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The role of surgery in stage IV breast cancer: Clinical experiences of 62 patients

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Ethics Committee Approval
The study was approved by the Karamanoğlu Mehmet Bey University Clinical Research Ethics Committee (Date: August 31, 2022, Decision No: 08-2022/10).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The effect of surgical intervention on the quality of life and survival of patients presenting with metastatic breast cancer is a controversial issue. In this study, we aimed to reveal the survival, clinical, and pathological differences in patients with breast cancer who had metastatic disease at diagnosis and who underwent and did not undergo surgery for the primary tumor in our clinic and to evaluate the efficacy of surgical approach on the course of the disease.
Methods: In this retrospective cohort study, the data of patients with metastatic breast cancer in our clinics between January 2000 and June 2021 were retrospectively analyzed. The study included those with primary metastatic disease. The study did not include male patients, patients with primary non-breast tumors, those who died of causes unrelated to breast cancer, those who underwent surgery for metastatic foci other than the primary tumor, and those who could not be followed up regularly for various reasons. In our study, there were two groups; those who received only systemic therapy were assigned to Group 1, while those who underwent surgical treatment for the primary tumor were assigned to Group 2. The clinicopathological and survival data of the groups were examined.
Results: Surgical intervention was performed on 62 of our patients. The 4-year survival rates were higher than those who did not undergo surgery (Group 1: 59.6 [14.7%], Group 2: 83.5 [6%]). The comparison of the two groups showed a longer median survival in patients in Group 2 who underwent surgery, albeit not statistically significant (77 [11.23] months in Group 1 and 84 [18.91] months in Group 2 [*P*=0.16]).
Conclusion: In conclusion, our study showed that surgical treatment may have positive effects on survival.

Keywords: breast cancer, metastasis, surgery, survival

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Introduction

Breast cancer remains the most common type of cancer in women [1]. Despite intensive efforts and screening programs for early diagnosis, 25% of newly diagnosed patients still present with metastatic disease at diagnosis [2]. The standard approach for the treatment of this patient population is systemic therapy. With a better understanding of tumor biology and developments in the drugs used for adjuvant therapy, the survival of these patients presenting with metastatic disease has improved over time [3].

The effect of surgical intervention on patients presenting with metastatic breast cancer is a controversial issue [4,5]. Some experimental studies suggest that there may be an increase in the release of some growth factors and angiogenic factors due to the removal of the primary tumor. It is believed that this may lead to the emergence of new metastases and a more aggressive course of existing metastatic foci [6]. However, no clinical data supporting these studies could be obtained. In contrast, the majority of recent clinical studies have shown that surgical treatment of the primary tumor, especially in selected cases of primary metastatic breast cancer, not only halts local progression but also prolongs overall and disease-free survival [7,8].

In this study, we aimed to reveal the survival, clinical, and pathological differences in patients with breast cancer who had metastatic disease at diagnosis and who underwent and did not undergo surgery for the primary tumor in our clinic and to assess the efficacy of surgery on the course of the disease.

Materials and methods

This study was approved by the Karamanoğlu Mehmet Bey University Clinical Research Ethics Committee (Date: August 31, 2022, Decision No: 08-2022/10), and patient files were reviewed with the approval of the ethics committee. The data of patients with metastatic breast cancer who were treated and followed up in our clinics (Karamanoğlu Mehmet Bey University Faculty of Medicine and Necmettin Erbakan University Meram Faculty of Medicine, General Surgery clinics) between January 2000 and June 2021 were analyzed retrospectively. Patient files were reviewed with the approval of the ethics committee. No additional consent was required from the patients. Patient data were collected from the hospital information management system. The study included those with primary metastatic disease. The presence of distant metastases was diagnosed by imaging techniques or histopathological methods. The groups were those who received only systemic therapy without any surgical intervention and were assigned to Group 1 (n=51), while those who underwent surgery for the tumor and then received adjuvant systemic therapy were assigned to Group 2 (n=62). This study did not include male patients, patients with primary non-breast tumors, those who died of causes unrelated to breast cancer, those who underwent surgery for metastatic foci other than the primary tumor, or those who could not be followed up regularly for various reasons.

Demographic data, site of metastasis, surgical and medical treatments, clinical and histopathological findings of the tumor, mortality rates, and overall survival of the patients were evaluated. The differences between Group 1 and Group 2 in terms of these data and the variables that may have an effect on overall survival were statistically analyzed.

Statistical analysis

The analyses of the study were carried out using the SPSS (Statistical Package for the Social Sciences, IBM Corp. Armonk, NY, USA) version 21.0 software package. The level of error was set at $P<0.05$. The normality of data distribution was evaluated by the Kolmogorov-Smirnov test. Frequency table results were given for categorical variables and descriptive measures for numerical variables. Student's t-test or Mann-Whitney U test was used to compare the groups. Chi-square analysis was used to test whether two categorical variables were independent or related to one another. Disease-free survival and overall survival were calculated using the Kaplan-Meier method. The log-rank test was employed to test whether there was a difference between the survival times of the groups. Risk factors that could affect survival were analyzed with the Cox proportional hazards model.

Results

Of the patients who had distant metastases at diagnosis and were included in our study, 51 underwent no surgical intervention and received only systemic therapy, while 62 underwent surgical treatment for the primary tumor. Comparative clinical and demographic outputs of the groups are in Table 1. The groups were the same in terms of age distribution (52.29 [13.43] and 52.14 [13.54], respectively; $P=0.95$). Twenty-four (47.1%) of the patients in Group 1 and 34 (54.8%) of the patients in Group 2 were postmenopausal ($P=0.41$). There was no difference between the groups in terms of birth rates (46 [90.2%] and 55 [88.7%], respectively; $P=0.79$). The groups were statistically the same in terms of variables such as alcohol use, rate of having any comorbidity, most common comorbid condition (hypertension), and family history of malignancy ($P>0.05$). The rate of smoking was higher in the non-surgical group (7 [13.7%] and 2 [3.2%], respectively; $P=0.04$).

The evaluation of tumor laterality revealed that both groups were similar ($P=0.51$). Of the patients in Group 1, 25 (49%) had right-side, 25 (49%) had left-side, and 1 (2%) had bilateral tumor. In Group 2, the tumor location in 29 (46.8%) patients was on the right side, and in 33 (53.2%) patients on the left side. In both groups, the most frequent site of involvement was the upper outer quadrant (25 (49%) and 27 (43.5%), respectively), while the least frequent site of involvement was the lower inner quadrant (4 (7.8%) and 3 (4.8%), respectively) (Figure 1). The groups were similar in terms of the quadrants of involvement ($P=0.83$).

Figure 1: Bar chart showing the localization of the tumors in both groups (*P*=0.83)

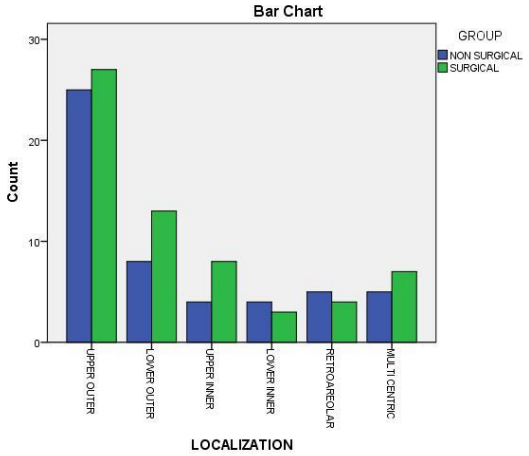


Table 1: Analysis and comparison of demographic and selected clinical characteristics between Non-surgical and Surgical metastatic breast cancer patients.

	Non-surgical group n (%)	Surgical group n (%)	*P*-value (chi-square)
Age	52.29 (13.43)	52.14 (13.54)	0.95
Follow-up time (months)	25.66 (20.44)	38.33 (24.22)	0.004
Comorbidity			
No	31 (60.8%)	38 (61.3%)	0.95
Yes	20 (39.2%)	24 (38.73%)	
Alcohol			
No	48 (94.1%)	59 (95.2%)	0.80
Yes	3 (5.9%)	3 (4.8%)	
Smoking			
No	44 (86.3%)	60 (96.8%)	0.04
Yes	7 (13.7%)	2 (3.2%)	
Malignancy in family			
No	40 (78.4%)	46 (74.2%)	0.59
Yes	11 (21.6%)	16 (25.8%)	
Childbirth			
No	5 (9.8%)	7 (11.3%)	0.79
Yes	46 (90.2%)	55 (88.7%)	
Tumor side			
Right	25 (49%)	29 (46.8%)	0.51
Left	25 (49%)	33 (53.2%)	
Bilateral	1 (2%)	0 (0%)	
Tumor localization			
Upper outer	25 (49%)	27 (43.5%)	0.83
Lower outer	8 (15.7%)	13 (21%)	
Upper inner	4 (7.8%)	8 (12.9%)	
Lower inner	4 (7.8%)	3 (4.8%)	
Central	5 (9.8%)	4 (6.5%)	
Multicentric	5 (9.8%)	7 (11.3%)	
Metastasis site			
Bone	14 (27.5%)	30 (48.4%)	0.07
Liver	4 (7.8%)	4 (6.5%)	
Lung	6 (11.8%)	4 (6.5%)	
Multi-organ	21 (41.2%)	13 (21%)	
Others	6 (11.8%)	11 (17.7%)	
Mortality			
No	40 (78.4%)	50 (80.6%)	0.77
Yes	11 (21.6%)	12 (19.4%)	

Among the diagnostic biopsy techniques, the tru-cut biopsy technique was the most frequently used technique in both groups (30 [58.8%] and 30 [48.4%], respectively). Fine-needle aspiration biopsy was the least preferred technique (6 [11.8%] and 6 [9.7%], respectively). The groups were statistically similar in terms of the biopsy techniques used (*P*=0.38). In both surgical and non-surgical groups, the most common histological type was infiltrative ductal carcinoma (37 [72.5%] and 51 [82.3%], respectively), followed by infiltrative lobular carcinoma and mixed type (has features of both infiltrative ductal and infiltrative lobular carcinoma), respectively (Figure 2). The groups were statistically similar in terms of histopathological types (*P*=0.31). In addition, both groups had statistically similar rates of tumor grade, estrogen receptor positivity, progesterone receptor positivity, Cerb-B2 positivity, triple negativity, and triple positivity (*P*>0.05). The histopathological features of the tumors in the Groups are summarized in Table 2. The evaluation of the groups in terms of the site of metastasis showed that Group 1 most frequently had multi-organ metastasis (n=21 (41.2%)), while Group 2 most frequently had bone involvement (n=30 [48.4%]) (Figure 3). The least frequent site of metastasis was the liver in both groups (4 [7.8%] and 4 [6.5%], respectively). Despite the proportional difference between Groups 1 and 2 in terms of the site of metastasis, there was no statistical difference (*P*=0.07).

Figure 2: Bar chart showing the histological types of the tumors in both groups (*P*=0.31)

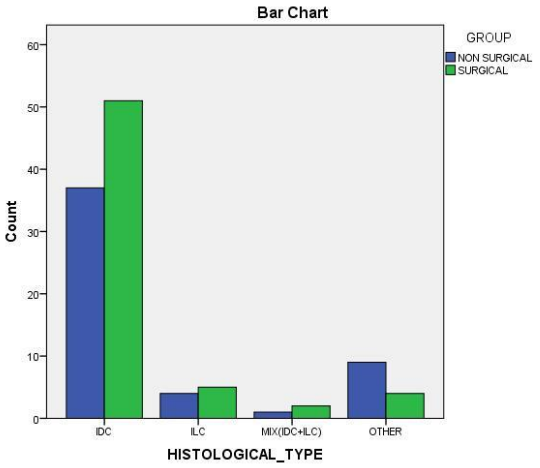
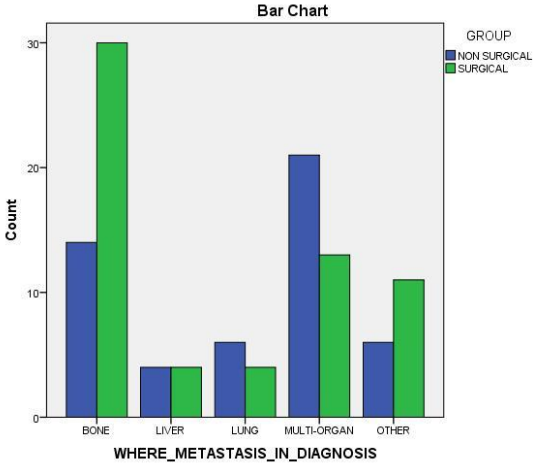


Table 2: Analysis and comparison of histopathological characteristics between Non-surgical and Surgical metastatic breast cancer patients.

	Non-surgical group n (%)	Surgical group n (%)	*P*-value (chi-square)
Tumor size (cm)		25.66 (20.44)	
Histological grading			
Grade 1	0 (0%)	0 (0%)	0.09
Grade 2	16 (88.9%)	38 (69.1%)	
Grade 3	2 (11.1%)	17 (30.9%)	
Type of biopsy			
Excisional	15 (29.4%)	26 (41.9%)	0.38
Tru-cut	30 (58.8%)	30 (48.4%)	
Fine needle	6 (11.8%)	6 (9.7%)	
Histological Type			
IDC	37 (72.5%)	51 (82.3%)	0.31
ILC	4 (7.8%)	5 (8.1%)	
Mix (IDC+ILC)	1 (2%)	2 (3.2%)	
Others	9 (17.6%)	4 (6.5%)	
Estrogen receptor			
Negative	13 (30.2%)	17 (31.5%)	0.89
Positive	30 (69.8%)	37 (68.5%)	
Progesterone receptor			
Negative	17 (39.5%)	18 (33.3%)	0.52
Positive	26 (60.5%)	36(66.7%)	
Cerb-B2			
Negative	13 (30.2%)	22 (40.7%)	0.28
Positive	30 (69.8%)	32 (59.3%)	
Triple-positive			
No	27 (62.8%)	38 (70.4%)	0.43
Yes	16 (37.2%)	16 (29.6%)	
Triple-negative			
No	41 (95.3%)	52 (96.3%)	0.81
Yes	2 (4.7%)	2 (3.7%)	

IDC: Infiltrative Ductal Carcinoma, ILC: Infiltrative Lobular Carcinoma

Figure 3: Bar chart showing the metastasis sites in both groups (*P*=0.07)



The treatment types of the patients in the Groups are summarized in Table 3. Of the patients in Group 2, 56 (90.3%) underwent a modified radical mastectomy, 4 (6.5%) underwent breast-conserving surgery, and 2 (3.2%) underwent a simple mastectomy. The groups were statistically similar in terms of chemotherapy types (P<0.001). The patients in both groups most frequently received palliative chemotherapy (30 [58.8%] and 23 [37.1%], respectively), followed by neoadjuvant (n=20 [39.2%]) and adjuvant (n=1 [2%]) chemotherapy in Group 1 and adjuvant (n=18 [29%]) and neoadjuvant (n=17 [27.4%]) chemotherapy in Group 2. Twenty-eight (54.9%) patients in Group 1 and 26 (41.9%) in Group 2 did not receive radiotherapy. Palliative radiotherapy was applied more in Group 1 (n=18 [35.3%]), while the rate of adjuvant therapy (n=18 [29%]) was higher in Group 2. The groups were significantly different in terms of radiotherapy types (P=0.04). The groups were statistically the same in the rates of hormone therapy and Herceptin (P>0.05).

Table 3: Analysis and comparison of treatment options between Non-surgical and Surgical metastatic breast cancer patients.

	Non-surgical group n (%)	Surgical group n (%)	*P*-value (chi-square)
Surgery			
MRM	0 (0%)	56 (90.3%)	<0.001
BCS	0 (0%)	4 (6.5%)	
SM	0 (0%)	2 (3.2%)	
Not applied	51 (100%)	0 (0%)	
Chemotherapy			
No	0 (0%)	4 (6.5%)	<0.001
Palliative	30 (58.8%)	23 (37.1%)	
Adjuvant	1 (2%)	18 (29 %)	
Neoadjuvant	20 (39.2%)	17 (27.4%)	
Radiotherapy			
No	28 (54.9%)	26 (41.9%)	0.04
Palliative	18 (35.3%)	18 (29%)	
Yes	5 (9.8%)	18 (29%)	
Hormonal therapy			
No	30 (58.8%)	28 (45.2%)	0.14
Yes	21 (41.2%)	34 (54.8%)	
Herceptin			
No	33 (64.7%)	46 (74.2%)	0.27
Yes	18 (35.3%)	16 (25.8%)	

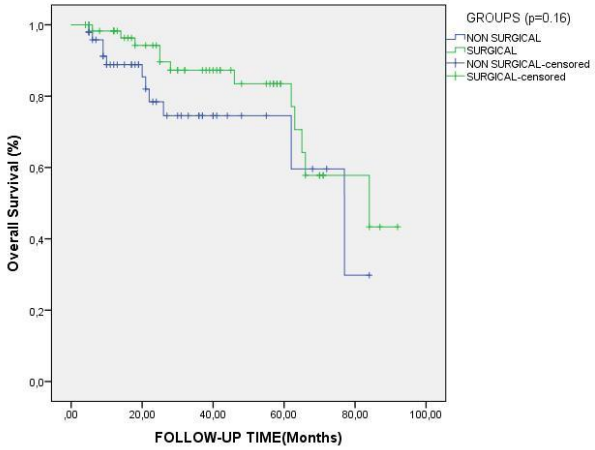
MRM: Modified Radical Mastectomy, BCS: Breast-Conserving Surgery; SM: Simple Mastectomy

The mean follow-up time was 25.66 (20.44) months in Group 1 and 38 (24.22) in the second group. This duration of Group 2 was statistically significantly higher (P=0.004). Eleven patients(21.6%) in Group 1 and 12 (19.4%) in Group 2 died during the follow-up. Although the mortality rate was lower in Group 2, groups were statistically similar in mortality rates (P=0.77).

Survival times were calculated using the Kaplan-Meier method. Figure 4 shows the overall survival curves of both groups. The estimated 4-year overall survival was 59.6 (14.7%) in the first and 83.5 (6%) in the second group. The median survival was 77 (11.23) months in Group 1 and 84 (18.91) months in Group 2. Despite the longer survival time of Group 2, the log-rank test showed no statistically significant difference in survival time between both groups (P=0.16).

Whether being in Group 1 or Group 2 was a risk factor that may affect survival was analyzed with the Cox proportional hazards model, which revealed that being in Group 1 or Group 2 had no statistically significant effect on overall survival (P=0.17). Among the many models created, only the model in which the group variable and the hormone therapy variable were used together was significant, and hormone therapy (Hazard Ratio: 2.75, 95% CI: 1.18–6.57, P=0.003) was associated with decreased mortality.

Figure 4: Kaplan-Meier curves of overall survival in the Non-Surgical (n=51) and the Surgical group (n=62).



Discussion

Surgical treatments for metastatic breast cancer have two basic goals: improving quality of life and prolonging survival [9]. The surgical intervention may aim at the primary tumor or may be performed as metastasectomy in some selected cases [10]. Today, the concept of "treatment" has lost its relatively more aggressive implication of eliminating all cancerous cells and has been defined more often as providing prolonged survival without obvious symptoms [10]. This approach has increased the tendency to prefer more aggressive methods for these patients [10].

The long-established and adopted approach to metastatic breast cancers was that surgery of the primary tumor was an inappropriate method [11]. The general approach has been surgery of the primary tumor only in cases of uncontrolled local disease and patient complaints [12]. In line with this view, 51 of 113 patients included in our study did not undergo any surgical intervention and received only systemic therapy. It has been assumed that surgical intervention activates growth factors in such patients, leading to a more aggressive metastatic disease and a decrease in survival [13]. However, it has been observed that the survival time is quite short after treatments are performed by adopting this approach, with an increase in the rates of progressive local disease that may impair the quality of life of the patients as well as associated disorders such as ulceration, pain, and bleeding [14]. Thereupon, local surgical treatment of the primary tumor has been performed more frequently, and the outcomes of surgical interventions, especially before adjuvant chemo-radiotherapy have been satisfactory in terms of quality of life and survival [11]. Surgical intervention was performed on 62 of our patients, with the 4-year survival rates being higher than those who did not undergo surgery. The comparison of the two groups showed a longer median survival in patients in Group 2 who underwent surgery, albeit not statistically significant.

The initial historical approach to breast cancer was the progression of the disease by spreading to adjacent tissues. Based on this view, it was believed that a broader and more aggressive treatment would be more positive in terms of local control of the disease and survival [15]. However, in the early 21st century, contrary to this view, it has been accepted that breast cancer has a more complex form of spread via the bloodstream and lymphatic system rather than in the form of local spread [16]. For this reason, it has been considered that local control is insignificant and has no

effect on secondary metastases that may develop [16]. Current studies have led to the development of an opinion of a combination of these views that have evolved over time. Early radiotherapy studies have yielded results supporting this view. These studies have shown that the treatment of residual or recurrent disease not only provides local control but also prevents the emergence of new metastases and reduces the risk of mortality [12]. The results of our study showed a higher survival rate in the surgical group, which supports this view.

Although experimental studies have proposed breast cancer stem cell theory, genetic repair model, parallel mutation hypothesis, increased angiogenic activity hypothesis, surgical trauma-induced increase in growth factors hypothesis, clonal dominance theory, immune system theory, and theory of metastatic disease due to surgical treatment of the primary tumor, they are no longer accepted as they cannot be supported by clinical studies [17]. Some hypotheses have also been put forward about by what mechanism the removal of the primary tumor leads to an improvement in survival, including the elimination of growth factors, which are secreted from the primary tumor and thought to be effective on metastatic disease, by primary tumor surgery; the elimination of immunosuppression caused by the tumor after surgery; an increase in the efficacy of adjuvant treatment methods due to the decrease in the possible necrotic tissue load in the tumor as a result of surgery [17].

There are numerous recent academic studies that support the positive effects of surgical intervention. The study by Copelci et al. concluded that surgical resection performed in selected patients with stage IV breast cancer increased survival [3]. Moreover, other studies show that resection of the primary tumor is an independent risk factor for survival, reduces mortality risk, is effective in preventing local symptoms of primary cancer, and can positively affect the quality of life [3,7,11,12,18,19]. Our study also yielded results supporting surgical intervention, similar to these studies in the literature. According to the results of another literature review by Ruiterkamp et al. [20], patients with metastatic breast cancer, especially young individuals with a single metastasis, benefit more from surgical treatment of the primary tumor, and mastectomy or lumpectomy may be preferred as a surgical technique for these patients, provided that adequate resection can be achieved. Contrary to all these studies, there are also published papers suggesting that primary surgery does not provide the benefit of improving quality of life and overall survival in stage IV breast cancer and that the data are insufficient to determine the efficacy of local surgical treatment [1,21,22].

Limitations

Our study has some inevitable limitations. First, the level of evidence is not strong enough because of the retrospective design of the study. Second, the data were collected from patient records and operative notes. Third, there were no objective examination findings. Fourth, the standardization in follow-up and treatment methods could not be strictly adhered to due to reasons such as advanced age and patient preference. Lastly, the relevant detailed information on chemotherapeutic agents and radiotherapy procedures could not be obtained.

Conclusion

In conclusion, our study showed that surgery of the primary tumor in these patients may have positive effects on survival. We are of the opinion that patients should be encouraged to participate in randomized controlled studies in order to eliminate the doubts caused by studies that have yielded contrary results and to provide standardization in the treatment of this disease.

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