resection improve outcomes for patients with incurable advanced breast cancer? The Breast 2011; 543-547.

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