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Primary Surgery in Metastatic Breast Cancer

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ABSTRACT

Objective: This study evaluated the effect of local-regional management of the primary tumor on the prognosis of patients with metastatic breast cancer. The primary outcome measure was overall survival, while progression-free survival was assessed as a secondary end-point.

Materials and Methods: We retrospectively analyzed metastatic breast cancer patients who underwent local-regional treatment over a 10-year period (May 2013 to May 2023). Sociodemographic and clinicopathological data were extracted from medical records and automated hospital systems. Statistical analyses were performed using SPSS.

Results: The study cohort consisted of 76 patients, with a mean age of 50 years and a median follow-up period of 58 months. The progression-free survival rate was 58%, while overall survival reached 75%, and the 5-year survival rate was 80%. Importantly, no deaths were observed among patients who achieved a pathological complete response during follow-up. Analysis of survival outcomes revealed that overall survival was significantly reduced in patients with axillary lymph node metastasis compared to those without ($p = 0.02$), in individuals with triple-negative breast cancer compared to those with hormone receptor-positive tumors ($p = 0.03$), in patients with T4 tumors compared to those with other T stages ($p = 0.04$), and in patients who experienced recurrence or distant metastasis during follow-up relative to those who did not ($p<0.01$).

Conclusion: In metastatic breast cancer, surgical resection of the primary tumor was associated with improved overall survival and progression-free survival. While a response to systemic chemotherapy was a favorable prognostic factor, increased tumor size, axillary lymph node positivity, triple-negative status, and the development of new metastasis and/or recurrence during follow-up were associated with poorer outcomes.

Keywords: Breast cancer; metastasis; surgery; survival

KEY POINTS

- Primary tumor resection in metastatic breast cancer was associated with favorable overall survival and progression-free survival outcomes.
- Patients who achieved a pathological complete response after systemic chemotherapy demonstrated excellent prognosis, with no mortality observed during follow-up.
- Triple-negative breast cancer, T4 tumors, and axillary lymph node involvement were associated with significantly poorer overall survival.
- The development of recurrence and/or new metastasis during follow-up was identified as a strong negative prognostic factor.
- Careful multidisciplinary patient selection may optimize the potential benefit of locoregional surgical treatment in metastatic breast cancer.

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Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide, accounting for approximately 11.6% of all cancer cases. In 2022, an estimated 2.3 million new cases were reported, ranking breast cancer the second most common cancer globally after lung cancer. Despite major advances in screening and treatment, breast cancer remains the fourth leading cause of cancer-related mortality, responsible for approximately 666,000 deaths annually, which represents 6.9% of all cancer-related deaths (1). In newly diagnosed breast cancer patients, synchronous distant metastasis is observed in 3.5% to 10% of cases (2-4).

The most common sites of distant metastasis in breast cancer are the bone, lung, liver, and brain. According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system, lymph node metastases other than those involving the ipsilateral axillary, internal mammary, and supraclavicular nodes are classified as distant organ metastases. Ipsilateral supraclavicular lymph node involvement is staged as N3c disease. Distant (non-regional) lymph nodes include the cervical, contralateral axillary, contralateral supraclavicular, and contralateral internal mammary nodes. Metastatic spread to these distant lymph nodes is categorized as M1 (stage IV) disease (5).

Survival outcomes strongly depend on the stage at diagnosis. In patients with non-metastatic localized breast cancer, the 5-year survival rate approaches 99%, whereas in locally advanced disease, it decreases to about 86%. However, in metastatic breast cancer (MBC) patients, this rate drops significantly to 27% (6, 7). Given the substantial reduction in survival rates, the importance of effective MBC treatment is increasingly recognized. Current guidelines recommend primary tumor resection in MBC primarily for symptomatic relief and as a palliative measure (8).

In a pivotal trial conducted by the South Western Oncology Group, patients with stage IV renal cell carcinoma were randomized to receive interleukin-based therapy alone or in combination with cytoreductive nephrectomy. The addition of surgery improved median overall survival (OS) from 8 months in the non-surgical group to 11 months among those who underwent nephrectomy (9). These findings have sparked interest in whether similar survival benefits could be achieved through aggressive local treatment in other metastatic cancers, including breast cancer.

Evidence from several studies has indicated that surgical intervention may confer a survival advantage in carefully selected patients with MBC (10-16). Improved OS has been most frequently observed in those with hormone receptor-positive disease, limited metastatic involvement, favorable response to systemic therapy (ST), and achievement of negative surgical margins. Nevertheless, the role of surgery in this setting remains controversial. While some investigations have demonstrated an association with improved OS, others report minimal or no survival advantage, supporting the use of surgery mainly for palliative purposes (17-20).

This study was designed to address the ongoing uncertainty regarding the survival impact of primary tumor resection in MBC. The main objective was to determine whether locoregional treatment of the primary lesion improved OS in patients with stage IV disease. OS serves as the primary endpoint, with progression-free survival (PFS) defined as the secondary outcome.

Materials and Methods

This retrospective analysis included patients who underwent surgical treatment over a 10-year period, from May 2013 to May 2023. Patient data were collected from the records of cases managed by a single academic breast surgeon. Inclusion criteria comprised patients whose treatment plans were discussed and approved by the breast council, and who consistently attended routine follow-up visits.

Data on patient demographics, clinicopathological characteristics, and treatment outcomes were extracted from automated hospital systems and manually maintained patient files. The study focused on patients with MBC, including those with oligometastatic or multiple metastases, who received adjuvant chemotherapy (CT) and were deemed by the breast council to gain benefit from primary tumor resection.

This study evaluated the prognostic impact of primary tumor resection in patients with MBC by analyzing OS and PFS as its primary and secondary end-points, respectively.

For each patient, demographic information including age and gender was recorded. Tumor characteristics were documented, including tumor size, laterality, histological type, grade, and hormone receptor status, as well as regional lymph node involvement and sites of distant metastasis. The diagnosis of distant organ metastases was established based on imaging findings and histopathological confirmation. Disease stage was determined according to the 8th edition of the AJCC staging system. Recurrence data, including the date and type of recurrence, were also collected. Information on treatment modalities, such as surgical procedures, radiotherapy, CT, and hormonal therapy, was obtained. Finally, follow-up data, including the date of the last visit, recurrence, metastasis, and mortality during the follow-up period, were recorded. In this study, PFS was evaluated by analyzing dates of recurrence and metastasis dates, while OS was assessed using recorded death.

Patients were excluded from the study if their medical records were missing or incomplete, if they failed to attend routine follow-up visits, or if there was no documented breast cancer

multidisciplinary council decision regarding their treatment plan.

Ethical Approval: This study received ethical approval from the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Scientific Research Ethics Committee (decision no: 19/20) on 03.11.2023. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was conducted using SPSS (IBM Inc., Armonk, NY, USA). Categorical variables were summarized using frequency and percentage values. For numerical variables, the arithmetic mean ± standard deviation was reported if the data followed a normal distribution; otherwise, the median (minimum-maximum) values were provided.

Comparisons between groups for categorical data were evaluated using the chi-square test, with Fisher's exact test applied in cases where the assumptions for the chi-square test were not fulfilled.

For comparisons between two groups, of continuous data normally distributed variables were analyzed using the independent samples t-test, whereas non-normally distributed variables were assessed with the Mann-Whitney U test.

Survival outcomes were evaluated with Kaplan-Meier analysis, and differences between groups were compared using the log-rank test. A two-sided *p*-value <0.05 was considered statistically significant.

Results

This study included patients who underwent surgical treatment between May 2013 and May 2023. A total of 1,404 patients who underwent breast cancer surgery by a single faculty member were reviewed. Among these, 76 (5.4%) diagnosed with stage 4 breast cancer (characterized by distant organ metastasis) were included in the study (Table 1).

The OS rate was 64.3% in patients aged 55 years and older, compared to 81.3% in those younger than 55 years.

Table 1. Sociodemographic characteristics

Number of patients (*n*)	**76**
Age	
Age, years, mean ± SD	49.9±12.5
<55 (*n*)	48
≥55 (*n*)	28
Follow-up, months, mean ± SD	58.1±30.6

SD: Standard deviation

During the follow-up period, no mortality was observed among patients who attained a pathological complete response (pCR). Patients with T4 tumors had significantly lower OS rates compared to those with other T stages ($p = 0.04$) (Table 2).

Axillary nodal involvement was a significant negative prognostic factor for both OS ($p = 0.02$) and PFS ($p = 0.001$). A higher number of involved lymph nodes was associated with poorer survival outcomes, achieving statistical significance for PFS ($p = 0.001$) and showing a significant trend for OS ($p = 0.03$) (Table 3).

Table 2. Pathological data

Tumor size, T score, *n* (%)	
Pathological complete response	11 (14)
T1	32 (42)
T2	22 (29)
T3	2 (3)
T4	9 (12)
Histologic grade, *n* (%)	
Grade I	8 (11)
Grade II	42 (55)
Grade III	26 (34)
Tumor type, *n* (%)	
Invasive ductal	52 (68)
Invasive lobular	5 (7)
Invasive	17 (22)
Mucinous	2 (3)
ER/PR (+), *n* (%)	60 (79)
HER2/neu (+), *n* (%)	23 (30)
Triple negative, *n* (%)	6 (8)
Ki-67% mean ± SD	26.2±2.3
Axillary lymph node, *n* (%)	
N0	27 (35)
N1	25 (33)
N2	19 (25)
N3	5 (7)

SD: Standard deviation; PR: Progesterone receptor; ER: Estrogen receptor

Table 3. Survival according to axillary lymph node status

Axillary lymph node	Overall survival (%)	Progression-free survival (%)
N0	92.6	88.9
N1	76.0	56.0
N2	57.9	31.6
N3	40.0	0

The OS rate was 50% in patients with triple-negative breast cancer (TNBC), compared to 77.1% in other patients. TNBC was significantly associated with reduced OS ($p = 0.03$).

Lung, liver, and brain metastases are classified as visceral organ metastases. The presence of visceral organ metastasis did not significantly affect the OS rate ($p = 0.6$) (Table 4).

In terms of distant organ metastasis, there was no difference between single and multiple metastases for, the OS rate ($p = 0.1$).

The surgical procedure performed on the patients was mostly mastectomy. All of the patients received adjuvant CT (Table 5).

Progression (including recurrence, metastasis, or death) occurred in 32 (42.1%) patients during the follow-up period. Of these, 19 patients (25%) had died. Among the deceased, 12 (15.8%) developed metastasis, while three (3.95%) experienced both recurrence and metastasis (Table 6).

In the cohort of 57 patients who did not die, metastasis developed in 11 (14.5%), and recurrence occurred in two (2.6%).

Table 4. Metastasis status

Solitary/multiple metastasis, *n* (%)	
Solitary	55 (72)
Multiple	21 (28)
Metastasis site, *n* (%)*	
Lung	13 (17)
Liver	8 (11)
Bone	35 (46)
Distant lymph node	46 (61)
Solid organ metastasis, *n* (%)	21 (28)

*Some patients had multiple metastatic sites

Table 5. Treatment

Preoperative chemotherapy, *n* (%)	60 (79)
Adjuvant chemotherapy, *n* (%)	76 (100)
Adjuvant radiotherapy, *n* (%)	66 (87)
Hormone therapy, *n* (%)	59 (78)
Trastuzumab	23 (30)
Surgical procedure, *n* (%)	
BCS + SLNB	3 (4)
BCS + ALND	4 (5)
Mastectomy + SLNB	5 (7)
Mastectomy + ALND	64 (84)

BCS: Breast-conserving surgery; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection

Patients who died were followed for an average of 52.3 months, while those who survived were followed for an average of 61.5 months. The PFS rate was 57.9%±6.2% (Figure 1). OS rate was 75%±5.9%. The 5-year survival rate was 80.3%±1.28% (Figure 2).

A total of 28 (36.8%) patients developed recurrence and/or metastasis during follow-up. The OS rate in these patients was 46.4%, compared to 91.7% in those without recurrence or metastasis. The development of recurrence and/or metastasis during follow-up significantly decreased the OS rate ($p<0.01$).

Table 6. Follow-up

Progression (recurrence, metastasis, and death), *n* (%)	**32 (42)**
Metastasis on follow-up, *n* (%)	26 (34)
Metastasis site, *n* (%)	
Lung	11 (14)
Liver	5 (7)
Brain	1 (1)
Bone	8 (11)
Adnexus	1 (1)
Recurrence on follow-up, *n* (%)	5 (7)
Recurrence site, *n* (%)	
Same breast	2 (3)
Contralateral breast	2 (3)
Bilateral breasts	1 (1)
Death, *n* (%)	19 (25)

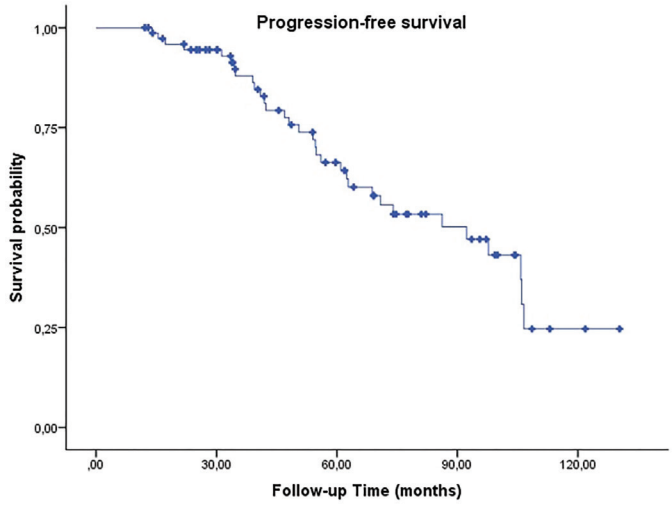

Figure 1. Progression-free survival

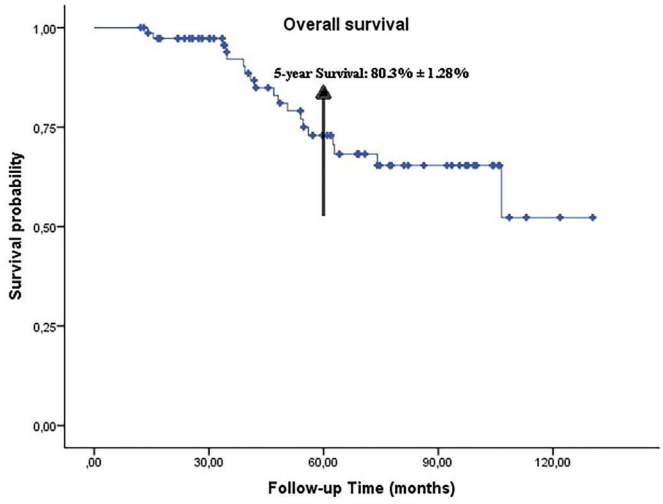

Figure 2. Overall survival

Discussion and Conclusion

MBC is generally considered an incurable disease, and systemic therapies remain the cornerstone of treatment (21). Current guidelines recommend primary tumor resection in MBC primarily for symptomatic relief and as a palliative measure (8). The role of locoregional therapy (LRT) in MBC treatment remains controversial, with no clear consensus in the literature regarding its impact on OS. However, the National Comprehensive Cancer Network guidelines suggest that LRT may be considered for selected patients (22).

In the randomized controlled MF07-01 trial conducted in 2021, a 10-year follow-up revealed that the OS rate in the LRT group was 14% higher compared to the group receiving ST alone (23). Similarly, a review of 24,150 cases from the National Cancer Data Base demonstrated significantly higher 5-year and 10-year OS rates in patients who underwent surgery compared to those treated with ST alone (11). However, conflicting evidence exists. A study conducted in India found no significant difference in OS rates between the LRT and ST groups (24). In addition, the ECOG-ACRIN 2108 multicenter trial reported no significant difference in OS rates between LRT and ST over a 3-year follow-up period (25).

The literature reports a 5-year survival rate of 27% for MBC (6, 7). In this study, the 5-year OS rate for MBC patients who underwent surgery was 80%, significantly higher than the reported average. Patients undergoing surgery may represent a selected group with better performance status and lower metastatic burden. These findings suggest that LRT may have a substantial impact on OS in MBC patients, though further research is needed to reconcile these disparities and establish definitive guidelines.

In the ECOG-ACRIN 2108 multicenter trial, during the 3-year follow-up period, locoregional progression or recurrence was significantly higher in the ST arm compared to the LRT arm (25.6% *vs.* 10.2%; $p = 0.003$) (25). In the present study, the PFS rate in MBC patients who underwent surgery was 58%, significantly higher than the PFS rates reported in the literature for patients receiving ST alone, again this may have been in part due to the selected nature of the study cohort.

In a study conducted in Türkiye in 2019, the average age at diagnosis for breast cancer was 51 years (range: 14–97) (26). Similarly, Soran et al. (23) reported a significant OS benefit in MBC patients under the age of 55 years who underwent primary surgery. Consistent with previous reports, the mean age at diagnosis in our cohort was 50 years. Although patients younger than 55 years showed a trend toward improved OS, this difference did not reach statistical significance. Studies with larger cohorts are warranted to confirm and further investigate this potential association.

In a meta-analysis, patients who received neoadjuvant CT and achieved a pCR demonstrated significantly higher OS rates (27). Consistent with these findings, there was no mortality during follow-up among patients who achieved pCR following preoperative CT in the cohort of the present study. These results suggest that MBC patients who respond favorably to CT have an improved prognosis. However, more comprehensive analyses involving longer follow-up periods and larger patient cohorts are necessary to validate these findings.

TNBC is characterized by rapid growth, aggressive clinical behavior, early metastasis, and poor prognosis, accompanied by greater proliferation (28). Consistent with previous literature, the pesent study found that TNBC patients who underwent surgical resection had a worse prognosis compared to those with hormone receptor-positive tumors. Moreover, a previous cohort study reported that LRT did not significantly impact OS in TNBC patients (14). Further research involving larger patient cohorts is necessary to explore the potential OS benefits of LRT in the TNBC population.

In another study, a significant OS benefit was observed with LRT in estrogen receptor (ER)/progesterone receptor (PR)-positive, HER2/neu-negative patients during a 10-year follow-up period. The only variable that demonstrated a statistically significant favorable prognostic effect was a positive ER status (23). In the present study, ER-positive and HER2/neu-negative status did not impact the prognosis. The prognosis was only poor for patients with TNBC.

Multivariate analyses revealed that the presence of visceral metastasis was an unfavorable prognostic factor (29-31). Among

patients with MBC, including those presenting with visceral metastases at initial diagnosis, receipt of LRT was associated with a significant improvement in OS compared with patients who did not undergo such treatment (14). In another study, surgery reduced OS in patients with multiple visceral organ metastases, while surgical treatment increased OS in those with bone metastasis (32). Contrary to some publications, our study did not identify a significant association between visceral involvement and OS outcomes. Larger studies with multivariate analyses are needed to further investigate this relationship.

According to aggregated study results, the greatest OS benefit from LRT was observed in subgroups with lower-volume metastatic disease, particularly in cases where metastasis was isolated to a single site or restricted to the skeletal system (10, 33). Another study found that MBC patients with a single bone metastasis had significantly higher OS rates (23). However, in this study, factors such as single organ metastasis, multiple organ metastasis, bone metastasis alone, and bone metastasis without visceral organ involvement did not affect OS, possibly due to the relatively small study cohort in the present study. Further studies with larger sample sizes are recommended.

Local progression within a study was characterized as 'local progression/symptom recurrence' (LPRS). The analysis indicated that surgical intervention for the primary tumor was associated with a reduced incidence of LPRS in MBC patients. Furthermore, the absence of LPRS constituted a significant prognostic factor, as evidenced by a markedly superior median OS of 45 months compared to 2.9 months in patients with LPRS ($p = 0.001$) (34). In the present study and, consistent with the literature, the development of recurrence and/or metastasis during follow-up was identified as a negative prognostic factor. In MBC, primary tumor resection was associated with a positive prognostic impact on OS and PFS. Response to systemic CT was also considered a favorable prognostic factor. Conversely, factors such as increased tumor size, axillary lymph node positivity, triple-negative status, and the development of new metastases or recurrence during follow-up were negative prognostic indicators. The treatment of MBC should be tailored to each patient. In multidisciplinary tumor boards, surgical treatment should be considered for suitable patients, with prognostic factors taken into account. Ongoing research will help clarify the role of primary surgery in this setting.

Ethics

Ethics Committee Approval: This study received ethical approval from the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Scientific Research Ethics Committee (decision no: 19/20) on 03.11.2023.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.E.; Concept: E.B., M.A.E.; Design: E.B., A.S.M.; Data Collection and/or Processing: A.S.M.; Analysis and/or Interpretation: E.B.; Literature Search: E.B.; Writing: E.B., M.A.E.

Conflict of Interest: The authors have no conflicts of interest to declare.

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