Could local curative breast surgery improve survival in women with oligometastatic breast cancer?

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Received: 13 October 2019
Accepted: 15 December 2019
Published: 27 April 2020

The Egyptian Journal of Surgery 2020, 39:283–288

Background
Patients who initially present with a few metastatic lesions from breast cancer are termed as having oligometastatic disease (OMD). The long-term OMD survivors are young patients with a good performance status. Recently, there has been an improvement in systemic and hormonal therapy which could improve patients' outcome. However, the roles of surgical management of the primary tumor for patients with OMD still need clarifications.

Aim
The aim was to evaluate treatment effects and patient outcome of surgical excision of the primary tumor in patients with cancer breast, who were initially presented with OMD.

Patients and methods
This study included 60 patients with breast cancer with OMD. Patients included in our study were divided into three groups, and each group included 20 patients: first, the first group underwent systemic therapy before surgery; second, the second group underwent surgery before systemic therapy; and third, the third group underwent systemic therapy alone. The authors followed all patients for ∼3 years and identified survival rates and patients outcome.

Results
Young patients underwent surgery more often than old patients after systemic therapy (P=0.006). There is a statistically significant difference between the studied groups regarding recurrence (P=0.038), death (P=0.017), recurrence-free survival (P<0.001), and overall survival (P=0.003). The group that underwent combined surgery and systemic therapy had the most significant longer recurrence-free and overall survival rates.

Conclusions
Surgical removal of the primary tumor has a curative role in patients with breast cancer with OMD, and it improves patients' outcome and survival rates.

Keywords:
metastatic breast cancer, oligometastatic disease, surgical role, survival

Egyptian J Surgery 39:283–288

1110-1121

Introduction

Breast cancer is the commonest diagnosed cancer among women worldwide [1]. Nearly, 5–9 percent of all diagnosed patients with breast cancer initially present with concomitant distant metastases, and the overall survival (OS) rate of those patients is ∼13% [2]. The current guidelines of management of breast cancer cases which were initially diagnosed with metastases were systemic endocrine therapy, chemotherapy, and antihuman epidermal growth factor receptor 2 therapies, and local breast surgery has a minor role in their management [3]. There is a category of patients initially presented with a few metastatic lesions from breast cancer which is termed oligometastatic disease (OMD), which forms ∼1–10% of newly diagnosed cases and were considered potentially curable [4]. The long-term OMD survivors are young patients with a good performance status [5]. Recently, there is improvement of the diagnostic tools and systemic and hormonal therapy that could improve patients' outcome.

However, the roles of initial surgical management of the primary tumor for patients with OMD still need clarifications. Many previous studies have emphasized that surgery improves patients' outcome and controls local manifestation. However, owing to their retrospective nature, their results have not been conclusive [6].

 DOI: 10.4103/ejs.ejs_187_19

The aim of the present study was to evaluate treatment effects and patients' outcome of surgical excision of the primary tumor in patients with cancer breast who initially presented with OMD.

Patients and methods

This randomized computer-based prospective study included 60 patients with stage IV breast cancer who were initially presented with OMD. Patients were managed at Department of Surgery, Zagazig University Hospitals, in the period between May 2016 and August 2019. Patients were diagnosed and classified as having breast cancer with OMD based on the staging system of the American Joint Committee on Cancer.

Inclusion criteria

All patients with oligometastatic breast cancer admitted to General Surgery Department during the period of the study were included.

Exclusion criteria

Excluded patients from our research were as follows:

(1) Patient's refusal to be included in the study.
(2) Patients without distant metastasis.
(3) Patients with metastases in more than sites.
(4) Patients with past previous or a synchronous cancer.
(5) Patients unfit for surgery.

We obtained an ethical approval for performing the study from the Institutional Review Board of Faculty of Medicine Zagazig University, and consent was obtained from all patients.

Patients included in our study were divided into three management groups, and each group included 20 patients: the first group underwent systemic therapy before surgery; the second group underwent surgery before systemic therapy; and the third group underwent systemic therapy alone.

Demographic and clinical data of included patients were recorded. Regarding surgery, all included patients underwent modified radical mastectomy.

Follow up

We followed all patients for ~3 years and identified survival rates and patients outcome. The detailed status of the primary tumor and metastasis number and sites was clinically and radiologically recorded at intervals of ~3 months.

Types of oligometastasis

Metastases to bone alone were found in 10 (16.7%) patients. Metastases to bone and liver were found in 25 (41.7%) patients. Metastases to liver only were found in five (8.3%) patients. Metastases to lung only were found five (8.3%) patients. Metastases to bone and lung were found in 15 (25%) patients.

Statistics

Data analysis was done by using the software SPSS (Statistical Package for the Social Sciences) (SPSS Inc., Chicago, IL, USA). Quantitative variables were analyzed using the means and SD. Kaplan–Meier plot was used to measure the fraction of living participants for a certain time after management. *P* less than 0.05 was considered significant.

Results

Patient characteristics

The study included 60 women with OM breast cancer. The first group of patients included 20 patients and was given systemic therapy before surgery, the second group of patients included 20 patients and underwent surgery before systemic therapy, and the third group of patients included 20 patients and were given only systemic therapy without surgery. Younger patients were more likely to undergo surgery after systemic therapy, whereas systemic therapy alone was given to older patients, and this was statistically significant (P=0.006) (Table 1 and Fig. 1).

There is a statistically significant difference among the studied groups regarding estrogen receptors (ER), progesterone receptors (PR), and Ki-67. The group that underwent systemic therapy only had a significantly higher percentage of negative ER, PR, and high Ki 67 labeling index than the groups that underwent surgery (P=0.002, 0.01, and 0.001, respectively). There is a nonsignificant difference between them regarding tumor grade, size, T and N classification, Lympho-vascular invasion (LVI), tumor type, site of metastasis, or number of organaffected.

Survival analyses

After a follow-up duration of 30 months, we found that mean recurrence-free survival in the group that underwent surgery first or after systemic therapy was 32.96 versus 24 for systemic therapy group only. Mean OS in the group that underwent surgery first or after systemic therapy 35.17 vs 24 for systemic therapy group only (Tables 2–4; Fig. 2).

Table 1 Comparison among the three studied group regarding demographic and clinicopathological data

Variables	Total (*N*=60)	Studied groups			*P*
		Surgery after systemic therapy (*N*=20)	Surgery only (*N*=20)	Systemic therapy only (*N*=20)	
Age group (years)					
<55	31 (51.7)	15 (48.4)	11 (35.5)	5 (16.1)	0.006*
≥55	29 (48.3)	5 (17.2)	9 (31)	15 (51.7)	
LVI					
Present	60 (100)	20 (33.3)	20 (33.3)	20 (33.3)	1
ER					
Negative	36 (60)	11 (30.6)	7 (19.4)	18 (50)∞	0.002*
Positive	24 (40)	9 (37.5)	13 (54.2)	2 (8.3)	
PR					
Negative	40 (66.7)	13 (32.5)	9 (22.5)	18 (45)	0.01*
Positive	20 (33.3)	7 (35)	11 (55)	2 (10)	
HER2					
Negative	34 (56.7)	11 (32.4)	15 (44.1)	8 (23.5)	0.081
Positive	26 (43.3)	9 (34.6)	5 (19.2)	12 (46.2)	
KI 67					
Low	18 (30)	7 (38.9)	11 (61.1)	0	0.001*
High	42 (70)	13 (31)	9 (21.4)	20 (47.6)	
Molecular					
Luminal A	14 (23.3)	5 (35.7)	9 (64.3)	0	0.028*
Luminal B	2 (3.3)	1 (50)	1 (50)	0	
HER2 amplified	24 (40)	8 (33.3)	4 (16.7)	12 (50)	
Triple (negative)	20 (33.3)	6 (30)	6 (30)	8 (40)	
Lymph node					
Present	60 (100)	20 (33.3)	20 (33.3)	20 (33.3)	1
Tumor size					
<5 cm	38 (63.3)	9 (23.7)	14 (36.8)	15 (39.5)	0.108
≥5 cm	22 (36.7)	11 (50)	6 (27.3)	5 (22.7)	
Type of surgery					
Simple mastectomy	12 (30)	6 (50)	6 (50)		1
Modified radical mastectomy	28 (70)	14 (50)	14 (50)		
Number of affected organs					
1	20 (33.3)	8 (40)	8 (40)	4 (20)	0.301
2	40 (66.7)	12 (30)	12 (30)	16 (40)	
Size of metastasis					
Bone	10 (16.7)	4 (40)	4 (40)	2 (20)	0.898
Bone+liver	25 (41.7)	7 (28)	9 (36)	9 (36)	
Liver	5 (8.3)	2 (40)	2 (40)	1 (20)	
Lung	5 (8.3)	2 (40)	2 (40)	1 (20)	
Lung+bone	15 (25)	5 (33.3)	3 (20)	7 (46.7)	

ER, estrogen receptors; HER2, human epidermal growth factor receptor 2; LVI, Lympho-vascular invasion; PR, progesterone receptors.
*Significant. ∞statistical tests used

There is statistically significant difference between the studied groups regarding recurrence (P=0.038), death (P=0.017), recurrence free survival (P<0.001), and OS (P=0.003). The group that underwent combined surgery and systemic therapy had the most significant longer recurrence-free and OS rates. The recurrence-free survival and OS rates were greatest in the women who underwent surgery after systemic therapy, followed by surgery before systemic therapy, and systemic therapy alone (P=0.003 and <0.001, respectively). Survival and recurrence analysis comparing groups that underwent surgery with third group that underwent only systemic therapy revealed that there is a statistically significant difference among the studied groups regarding recurrence, death (P=0.018), recurrence-3free survival (P=0.001), and OS (P=0.0026). The group that underwent surgery either alone or after systemic therapy had the most significant longer recurrence-free and OS.

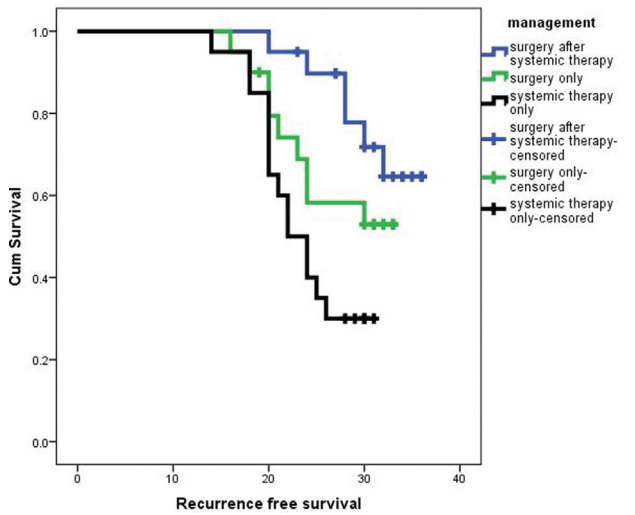
Discussion

There is a marked improvement in chemotherapy, radiotherapy, hormonal, and targeted therapies, which improved the outcome of metastatic breast cancer. However, local surgery for stage IV breast cancer was maintained for palliative management of patients to control local symptoms [7]. In case of patients with OMD, there are many evidences and studies supporting primary surgical excision of the tumor [8]. There are conflicting results showed by previous researchers that advanced local surgery might increase the rate of growth of distant metastases as a primary tumor suppresses the metastases growth through secretion of angiostatin. So resection of the primary tumor decreased the secretion of angiostatin and stimulated growth factors release, thus promoted growth of the tumor [9]. By contrast, several studies have showed the benefits of local surgery in improvement of the prognosis of patients with several cancers [10–13]. Our study assessed the outcomes and prognostic benefits of surgical excision of the tumor in patients with OM breast cancer, and we have showed that surgical intervention after systemic therapy is related to better patient outcome. Similarly, previous studies [6,8,14]. Xiong *et al.* [8] showed that tumor resection would benefit patients with only spread to bone and/or patients with soft tissue metastasis. Yang *et al.* [6] demonstrated that surgical excision of the tumor in patients with OMD was associated with improved outcome and good prognosis.

Collectively, these data proved the curative role of surgery in patients with OMD and in that condition, surgery is not limited for only palliation.

Although many previous reports showed similar results [6,8,14], others demonstrated no benefits of curative surgery, and that there are no differences in outcomes and survival rates between women diagnosed with OMD and treated with surgery and those treated with only systemic therapy [15–17]. Our survival results demonstrated the greatest benefits and favorable outcome was mainly seen in females with OMD treated with surgery which was preceded by systemic therapy, and that surgical resection of the tumor is associated with improved survival. Our results could be explained by that surgical resection of the tumor improves patients' survival by decreasing burden of the tumor and by increasing chemosensitivity [18]. The most common target of metastases from breast cancer is the skeleton [8]. Patients with skeletal metastasis were found to be more responsive to systemic therapy. Thus, patients with skeletal metastasis would gain more benefit from local breast surgery [8].

Figure 1



Kaplan–Meier graph showing significant difference among the three studied groups regarding recurrence-free survival.

Table 2 Comparison among the three studied groups regarding patient outcome

Variables	Total (*N*=60)	Studied groups			*P*
		Surgery after systemic therapy (*N*=20)	Surgery only (*N*=20)	Systemic therapy only (*N*=20)	
Recurrence					
No	31 (51.7)	14 (45.2)	11 (35.5)	6 (19.4)	0.038*
Yes	29 (48.3)	6 (20.7)	9 (31)	14 (48.3)	
Death					
No	31 (51.7)	15 (48.4)	10 (32.3)	6 (19.4)	0.017*
Yes	29 (48.3)	5 (17.2)	10 (34.5)	14 (48.3)	
Recurrence-free survival					
Mean±SD	26.95±5.89	30.6±4.72∞	26.65±5.99	23.6±4.88	<0.001**
Range	14–36	20–36	16–33	14–31	
Overall survival					
Mean±SD	28.72±5	31.65±4.55∞	27.8±4.78	26.7±4.45	0.003*
Range	20–38	22–38	20–33	20–33	

Table 3 Comparison between surgically and non-surgically managed groups regarding demographic and clinicopathological data

Variables	Total (*N*=60)	Studied groups		*P*
		Surgery either alone or after systemic therapy group (*N*=40)	Systemic therapy only (*N*=20)	
Age group (years)				
<55	31 (51.7)	26 (83.9)	5 (16.1)	0.003*
≥55	29 (48.3)	14 (48.3)	15 (51.7)	
LVI				
Present	60 (100)	40 (66.7)	20 (33.3)	1
ER				
Negative	36 (60)	18 (50)	18 (50)∞	0.001**
Positive	24 (40)	22 (91.7)	2 (8.3)	
PR				
Negative	40 (66.7)	22 (55)	18 (45)	0.007*
Positive	20 (33.3)	18 (90)	2 (10)	
HER2				
Negative	34 (56.7)	26 (76.5)	8 (23.5)	0.065
Positive	26 (43.3)	14 (53.8)	12 (46.2)	
KI 67				
Low	18 (30)	18 (100)	0	<0.001**
High	42 (70)	22 (53.4)	20 (47.6)	
Molecular				
Luminal A	14 (23.3)	14 (100)	0 (0)	0.01*
Luminal B	2 (3.3)	2 (100)	0 (0)	
HER2 amplified	24 (40)	12 (50)	12 (50)	
Triple (negative)	20 (33.3)	12 (60)	8 (40)	
Lymph node				
Present	60 (100)	40 (66.7)	20 (33.3)	1
Tumor size				
<5 cm	38 (63.3)	23 (60.5)	15 (39.5)	0.185
≥5 cm	22 (36.7)	17 (77.3)	5 (22.7)	
Number of affected organs				
1	20 (33.3)	16 (80)	4 (20)	0.154
2	40 (66.7)	24 (60)	16 (40)	
Size of metastasis				
Bone	10 (16.7)	8 (80)	2 (20)	0.578
Bone+liver	25 (41.7)	16 (64)	9 (36)	
Liver	5 (8.3)	4 (80)	1 (20)	
Lung	5 (8.3)	4 (80)	1 (20)	
Lung+bone	15 (25)	8 (53.3)	7 (46.7)	

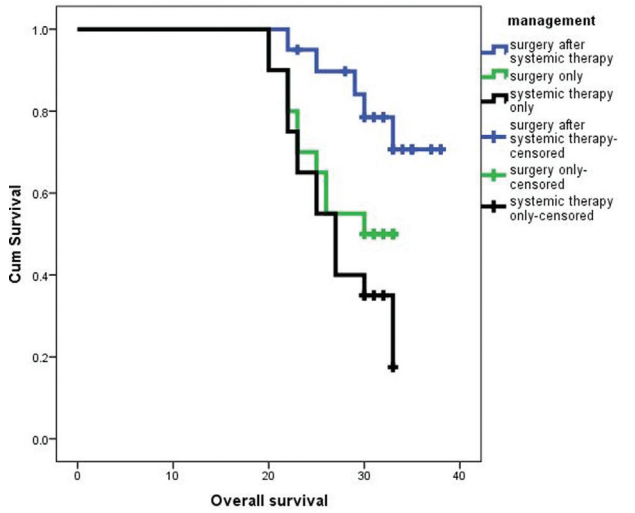
ER, estrogen receptors; LVI, Lympho-vascular invasion; PR, progesterone receptors. *Significant. **Highly significant. ∞statistical tests used.

Table 4 Comparison between surgically and nonsurgically managed groups regarding patient outcome

Variables	Total (*N*=60)	Studied groups		*P*
		Surgery after systemic therapy and surgery only group (*N*=40)	Systemic therapy only (*N*=20)	
Recurrence				
No	31 (51.7)	25 (80.6)	6 (19.4)	0.018*
Yes	29 (48.3)	15 (51.7)	14 (48.3)	
Death				
No	31 (51.7)	25 (80.6)	6 (19.4)	0.018*
Yes	29 (48.3)	15 (51.7)	14 (48.3)	
Recurrence-free survival				
Mean±SD	26.95±5.89	28.63±5.68	23.6±4.88	0.001**
Range	14–36	16–36	14–31	
Overall survival				
Mean SD	28.72±5	29.73±5	26.7±4.45	0.0026*
Range	20–38	20–38	20–33	

*Significant. **Highly significant.

Figure 2



Kaplan–Meier graph showing significant difference among the three studied groups regarding overall survival.

Conclusion

We concluded that removing the primary tumor surgically in patients with OM breast cancer by simple mastectomy, modified radical mastectomy, or radical mastectomy, according to tumor size, is beneficial for patients and improves the long-term outcomes and survival rates, particularly in young females with a long life expectancy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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