



Research Article

Does Surgical Resection of the Primary Tumor in Patients with Stage IV Breast Cancer Improve Survival?

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Abstract

Several lines of evidence suggest that it is time to re-examine the approach to the patient diagnosed with distant metastases at the initial breast cancer presentation.

The aim of this study was to evaluate the impact of surgical therapy of the primary tumor and other clinical and staging factors on overall survival of patients with stage IV breast cancer. *Patients and methods:* This retrospective study included patients with stage IV breast cancer from 2000 to 2008. Patient's characteristics and survival distilled from medical files were evaluated using multivariate analysis.

Results: Of 330 patients included in this study, 132 underwent surgery in the form of mastectomy. Local surgery of the primary tumor, lower TN staging, younger age, positive receptor status, lack of Her-2 amplification, bone –only metastasis and one site metastasis were associated with significantly higher survival while grade and pathological type were not. Median overall survival time for no surgery group was 15 months and 27 months for mastectomy group ($P = 0.003$). Three-year survival rate was higher for patients who did have surgery (34% vs 16%). *Conclusion:* Removal of the primary tumor in patients with primary distant metastatic breast cancer was associated with significantly higher survival. However, carefully designed prospective randomized trials are needed to confirm these results.

Keywords: Breast cancer; metastasis; surgery; Stage IV; Mastectomy

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Introduction

With an increasing incidence, breast cancer is still the number one cancer affecting women in the western world. Of all these women, 3-10% had distant metastases at initial presentation [1]. The vast majority of patients with metastatic breast cancer do not survive beyond 5 years after diagnosis [2].

Traditionally, metastatic breast cancer (MBC) is considered to be incurable and the goals of treatment are the prolongation of life and the palliation or prevention of symptoms. In stage IV disease, local surgery is reserved for patients who develop complications such as bleeding, ulceration and infection at the primary tumor site, a type of surgery that historically has been described as "toilette" mastectomy. If the total tumor burden plays a role in survival, the removal of the breast lesion is a part of a multimodality strategy in preventing further growth and dissemination of the disease [3]. A strong correlation was found between the level of circulating tumor cells (CTCs) and the prognosis of MBC; the number of CTCs before treatment is an independent of overall survival in these patients [4-6].

Improved survival can also be caused by the fact that surgical resection restores the immune system [7]. Tumor-induced immunosuppression is a mechanism allowing tumors to escape immune destruction. It is reasonable that immunosuppression intensifies with increasing tumor burden. Surgery reduces the quantity of immunosuppressive factors, allowing the immune response to recover.

Contrary to the proposed biological mechanisms in favour of surgical removal of the primary, there have been observation indicating that surgical resection of the breast lesion in MBC may accelerate relapse by two mechanisms: (1) due to removal of inhibitors of angiogenesis, there will be an angiogenic surge; (2) surgical wounding will

lead to the release of growth and immunosuppressive factors [8, 9].

The aim of this retrospective study was to evaluate the impact of surgical therapy of the primary tumor on survival outcome in patients with metastatic breast cancer and to analyse other prognostic factors affecting survival in those patients.

Patients and Methods

This retrospective study included all women with stage IV breast cancer at time of diagnosis presented to Clinical Oncology and Nuclear Medicine Department, Mansoura University (MU) in the period from January 2000 to December 2008 inclusive.

Information recorded for each patient included clinical, pathological features, and survival. Staging was based on clinical TNM classification [10]. The histologic grade was grouped into four categories: well differentiated, moderately differentiated, poorly differentiated and unknown. Hormone receptor status was classified as positive negative and unknown. Metastatic site involvement was categorized as one or more and in the following categories: only bone, only visceral, combination of bone and visceral. Additional data included Her-2 status positive, negative or unknown as assessed by FISH technique. Pathology was classified as ductal, lobular and others. Surgical interference was categorized as no or yes.

Overall survival rate was calculated from date of diagnosis to date of breast-cancer related death or last follow-up.

Statistical methods: The data were encoded in a computer using the Statistical Package for Social Sciences (SPSS) version 15.0 (Chicago, IL, USA). Distributions of survival functions were estimated using the Kaplan-Meier method. Non-normally distributed data was expressed as number and percentage. Log rank test was used to analyse the difference between the curves. P values of <0.05

were considered significant.

Results

Of 360 patients with stage IV breast cancer at time of diagnosis presented to Clinical Oncology and Nuclear Medicine Department MU, 30 patients lost follow-up. So our study included 330 patients only. Forty percent of them (132 patients) were undergone surgery of the primary tumor and 60% (198 patients) did not. Of the 132 patients who were operated, 39 patients (29.5%) were operated with curative intent as the distant metastases were not apparent before surgery but diagnosed in a period of few days to 1 month after surgery.

All patients underwent mastectomy but axillary lymph node dissection was performed in 106 patients (80%).

Patients characteristics are listed in Table 1; patients ≤ 50 years were more common (66.7%). Positive receptor status and Her-2 amplification were recorded in 66% and 50.6% respectively. About 74% of patients had one site of metastasis and visceral metastases were higher (45%). Median overall survival time was statistically significant higher ($p=0.003$) for the surgery (27 months; 95%CI: 23.247-30.753) versus no surgery group (15 months; 95% CI: 12.242-17.758).

On multivariate analysis, patients with younger age, one site of metastasis, bone only metastasis, smaller size of the primary tumor, positive receptor status, lack of Her-2 amplification and absence of lymph node involvement had statistically significant higher survival rate. Histologic grade and pathological type had insignificant impact on survival ($p=0.7, 0.82$ respectively), Table 2.

Patients who were operated had higher significant survival rate (34 % versus 16 %) Figure 1.

Table 1 Patients characteristics

Character	No	%
Age:		
$\leq 50y$	220	66.7
$>50 y$	110	33.3
Hormone receptor status		
Positive	218	66.1
Negative	66	20
Unknown	46	13.9
Her-2 status		
Positive	167	50.6
Negative	105	31.8
Unknown	58	17.6
Histologic grade		
Well differentiated (G1)	16	4.8
Moderately differentiated (G2)	82	24.9
Poorly differentiated (G3)	205	62.1
Unknown	27	8.2
TNM staging		
T1/T2	119	36.1
T3/T4	211	63.9
N0	106	32.1
N1/N2/N3	224	67.9
Pathology		
Ductal	225	68.2
Lobular	37	11.2
Others	68	20.6
Local surgery		
No	198	60
Yes	132	40
Metastatic site		
Bony	115	34.8
Visceral	148	44.9
Both	67	20.3
Number of metastatic site		
1	247	74.8
≥ 2	83	25.2

Table 2 multivariate analysis between variables affecting survival

Character	95% CI	P
Age:		
≤50y	23 (19.84 -26.15)	0.000
>50 y	16 (13.26-18.73)	
Hormone receptor status		
Positive	26(23.41-28.58)	0.000
Negative	17 (15.50-18.44)	
Her-2 status		
Positive	19(17.25-20.71)	0.000
Negative	33(28.03-37.99)	
Histologic grade		
Well differentiated (G1)	26 (19.16-34.84)	0.07
Moderately differentiated (G2)	23(19.45-26.55)	
Poorly differentiated (G3)	21(18.22-23.77)	
TNM staging		
T1/T2	29(24.59-33.43)	0.000
T3/T4	18(16.36-19.63)	
N0		
N1/N2/N3	30(23.79-36.20)	0.000
	18(16.46-19.54)	
Pathology		
Ductal	22(19.18-24.81)	0.082
Lobular	20(17.02-22.97)	
Others	19(15.74-22.25)	
Metastatic site		
Bony	27(22.09-31.904)	.000
Visceral	18(15.83-20.168)	
Both	17(10.7-23.23)	
Number of metastatic site		
1	32(28.18-35.81)	.00
≥2	19(17.5-20.49)	

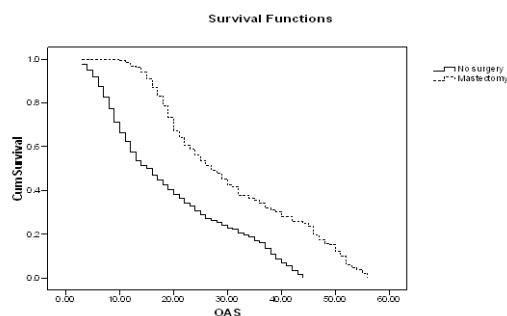


Figure 1 Overall survival in both groups

Discussion

Several lines of evidence suggest that it is time to re-examine the approach to the patient diagnosed with distant metastases at the initial breast cancer presentation.

Improved imaging technology has resulted in the diagnosis of stage IV disease with considerably lower tumor burdens than were seen in the past. Also, improvements in systemic therapies for women with breast cancer raise the possibility of cure for a select groups of patients with stage IV and helped to increase 5-year survival from about 10% in 1970s to about 40% in the late 1990s [11]. Data from the National Cancer Database (NCDB) and the Surveillance, Epidemiology and End Results (SEER) database demonstrate a 5-year survival of 26% for patients with stage IV breast cancer [12].

The present study shows survival gain in operated patients, those with younger age, smaller tumor size, one site of metastasis, bony metastasis, positive receptor status, lack of Her-2 amplification and absence of lymph node involvement. Several retrospective studies from single institution and population databases have demonstrated improved survival in women with stage IV disease who undergo surgery for an intact primary tumor [13-15] that coincided with our results.

The biological rationale for an improvement in survival seen with resection of the primary tumor in metastatic breast cancer is based on several lines of reasoning. The primary tumor may act as a "seed source" for development of new metastases and its removal would theoretically diminish the chances of disease progression [16]. Decreasing the tumor burden by removal of the primary could also increase the efficacy of chemotherapy by reducing the chances of a resistant clone appearing [8]. Regarding the timing of surgery (early, after response to systemic therapy or later, only if indicated for palliation) has been examined, large databases such as NCDB and SEER capture the first course of treatment most accurately and

therefore women reported as having had surgical therapy would most likely have received this early in their course [17].

In addition to improvement in survival with mastectomy, an improvement in quality of life because of discontinuation of chemotherapy is also potential benefit [18]. It is useful to remember that the 30 day operative mortality of mastectomy as long as the 1970s was 0.35%; major complications are infrequent and at present, hospitalizations of longer than 2 days after mastectomy are uncommon. These morbidity and mortality statistics compare favorably with the toxicity profiles of many systemic agents used in the metastatic setting [19]. However, association between surgery and survival could be due to the fact that women with favorable disease characteristics were often operated [20].

Multivariate analysis demonstrated a significant association between overall survival and younger age, smaller tumor size, and positive ER or PR status in our study comparable to that found by Gnerlich *et al.* [8]. Only bony metastasis had significantly better overall survival. This result is consistent with the known indolent course of osseous metastasis.

A large proportion of patients treated with local surgery of the primary tumor also underwent a lymph node dissection (80%). Few studies showed a non significant association with survival in patients who underwent lymph node dissection [20] while Rapiti *et al.* [13] suggests a trend toward a larger benefit for women had axillary dissection which can be explained by decrease tumor burden by axillary dissection when there is lymph node involvement.

The main limitation of our study, is its retrospective nature i.e. surgery has not been assigned by randomization so the only way to overcome this problem is to perform a well designed prospective study. More specific questions of such a trial are the optimal sequencing of systemic treatment and surgery and the prognostic value of the response of the primary tumor to systemic treatment with or without

surgery.

Conclusion

Removal of the primary tumor in patients with primary distant metastatic breast cancer was associated with significantly higher survival. However, carefully designed prospective randomized trials are needed to confirm these results.

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