Pan Arab Journal of Oncology

Original Article

Local Surgery in Metastatic Breast Cancer at the Time of Initial Diagnosis

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ABSTRACT

Objectives The role of loco-regional surgery in treatment of de-novo metastatic breast cancer (MBC) is unclear. Conflicting results have been reported by various analyses. We aimed to compare the effect of loco-regional treatment on outcome in women with MBC at initial presentation.

Materials & Methods Breast cancer patients files designated as stage IV in the time period from January 2010 till December 2015 were extracted. Then two groups were formed; patients who underwent surgery for the primary breast tumor and patients with an intact primary. Data collected comprised patients' baseline clinical characteristics, metastatic site (s), surgical procedure, management, disease progression and last follow-up.

Results Of the 112 eligible patients, 54 patients (48%) underwent primary surgery (majority modified radical mastectomy n= 40; 74.07%). Median OS was 29 months (95% CI 20.21- 37.79) in the locoregional treatment group and 21 months (95% CI 8.80-33.20) in the non-surgical group (p= 0.177). Median PFS was 16 months (95% CI 14.11- 17.88) in the surgical arm and 12 months (95% CI 9.97-14.04) in the non-surgical one (p=0.286). OS and PFS between patients in both groups after adjusting for age, ER, HER2, menopausal status, and metastatic sites (locoregional treatment vs no-locoregional treatment, HR=0.76 (95% CI 0.42-1.36; p=0.356). Estrogen receptor negative status was independently associated with PFS, whilst oligometastatic subjects experienced improvement in both outcomes.

Conclusion Primary tumor removal for breast cancer patients with synchronous stage IV disease failed to improve outcome. This approach requires further confirmatory prospective studies to establish patients that may benefit from current findings.

Keywords
Breast cancer
Stage IV
De-novo metastatic
Surgery
Loco-regional treatment

INTRODUCTION

About 6% of patients diagnosed with breast cancer are found to be metastatic from the start[1]. Despite the advances in treatment approaches, metastatic breast cancer (MBC) remains an incurable disease, with treatment principally focusing on extending survival and palliating symptoms. Patients with MBC have a median overall survival of about 2-3 years, and low 5-year survival rates as about 27%[2,3]. Systemic therapy plays the principal role of MBC patients' treatment trajectory. Primary tumor-directed therapy as loco-regional surgery or radiation therapy has been reserved only as a palliation to a fungating or bleeding breast mass[4,5].

However, Khan et al. were the first to challenge surgery to the primary tumor in these patients back in the 1990s and early 2000s[6].The National Cancer Database of the American College of Surgeons from 1990 - 1993 was reviewed, it was found that patients who were treated with surgical removal of the primary cancer with free margins had a better 3-year survival rate than those who were not surgically treated (35% vs. 26 %). Khan's theory was supported by a number of studies that have demonstrated improved survival of patients with other types of cancers presenting with stage IV disease, especially those with metastatic

tumors of colorectal, renal cell, gastric and ovarian origin[7-10]. From these studies, Flanigan et al. demonstrated in a randomized trial that survival among patients with metastatic renal cell carcinoma post nephrectomy receiving interferon was better than in those who received interferon solely[10].

Several retrospective studies emerged afterwards comparing surgery versus no local therapy in MBC patients presenting with an intact primary tumor, all show a survival advantage for the surgical cohort[11-14]. These studies postulated some theories that support their hypothesis, such as (1) cessation of the primary tumor to continuously shed metastatic cells, (2) decreasing the tumor burden, rendering the systemic therapy more effective, (3) removing some of the products released by the primary tumor into the circulation, which when secreted, stimulates the growth of the established distant metastases, or (4) decrease in the number of circulating tumor cells (CTC) which has been found to be a predictor of the overall survival in the MBC patients in some studies[15]. All of the previous retrospective studies are criticized to have a strong selection bias accounting to the improved survival observed with the primary tumor surgery.

A lack of survival benefit was reported after surgical resection of the primary tumor in other studies[16,17]. Leung et al. was one of the negative retrospective studies showing no survival benefit, and any survival benefit observed was attributed to systemic treatment[16]. Badwe et al.; an open-label randomized control trial, also reported no survival benefit of removing the primary tumor[17].

Patients and method

After institutional review board and ethical commitee approval was granted, we reviewed the medical records of breast cancer patients who presented to the Clinical Oncology and Nuclear Medicine department, Ain Shams University Hospital between January 2010 to December 2015 labelled as stage IV intact primary cancer or with surgically removed primary breast tumor at the time of diagnosis of the stage IV disease. Initial information collected encompassed demographics, tumor characteristics (tumor size, location, grade, estrogen-, progesterone-, and Her2/neu-receptor status, histology, lymph node status), site(s) and number of metastases, type and timing of operation, radiotherapy usage, and systemic treatment regimens(s) including chemotherapy and hormonal therapy details. In addition, information was collected on overall survival of the patients (from the time of initial presentation until last follow-up or death), their disease progression (progression free survival and location of progressive disease) for the first three lines of systemic treatment.
The response evaluation criteria in solid tumors (RECIST) guidelines, v1.1[18] were used to assess response to therapy of the intact primary tumor and sites of metastasis. The breast cancer staging guidelines in the AJCC Cancer Staging Manual, 7th edition[19], were used to describe tumor size and lymph node involvement.

All patients had established distant metastases at the time of or within one month of the diagnosis of their breast cancer disease. Patient division to two groups was done; surgical and non-surgical. The surgery group included patients who underwent the procedure of removing the primary breast tumor (either mastectomy or lumpectomy) with axillary clearance, or simple mastectomy without axillary clearance. Surgery was done to the patients as a part of their definitive treatment before diagnosing the already present metastatic deposits. The non-surgery group consisted of patients with an intact primary tumor with no operative intervention. Both groups did not perform any form of surgical manipulation to the metastatic sites. Systemic therapy was received by all patients varying from an anthracycline-based chemotherapy or anti-hormonal treatment with either tamoxifen or an aromatase inhibitor. None of the Her2/neu positive patients in both groups received trastuzumab or any other anti-Her2 therapy due to financial constraints.

One hundred and twelve patients fulfilled the inclusion criteria for this study. Study end points were death and progression of metastatic disease. Time-to-event analyses were reported for both end points. Kaplan-Meier curves were plotted, and the log-rank test as a comparative for the difference in survival between the surgery and non-surgery groups. Patient characteristics were assessed for the surgery and non-surgery groups by c^2 test. All tests were two sided, and P values < .05 were considered statistically significant. All analyses were performed using Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Results

The study was conducted on 112 metastatic breast cancer (MBC) patients; 54(48%) underwent a surgical based therapy either partial or total mastectomy whilst the other comparable group 58(52%) did not. Patients were stratified according to their clinical features and treatment received into different risk subgroups; the majority of them were over 50 years of age, positive for ER, PR and negative for Her2. Two factors, namely lymphovasular and perineural invasion (LVI and PNI, respectively) were further reported more frequently in the surgical group. (Table 1)

After a median follow-up of 23.5 months (IQR 12-34) 31 deaths (2 cases were of unknown cause) were observed in each arm (surgical treatment 57.4% & non- surgical treatment 53.4%) thus no difference was observed between the groups regarding outcome. Median OS was 29 months (95% CI 20.21- 37.79) in the locoregional treatment group and 21 months (95% CI 8.80-33.20) in the non-locoregional treatment group (p= 0.177). Median PFS was 16 months (95% CI 14.11- 17.88) in the surgical arm and 12 months (95% CI 9.97-14.04) in the non-surgical one (p=0.286). (figures 1 a/b)

In ER negative patients surgical treatment was significantly associated with an increase in OS and PFS: p=0.006, p=0.035 respectively. Similar results were obtained for Her2 positive MBC patients; surgically treated patients had 50% increase in their OS time (p=0.03) It is worth noting that exclusion of patients with incomplete data for the Her2 status was done. The analysis suggested that surgically treated patients who achieved disease stability had a significant increase in the PFS compared to those who did not (p=0.03). PFS significance was observed for age and oligometastatic state (p values 0.014 & 0.010 respectively). There were no significant differences detected in the remaining subgroups surgically treated or not concerning OS and

Table 1. Clinical and treatment characteristics of the patients in surgical and non- surgical arms.

Variable	Surgery	No surgery	P value
Age			
<40 years	10	8	
40-50 years	20	22	0.632
>50 years	23	28	
Menopausal status			
Pre	27	27	0.715
Post	27	31	
ECOG Performance status			
0	0	2	
1	51	46	0.053
2	3	10	
Surgery			
MRM	40	-	
BCS	12	-	-
Simple mastectomy	2	-	
Laterality			
Right	16	20	
Left	34	33	0.879
Bilateral	4	5	
Histologic subtype			
IDC	45	55	
ILC	7	3	0.216
Mixed	2	0	
Grade			
Grade I	1	0	
Grade II	46	49	0.539
Grade III	7	9	
LVI			
Negative	17	1	
Positive	14	3	<0.001
Unknown	23	54	
PNI			
Negative	18	1	
Positive	4	1	<0.001
Unknown	32	56	
ER			
Negative	6	17	0.067
Positive	47	39	
Unknown	1	2	
PR			
Negative	11	23	
Positive	42	33	0.064
Unknown	1	2	
Her2			
Negative	46	40	
Positive	5	11	0.127
Unknown	3	7	
Site of metastasis			
Visceral	20	22	
Bone	27	25	0.631
Bone & viscera	7	11	
Oligometastasis			
Yes	9	9	0.869
First line ET			
Yes	43	41	0.095
Second line ET			
Yes	23	31	0.205
Third line ET			
Yes	5	12	0.077
First line CT			
Yes	46	44	0.276
Second line CT			
Yes	20	18	0.927
Third line CT			
Yes	7	12	0.276

PFS (Table 2)
A Log rank (Mantel-Cox) test was applied to assess the prognostic value of surgical treatment in MBC and in this analysis we excluded patients with incomplete data. No significant difference for disease outcome was observed between patients who underwent surgery and those who did not regarding the different risk factors including the receptor status, clinical response and extent of metastases (p>0.05) (Table 3)

Cox regression analysis between the two groups demonstrated no difference in OS and PFS between patients treated with locoregional surgery or no surgery after adjusting for age, ER, HER2, menopausal status, and metastatic sites/ load (locoregional treatment vs no-locoregional treatment, adjusted HR=0.76, 95% CI 0.42–1.36; p=0.356). HER2+ status was independently associated with OS and ER- status with PFS whilst oligometastatic patients fared significantly better in both outcomes. (tables 4 & 5)

Oligometastatic status was independently associated with OS (HR=0.11, 95% CI 0.03–0.47; p=0.003) and PFS (HR=0.12, 95% CI 0.03–0.50; p=0.004). ER- status was significantly associated with increased risk of progression (HR=2.59, 95% CI 1.31 –5.13; p=0.006). (tables 4 & 5)

The site of metastasis at initial presentation was not associated with OS or PFS. However, site of distant metastases was associated with OS and PFS in subgroup analyses of patients treated with locoregional surgery (Bone vs Both visceral and bone OS HR=6.60, 95% CI 2.10, 20.71, p=0.001 and PFS HR=4.73, 95%CI 1.61, 13.9, p=0.005). (tables 6 & 7)

Table 2. Comparative analyses for the survival outcome in MBC surgically & non-surgically treated

Variable	Number of patients (%)			Estimate OS (months) median		Log rank (Mantel-Cox) test		Estimate PFS (months) median		Log rank (Mantel-Cox) test	
	Total no (%)	Surgically treated 54 (48%)	Non-surgical treatment 58 (52%)	Surgically treated 54 (48%)	Non-surgical treatment 58 (52%)	X^2	P value	Surgically treated 54 (48%)	Non-surgical treatment 58 (52%)	X^2	P value
Age group											
≤40	18(16)	10(56)	8(44)	21	51			10	10		
40 – 50	43 (38)	21(49)	22(51)	29	19	2.1	0.14	16	17	8.5	**0.014**
>50	51 (46)	23(45)	28(55)	30	14			15	10		
Menopausal status											
Pre	54 (48)	27(50)	27(50)	29	27	1.7	0.19	14	12	0.03	0.86
Menopause	58 (52)	27(47)	31(53)	30	14			16	11		
ER											
Negative	25 (22%)	8(15)	18(30)	15	8.0	7.5	**0.006**	10	9	4.4	**0.035**
Positive	87 (78%)	46(85)	40(70)	29	27			16	12		
PR											
Negative	35 (31%)	12(22)	23(40)	19	14	1.4	0.24	14	17	0.7	0.402
Positive	77 (69%)	42(78)	35(60)	29	26			15	11		
Her2R											
Negative	81 (72%)	38(78)ǂ	43(90)ǂ	29	27	4.8	**0.03**	15	12	0.2	0.653
Positive	16 (14%)	11(22)ǂ	5 (10)ǂ	22	11			13	11		
Unknown*	15 (13%)										
Progression											
No	46 (41%)	21(39)	25(43)	30	14	0.6	0.42	NA: as the status here is progression			
Yes	66 (59%)	33(61)	33(57)	27	27						
Metastases											
Oligo	18 (16)	9 (50)	9 (50)	NA	NA	NA	NA	29	18	6.6	**0.010**
Multiple	94 (84)	49 (52)	45 (48)					14	12		
Site of metastases											
Visceral	42 (37.5)	20(37)	22(38)	21	19	2.3	0.3	13	9	0.6	0.742
Bone	52 (46.4)	27(50)	25(43)	29	17			16	13		
Both	18 (16.1)	7(13)	11(19)	11	26			10	12		

Abbreviations: Unknown*: the unknown group is not included in the survival analysis; ǂ : the percentage of only Her2R known results; ER: Estrogen receptors; PR: Progesterone receptor. NA: Not applicable; statistics is not calculated because all surgically treated patients are censored

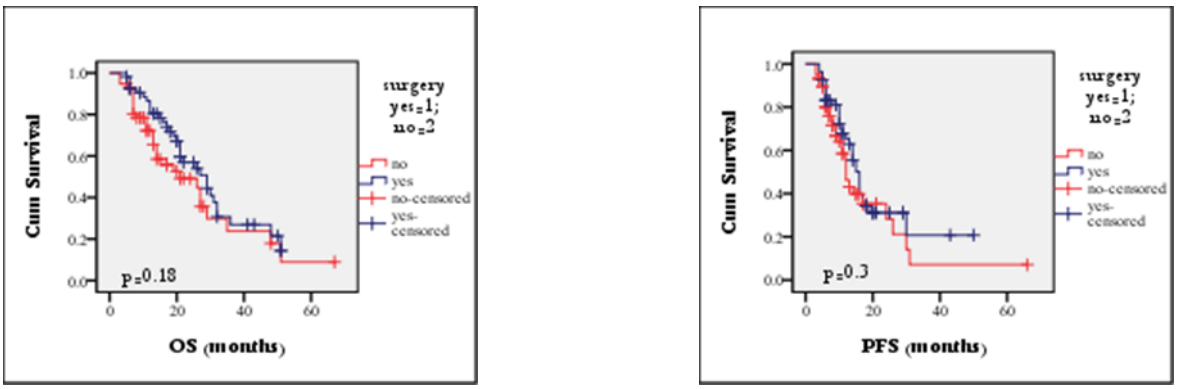

Figure 1. Kaplan Meier curve demonstrating a non-significant difference for OS (A) and PFS (B) between MBC patients surgically treated or not (p=0.177 & 0.286 respectively).

Table 3 . Impact of surgical resection of Breast cancer on OS and PFS in breast cancer patients with different risk factors

Variable	Number of patients (%)			Estimate OS (months) Median (95%CI)		Log rank (Mantel-Cox) test		Estimate PFS (months) Median (95%CI)		Log rank (Mantel-Cox) test	
	Total no (%)	Surgically treated 54 (48%)	Non-surgical treat-ment 58 (52%)	Surgically treated 54 (48%)	Non-surgical treat-ment 58 (52%)	X^2	P value	Surgically treated 54 (48%)		X^2	P value
Age group											
≤40	18(16)	10(56)	8(44)	21(7-35)	51	1.8	0.1750.	10		0.240	0.624
40 – 50	43 (38)	21(49)	22(51)	29(17-41)	19(7-31)	3.4	066	16		0.005	0.944
>50	51 (46)	23(45)	28(55)	30(15-45)	14(7.5-20.5)	1.	0.213	15		5.139	**0.023**
Menopausal status											
Pre	54 (48)	27(50)	27(50)	29(20-38)	27(20-34)	0.2	0.7	14(12-16)		0.1	0.8
Post	58 (52)	27(47)	31(53)	30(14-46)	14(8.5-19)	1.8	0.2	16(10-22)		4.7	**0.03**
ER											
Negative	25 (22)	8(15)	17(30)	19(4.6-33.6)	11(5.7-16.3)	1.5	0.3	11(5.6-17)		0.6	0.416
Positive	86 (78)	46(85)	40(70)	29(24.5-33.4)	27(20.7-33.3)	0.09	0.8	16(14-18)		1.8	0.177
PR											
Negative	35 (31)	12(22)	23(40)	19(12.3-26)	13(1.9-24)	1.3	0.3	14(5.9-22)		0.02	0.877
Positive	77 (69)	42(78)	35(60)	26(25-33)	26(13-39)	0.8	0.4	15(13-17)		2.6	0.106
Her2R											
Negative	81 (72)	38(78)ǂ	43(90)ǂ	29(24-34)	27(18-36)	0.7	0.4	15(13 -17)		0.8	0.383
Positive	16 (14)	11(22)ǂ	5 (10)ǂ	22(13-31)	11(6-16)	0.02	0.9	13(7 -19		0.05	0.822
Response								**NA**			
Remission	46 (41)	21(39)	25(43)	30(8.6-51)	14(0.0-29)	1.4	0.2				
Relapse	66 (59)	33(61)	33(57)	27(19-35)	27(18-36)	0.8	0.4				
Metastases											
Oligo	18 (16)	9 (50)	9 (50)	NA	NA	NA	NA	29		1.07	0.299
Multiple	94 (84)	49 (52)	45 (48)	22(16-28)	14(8.0-19)	1.5	0.2	14(10.9 -17) 18 (1.4 – 34.6) 12(9.9 -14)		1.16	0.280
Site of metastases											
Visceral	42 (37.5)	20(37)	22(38)	21	19	0.2	0.651	13	9	0.99	0.319
Bone	52 (46.4)	27(50)	25(43)	29	17	4.3	**0.037**	16	13	1.35	0.246
Both	18 (16.1)	7(13)	11(19)	11	26	1.7	0.191	10	12	0.74	0.390

HR=hazard ratio; CI=confidence interval; HER2=human epidermal growth factor receptor 2

Table 4. Univariate Cox Regression analysis for OS & PFS in all MBC cohort (n=112)

Variable	OS (months)				PFS (months)			
	HR	95% CI for HR		P value	HR	95% CI for HR		P value
		lower	Upper			lower	Upper	
Surgery								
No	Ref				Ref			
Yes	0.714	0.431	1.181	0.190	0.768	0.465	1.268	0.303
Age								
Age<50	Ref				Ref			
Age>50	1.226	0.743	2.025	0.424	1.196	0.723	1.976	0.486
Menopausal Status								
Pre	Ref				Ref			
Post	1.368	0.829	2.256	0.220	1.250	0.758	2.061	0.383
Estrogen receptors								
ER+	Ref				Ref			
ER-	**1.931**	1.096	3.416	**0.024**	3.043	1.723	5.372	**0.000**
Her2 receptors								
Her2 negative	Ref				Ref			
Her2 positive	2.037	1.041	3.985	**0.038**	1.720	0.881	3.358	0.112
Metastases								
Multiple	Ref				Ref			
Oligo	0.093	0.023	0.382	**0.001**	0.098	0.024	0.405	**0.001**
Site of metastases								
Bone	Ref				Ref			
Visceral	0.867	0.484	1.551	0.630	0.924	0.517	1.652	0.790
Both	1.564	0.819	2.986	0.175	1.598	0.838	3.046	0.154

Table 5. Multivariate Cox Regression analysis for OS and PFS in MBC patients (n=112)

Variable		OS (months)		PFS	
		HR (95%CI)	P-value	HR (95%CI)	P-value
Surgery	No	Ref		Ref	
	Yes	0.76 (0.42, 1.36)	0.356	0.91 (0.51, 1.62)	0.750
Age	Age <50 years	Ref		Ref	
	Age>50 years	0.70 (0.26, 1.86)	0.471	0.85 (0.31, 2.32)	0.758
Menopausal Status	Pre	Ref		Ref	
	Post	1.51 (0.56, 4.07)	0.419	1.21 (0.44, 3.36)	0.710
Estrogen Receptor	ER+	Ref		Ref	
	ER-	1.50 (0.77, 2.90)	0.229	2.59 (1.31, 5.13)	**0.006**
HER2 Receptor	HER2-	Ref		Ref	
	HER2+	1.56 (0.69, 3.51)	0.285	1.01 (0.46, 2.24)	0.979
Site of Metastases	Bone	Ref		Ref	
	Visceral	0.77 (0.41, 1.46)	0.431	0.86 (0.45, 1.64)	0.657
	Both	1.08 (0.51, 2.32)	0.832	1.11 (0.52, 2.36)	0.779
Oligometastates	No	Ref		Ref	
	Yes	**0.11 (0.03, 0.47)**	**0.003**	**0.12 (0.03, 0.50)**	**0.004**

Table 6. Univariate Cox Regression analysis for OS and PFS after surgery in MBC patients (n=54)

Variable	OS (months)				PFS (months)			
	HR	95% CI for HR		P value	HR	95% CI for HR		P value
		lower	Upper			lower	Upper	
Age								
Age<50	Ref				Ref			
Age>50	.9377334	.4456561	1.973145	0.865	.8394704	.3987993	1.767081	0.645
Menopausal Status								
Pre	Ref				Ref			
Post	1.073155	.5251859	2.192865	0.846	.9113975	.4472732	1.857132	0.798
Estrogen receptor								
ER+	Ref				Ref			
ER-	1.170807	.4246468	3.228066	0.761	3.133161	1.132792	8.665932	**0.028**
Her2 receptor								
Her2 -	Ref				Ref			
Her2+	2.54381	.845026	7.657716	0.097	1.335559	.4596455	3.880636	0.595
Site of metastases								
Bone	Ref				Ref			
Visceral	1.083539	.4822362	2.434609	0.846	1.395274	.6188072	3.146037	0.422
Both	3.269038	1.280745	8.344058	**0.013**	4.140227	1.626942	10.53601	**0.003**

Table 7. Multivariate Cox Regression analysis for OS and PFS in MBC patients after surgery (n=54)

Variable		OS (months)		PFS (months)	
		HR (95%CI)	P-value	HR (95%CI)	P-value
Age	**Age <50 years**	Ref		Ref	
	Age>50 years	0.72 (0.15, 3.46)	0.684	0.81 (0.17, 3.85)	0.787
Menopausal Status	**Pre**	Ref		Ref	
	Post	2.29 (0.46, 11.3)	0.311	1.35 (0.29, 6.40)	0.703
Estrogen Receptor	**ER+**	Ref		Ref	
	ER-	0.97 (0.33, 2.89)	0.957	2.34 (0.74, 7.47)	0.15
HER2 Receptor	**HER2-**	Ref		Ref	
	HER2+	**3.17 (0.98, 10.3)**	**0.055**	1.09 (0.34, 3.48)	0.881
Site of metastases	**Bone**	Ref		Ref	
	Visceral	1.46 (0.56, 3.82)	0.435	1.59 (0.62, 4.06)	0.333
	Both	**6.60 (2.10, 20.71)**	**0.001**	**4.73 (1.61, 13.9)**	**0.005**

Discussion

The lack of surgical resection in most metastatic malignancies as the accepted status quo has been questioned for multiple reasons. Essentially, the prevailing dogma is that surgical resection for metastatic cancer does not lead to any survival advantage as it is the metastatic tumor burden mainly, not the primary tumor that results in mortality. Additionally, many patients with widespread cancer are debilitated and are often not considered fit to undergo the stress of anesthesia and operative interventions[14].

The current study posed no challenge to this prevailing concept as female patients with MBC, who underwent surgical resection for their primary breast tumor accompanied by axillary clearance, failed to show a significant survival benefit compared to those who were not candidates for such a procedure. This contrasted previous retrospective studies that have shown that surgical removal of the breast tumor in patients with MBC was associated with a significantly higher overall survival rate[6,11,20-22]. Babiera et al. showed only a trend towards improvement in OS had been observed in the surgical group, while a statistically significant improvement was observed for progression-free survival[12]. Fields et al. had observed statistical overall survival benefit towards the surgical group, while the progression-free survival was of non-statistical significance between surgical and non-surgical groups[14]. O'Reilly et al. has shown that a surge of angiogenesis in distant metastatic disease sites may allow for a highly chemo-sensitive state in the rapidly growing metastases and may account for the prolonged survival seen in patients with metastatic cancers who received chemotherapy soon after surgery[23]. On the contrary, Leung et al. showed no survival benefit between the two groups, and any survival benefit observed was attributed to systemic treatment[16].

Estrogen receptor (ER) positive tumors had a significant survival and PFS when surgically treated having median OS of 29 & 27 months vs 15 & 8 months, indicating that tumor biology played a substantial role in outcome. Similarly, the data from Neuman et al. suggested that the survival benefit from primary tumor surgery is most relevant in patients with ER-positive or HER2-positive disease, potentially resulting from decreased mortality due to effective systemic treatment in these patient subgroups[20]. On the other hand, Badwe et al. didn't show any evidence that any patient subgroup defined by menopausal status, metastatic disease burden, estrogen or progesterone receptor status, or Her2 receptor status derived any survival benefit from the surgical procedure[17].

In contradiction to Neuman et al., patients with negative Her2 tumors had a better survival (29 & 27 months) vs. over-expressed Her2 patients (22 &11 months), which can be attributed mainly to the fact that Her2 over-expressed metastatic breast cancer patients didn't receive anti-Her2 therapy throughout their treatment course due to financial limitations, if anything proving as a testament to the power of this targeted therapy in improving disease outcome per se.

The site of metastases influences the survival of patients with stage IV breast cancer, with the skeletal metastases patients having the best prognosis with prolonged survival over skeletal and visceral or only visceral metastases[24]. Many studies addressed the effect of site of metastases on the survival of the metastatic breast patients undergoing surgery for their primary breast tumor. Some of them observed that patients with metastatic spread limited to the skeleton benefit the most from surgical removal of the primary breast tumor compared to patients with involvement of other metastatic sites[11,13,14,25]. Other studies showed no survival difference as regards the site of metastatic deposits in patients undergoing surgery. Leung et al. was one of these studies, which concluded that metastases site did not play a role in survival advantage for the surgery versus no surgery groups[16]. In our study, patients with only-bone metastases were the patients who benefited most from the surgery to their primary tumor. Patients with purely visceral and those with bone and visceral metastases didn't show that significant benefit, probably due to the small number of patients in this retrospective study.

One of the addressed variables that had a significant effect on survival in patients in the surgery group over the non-surgery group was the number of sites of metastatic lesions. The term 'oligo-metastasis' was first defined by Hellman and Weichselbaum[26]; clinically, oligo-metastatic breast cancer is "characterized by solitary/few detectable lesions, usually limited to single organs, in which local therapy with curative intent could improve survival". This 'potentially curable' stage IV subset is predicted to constitute 1–10% of newly diagnosed MBC population[27]. Bafford et al. observed that patients underwent surgery for their primary breast tumor had better survival compared to those who did not[28]. The study attributed this survival benefit to the fact that surgery was offered to metastatic breast cancer patients with fewer sites of metastatic disease; i.e. fewer sites of metastatic involvement was associated with better survival in patients allocated in the surgical study group. In the current study, patients diagnosed with the pre-defined oligo-metastatic state had a significant PFS & OS benefit to the surgical intervention but the small numbers and censoring of cases (in the surgical group) would suggest it requires further validation.

A renown limitation of retrospective reviews is inability to control selection bias. Patients who were selected for the surgery were usually slightly younger (though this was not the case in the current study), with better general condition, less co-morbid diseases and were generally considered amendable for the procedure compared to patients who were not subjected to surgery. Altogether, the differences found in the survival between both groups could merely be a reflection of the lower usage of a radical surgical approach in MBC patients with perceptible poorer disease prospects.

Results of the current study contribute to the growing body of literature addressing the question of whether upfront, or actually any form of, surgical resection to the primary breast tumor in patients presenting de novo with stage IV disease enhances survival. A lack of target (ER negative), unavailability of a targeted drug (anti-Her2) & a low metastatic (oligo)burden seem to interplay in this analysis as a reminder of the importance of the well-established systemic approach coupled with a cautious local intervetion to a somewhat limited spreading disease.

Findings from this and other studies, meta-analysis and systematic reviews[29,30] provide various degrees of support for prospective, randomized trials to more conclusively fortify the hypothesis that better control of local disease in stage IV breast cancer patients will in fact improve survival. The latest fourth ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer, addressed breast surgery in patients with de novo metastatic disease and acknowledged the lack of evidence present concerning prolonged survival, nevertheless, the recommendation to select specific subgroups that may benefit from this approach; such as oligometastatic/ low volume metastatic burden and bone confined metastatic subjects that may find this in their best interest. Essentially, it remains a question of patients' choice stressing the importance of QOL in the meantime and the necessity for further validation of this approach via prospective clinical trials. [31]

Conclusion

The chasm remains uncrossed; so despite all rhetoric that can be used the data stands unmoved. In the era of tailored precision medicine perhaps the solution lies in certain intrinsic tumour biology signals that may guide in the usage of this procedure, but in general the facts firmly negate the surgical approach in the majority of MBC patients for the time being.

Funding

This work did not receive any specific grant nor funding.

Conflict of Interest

All authors declare that they have no conflict of interests.

Acknowledgements

To patients participating in this work, all health care personnel involved in their care and the Clinical Oncology Department at the Faculty of Medicine, Ain Shams University for making this study possible.

Ethical approval

Institutional research committee granted ethical approval and for this study category a formal consent is not required.

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