

The Benefit of Locoregional Surgical Intervention in Metastatic Breast Cancer at Initial Presentation

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Abstract: This study aims to determine the value of locoregional surgery compared with no surgery on the outcome of women with metastatic breast cancer at initial presentation. For that, fifty seven patients initially presented with stage IV breast cancer were prospectively randomized to undergo mastectomy in group I (27 patients) or no surgery in group II (30 patients). All patients received systemic treatment including chemotherapy, hormonal treatment in receptor positive patients and palliative radiotherapy for patients with bone metastases. The median overall survival (OS) was 18 and 11 months in group I and II, respectively; however the difference did not reach statistical significant ($p=0.085$). The 2-year OS was 46% in group I and 22% in group II. Tumor size, clinical lymph node stage, Eastern Cooperative Oncology Group Performance Status (ECOG- PS) and the number of metastatic sites were significant independent prognostic factors affecting the OS in univariate analysis, and bone metastases was highly statistically significant. In multivariate analysis ECOG- PS was a significant factor and both the number of metastatic sites and bone metastases were highly significant. Although, locoregional surgery tends to increase overall survival in patients presented with metastatic breast cancer and patients with better ECOG- PS and single bone metastasis are more likely to benefit from surgery, further studies are needed involving a large number of cases, multi-institutional trials and longer follow-up to verify these findings.

Keywords: Breast Cancer, Metastasis, Locoregional Treatment, Surgery

1. Introduction

At diagnosis of breast cancer 5-10% of patients have distant metastases; nearly one-fifth of the patients survives for 5 years [1]. A retrospective study found a significantly longer median overall survival among patients presenting with stage IV disease than among those with relapsed disease [2]. The prognosis of patients who presented with metastasis has improved over time due to new treatments modalities [3].

Surgery was performed for patients with bleeding, ulceration and infection at the primary tumor site that named a toilette mastectomy. Several retrospective studies showed that surgical resection of the primary tumor might benefit the patients with distant metastases [4, 5]. Khan et al pointed to the total tumor burden which plays a central role in the survival of patients and the primary tumor has considered a

source for other metastatic sites [6].

Fifty percent reduction in breast cancer mortality was observed in women underwent surgery of the primary tumor comparing with women who did not undergo surgery, the benefit was obvious after tumor resection with free margins, but no significant survival benefit for axillary surgery was observed [7]. However, two randomized controlled trials proposed that locoregional therapy with surgery and radiotherapy didn't improve the survival in patients with stage IV breast cancer [8, 9]. After previous controversies, we design this prospective study aiming to determine the value of locoregional surgery compared with no surgery on overall survival of women with metastatic breast cancer at initial presentation.

2. Patients and Methods

2.1. Inclusion Criteria

Female patients initially presented with pathologically confirmed operable stage IV breast infiltrating duct carcinoma were enrolled in this prospective study. The patients presented in Surgery department and Clinical Oncology & Nuclear Medicine department, Mansoura University Hospitals in the time period from January 2012 to December 2013. Patients consent and approval of the ethical committee were taken.

The patients had 2 or less Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and adequate bone marrow, renal and liver functions. Patients with a serious concomitant illness, prior malignancies or contralateral breast cancer were excluded from the study.

2.2. Pretreatment Evaluation

A complete medical history and physical examination were assessed. Pathological documentation was done including ER and PR. The stage of the tumor was classified according to the clinical and radiological findings and criteria of the American Joint Committee on Cancer AJCC TNM (7th edition, 2010) staging for breast cancer. Laboratory investigations including complete blood picture, serum creatinine, AST, ALT and bilirubin were done for patients. Base line bilateral mammosonography, chest x-ray, abdomeno -pelvic ultrasonography and bone scan were done. Computed tomography or MRI was obtained to confirm distant metastases.

2.3. Study Design

The patients randomized to either group I to whom mastectomy was done with adding axillary clearance in node positive patients followed by chemotherapy or group II patients who were given chemotherapy without surgical intervention. The selection was done using the simple randomization method. Chemotherapy regimen consisted of Anthracycline-containing regimen; fluorouracil (500 mg/m²)/doxorubicin (50 mg/m²)/cyclophosphamide (500 mg/m²) or fluorouracil (500 mg/m²)/epirubicin (100 mg/m²)/cyclophosphamide (500 mg/m²) in day 1, every 3 weeks for three cycles to be continued to 6 cycles in patients with non-progressive disease or changed into docetaxel (75 mg/m²) every 3 weeks in patients with progression. Laboratory work was done before each cycle. Hormonal treatment was given to all patients with positive hormone receptors in the form of tamoxifen for premenopausal and aromatase inhibitors for postmenopausal women after chemotherapy. Patients with bone metastases received palliative radiotherapy.

2.4. Patient Follow-up

Follow-up visits were conducted during treatment, monthly in first year, every 3 months thereafter. Patients were evaluated clinically and radio logically for treatment toxicities and disease status at each visit.

The data of each patient were recorded including age at diagnosis, menopausal status, pathological grade, tumor size, clinical nodal stage, performance status, estrogen and progesterone receptor status and the interpretation of metastases. The end point of the study was overall survival (OS) that was calculated from date of diagnosis to date of death or date of last follow-up.

2.5. Statistical Analysis

Statistical analysis was completed using SPSS (Statistical Package for Social Science) program version 16. Descriptive statistics were recorded as frequencies and percentage or median and range. Comparison between the two groups was done with chi square test or Fisher's exact test, as appropriate. Overall survival was estimated by the Kaplan–Meier method and compared across groups using the log-rank statistic. Cox proportional hazards models used to calculate the univariate and multivariate analyses for prognostic factors which affected the survival. The differences were considered statistically significant for the analysis when p was ≤ 0.05 .

3. Results

From January 2012 to December 2013, 57 eligible women with stage IV breast cancer were enrolled into this study. Surgery was done for 27 patients (Group I) followed by systemic treatment and 30 patients received systemic treatment without performing surgery (Group II). Table (1) summarized the well balanced patients and tumor characteristics stratified by both groups.

Table 1. Baseline patients' characteristics in both groups.

	Group I		Group II		p values
	Surgery		No surgery		
	(n =27)		(n =30)		
Characteristics	No. of Patients	(%)	No. of Patients	(%)	
Age(years)					
Range	30 -60		32-65		0. 66
Median	45		44		
Menopausal status					
Premenopause	15	(55.6)	16	(53.3)	0.87
Postmenopause	12	(44.4)	14	(46.7)	
Tumor grade					
Low	1	(3.7)	1	(3.3)	0.90
Intermediate	11	(40.7)	13	(43.3)	
High	15	(55.6)	16	(53.3)	
Tumor stage (T)					
T1	1	(3.7)	1	(3.3)	0.84
T2	14	(51.9)	16	(53.3)	
T3	8	(29.6)	7	(23.3)	
T4	4	(14.8)	6	(20.0)	
Lymph nodes (Clinical N)					
0	6	(22.2)	7	(23.3)	0.31
1	13	(48.1)	9	(30.0)	
2	8	(29.6)	12	(40.0)	
3	0	(0)	2	(6.7)	
ECOG- PS					

	Group I		Group II		p values
	Surgery		No surgery		
	(n =27)		(n =30)		
Characteristics	No. of Patients	(%)	No. of Patients	(%)	
0- 1	25	(92.6)	27	(90.0)	0.73
2	2	(7.4)	3	(10.0)	
Hormone Receptors					
ER+	16	(59.3)	14	(46.7)	0.34
PR+	15	(55.6)	11	(36.7)	0.15
Number of sites metastases					
1	22	(81.5)	20	(66.7)	0.24
2	4	(14.8)	8	(26.6)	
3 or more	1	(3.7)	2	(6.7)	
Sites metastases					
Bone	19	(70.4)	17	(56.7)	0.28
Viscera	9	(33.3)	14	(46.7)	0.31

ECOG- PS, Eastern Cooperative Oncology Group Performance Status

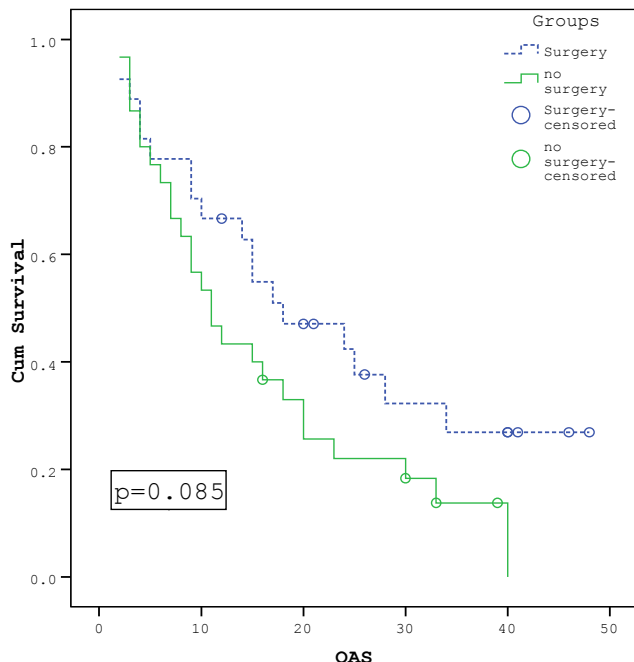


Figure 1. Overall survival in both groups.

During the follow up period ranged from 2 to 48 months (median of 15 months), there were 18 deaths (66.7%) in group I, while 26 deaths (86.7%) were found in group II, on basis of an intention-to-treat analysis. Overall survival was longer in patients underwent surgery (group I) than in patients with no surgery (group II), the median OS were 18 and 11 months, respectively. However the difference between Kaplan-Meier curves for both groups did not reach statistical significant. The 2-year OS were 46% in group I and 22% in group II. (Hazard ratio (HR), 0.346; 95 % confidence interval, 0.031 to 3.817 p=0.085) (Fig. 1).

On analyzing the prognostic factors affecting the overall survival, it was found that tumor size, clinical lymph node stage, ECOG- PS and the number of metastatic sites were significant independent predictors for survival in univariate analysis, and moreover bone metastases were highly

statistically significant (Table 2). However in multivariate analysis ECOG- PS was a significant factor and both the number of metastatic sites and bone metastases were highly.

Table 2. Univariate analysis of prognostic factors affecting the overall survival.

Factor	Wald	Exp(B)	95% C.I. for Exp(B)	P value
Patients age	0.062	1.003	0.977 - 1.030	0.803
Menopausalstatus	0.052	1.073	0.585 - 1.971	0.819
Grade	1.046	0.766	0.459 - 1.277	0.306
Tumor size	7.669	1.825	1.192 - 2.794	0.006*
Clinical lymph node	8.115	1.782	1.198 - 2.653	0.004*
ECOG- PS	10.986	6.074	2.090 - 17.650	0.001*
Estrogen receptor	2.783	1.693	0.912 - 3.141	0.095
Progesterone receptor	1.262	1.444	0.760 - 2.743	0.261
Number of sites metastases	11.333	2.497	1.466 - 4.255	0.001*
Bone metastases	28.438	9.235	4.079 - 20.906	<0.001**

ECOG- PS: Eastern Cooperative Oncology Group Performance Status,

CI: confidence interval,

* Significant difference (p ≤ 0.05)

**Highly Significant<0.001

Table 3. Multivariate analysis of prognostic factors affecting the overall survival.

Factor	Wald	HR	95% CI	P-value
Age	1.033	1.041	0.963 - 1.125	0.310
Menopausal status	1.461	0.372	0.075 - 1.848	0.227
Grading	1.846	0.638	0.334 - 1.220	0.174
Tumor size	2.172	1.438	0.887 - 2.329	0.141
Clinical lymph node	0.813	1.235	0.781 - 1.952	0.367
ECOG-PS	9.125	8.721	2.140 - 35.552	0.003*
Estrogen receptor	0.616	1.377	0.620 - 3.058	0.432
Progesterone receptor	0.391	1.288	0.583 - 2.846	0.532
Number of sites metastases	15.962	5.653	2.417 - 13.222	≤0.001**
Bone metastases	20.976	11.831	4.110 - 34.058	≤0.001**

ECOG- PS: Eastern Cooperative Oncology Group Performance Status,

CI: confidence interval.

* Significant difference (p ≤ 0.05)

** Highly Significant<0.001

4. Discussion

Unlike Halstead theory, the Fisher theory described breast cancer as a systemic disease and that tumors have the capacity to metastasize before diagnosis. This advocated the systemic therapy with no survival advantage for local treatment [10]. On the other hand, the removal of the primary tumor as part of a multimodal strategy prevents further metastasis of cancer cells. Consistent with this hypothesis, some studies mentioned a strong correlation between the level of circulating tumor cells and prognosis of metastatic breast cancer [11].

This improvement in survival was reported by Khan et al

[6] in a retrospective study of 16,023 stage IV breast cancer patients in which surgery of the primary tumor was associated with a 39% reduction in the risk of death, with a 3-year survival of 24.9% for the entire group, 35% for patients with excised tumor to negative margins, 26% for those with positive margins, and 17.3% for those not having surgery.

The median survival of surgically treated patients was 27.1 months versus 16.8 months for patients without surgical resection ($P < 0.0001$) in a retrospective study of 395 metastatic patients [12]. McGuire et al noted 33% overall survival rate in surgery group versus 20% in no surgery group ($p = 0.0015$) [13].

In our study, we tried to clarify the value of removal of the primary tumor in comparison with no surgery on overall survival in women with stage IV breast cancer. It was found that the median overall OS was longer in group I (18 months) than group II (11 months). The 2-year OS were 46% and 22% in group I & II, respectively, but the difference did not reach statistical significance ($p = 0.085$). Meanwhile 18 deaths (66.7%) in group I and 26 deaths (86.7%) were observed in group II.

This result was comparable to other retrospective studies which reported a trend towards increased survival but not statistically significant. No survival benefit was observed in patients with triple-negative disease with surgery, while improvement survival in patients with ER/PR positive or HER-2/neu-amplified disease occurred ($P = 0.004$) [14, 15]. Leung et al stated that loco-regional therapy does not improve survival in patients receiving chemotherapy [16]. In a study of 378 patients who received locoregional therapy that consisted of surgery alone in 67% of patients, radiotherapy alone in 22%, and both in 11%. The rates of 5-year OS were higher in patients with age < 50 , ECOG performance status 0-1, estrogen receptor-positive disease, clear surgical margins, single site and bone-only metastasis [17]. Surgical control of the primary breast tumor has been considered as a locoregional therapy in combination with systemic therapy in breast cancer with metastasis to a single organ, especially bone-only metastasis [18].

In our study, tumor size, clinical lymph node stage, ECOG- PS and the number of metastatic sites were significant independent predictors for survival in univariate analysis, and bone metastases were highly statistically significant. However in multivariate analysis ECOG- PS was a significant factor and both the number of metastatic sites and bone metastases were highly significant. Blanchard et al, multivariate analysis which encompassed surgical treatment, age, race, estrogen and progesterone receptor status, number of metastatic sites and presence of visceral metastases also concluded that surgery was an independent factor with improved survival ($P = 0.006$) [12].

Additionally, no significant benefit from surgical resection of the primary breast cancer was detected in Bafford et al study. They suggested benefit only among patients who underwent surgery before diagnosis of metastases and that stage migration bias might explain the survival benefit of resection [19].

Prospectively two randomized controlled trials presented in San Antonio Breast Cancer Symposium 2013 found no survival benefit from this approach. With a median follow-up of 17 months, a study was done on 350 metastatic breast cancer patients who initially responded to treatment with 6 cycles of anthracycline based chemotherapy. They did not have a better overall survival if treated with surgery followed by radiotherapy than who had no locoregional treatment. The median OS were 18.8 and 20.5 months ($HR = 1.07$, 95% $CI = 0.82-1.40$, $p = 0.60$) and the 2-year OS were 40.8% and 43.3%, respectively [20]. The authors explained the results with Fisher's study on mice in which tumor growth factor was responsible for metastatic tumor progression after excision of the primary tumor [21].

In the second trial, 278 treatment-naïve patients assigned to either surgical resection of their primary tumor with radiation therapy only to the whole breast following breast conserving surgery or no resection. All patients then received standard systemic treatment for the metastatic disease. At 54 months the survival rate was 35% in the surgery group and 31 % in no surgery group ($p = 0.24$). Surgery in patients who had solitary bone metastasis had statistically significant survival benefit compared with no surgery and with that in multiple bone metastases ($p = 0.03$) [22].

The factors affected the decision to resect the primary tumor in patients with metastatic breast cancer in the retrospective studies, including patient age, performance status, number and location of metastatic sites, hormone receptor status that could tolerate surgery and live long enough to have benefit. Despite adjusting for many of those factors, selection bias was not completely eliminated that explained the improved outcomes seen in those non-randomized trials [23].

5. Conclusion

Locoregional surgery tends to increase overall survival in patients presented with metastatic breast cancer but the difference was statistically insignificant. Patients with better ECOG- PS and single bone metastasis are more likely to benefit from surgery. Large studies are needed that involve a large number of cases, multi-institutional trials and longer follow-up to verify the finding.

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