



Survival and Treatment Outcomes in Patients with Extracranial Oligometastatic Breast Cancer: Single-Center Experience

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OBJECTIVE

Oligometastatic tumors are usually characterized by a solitary or small number of metastatic lesions confined to a single organ. This study aims to investigate the prognostic factors for overall survival in patients with extracranial oligometastatic breast cancer and share our own experiences.

METHODS

We evaluated 130 patients who were admitted for the diagnosis of extracranial oligometastatic breast cancer at the University of Health Sciences İstanbul Training and Research Hospital Department of Radiation Oncology between 2013 and 2017.

RESULTS

Age ($p=0.003$), type of surgery ($p<0.001$), estrogen receptor status positivity ($p=0.011$), location of metastasis ($p<0.001$), premenopausal status ($p=0.001$), number of metastases ($p=0.029$), administration of chemotherapy ($p<0.001$) and application of curative radiotherapy ($p<0.001$) were the prognostic factors affecting overall survival in univariate analysis. Age <50 (HR: 5.434; 95% CI: 1.025-28.80; $p=0.047$), only bone metastasis (HR: 0.165; 95% CI: 0.073-0.370; $p<0.001$), premenopausal status (HR: 0.125; 95% CI: 0.022-0.723; $p=0.020$) and chemotherapy administration (HR: 4.342; 95% CI: 1.792-10.52; $p=0.001$) were independent prognostic factors that positively affected overall survival in multivariate analysis.

CONCLUSION

Oligometastatic breast cancer is a separate subgroup with long-term prognosis for patients with metastatic breast cancer. In patients with extracranial oligometastatic breast cancer, long-term disease control may be possible using more aggressive multidisciplinary treatments, particularly in patients with bone-only metastases.

Keywords: Breast cancer; oligometastases; survival.

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Introduction

Metastatic breast cancer is often viewed as incurable, and its 5-year survival rate is 27%.^[1] Oligometastatic

tumors are usually characterized by a solitary or small number of metastatic lesions confined to a single organ.^[2] The guidelines of the fourth ESO-ESMO International Consensus have expanded the definitions

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of oligometastatic disease from a single organ to a limited number of metastatic lesions, with low-level metastatic disease (up to five lesions, and not always in the same organ).[3] Stage IV disease is observed in approximately 1%–10% of patients with newly discovered metastatic breast cancer.[4–7] However, it is not evident which subgroups of patients with metastatic breast cancer would benefit from surgery of the primary lesion. Treatment objectives for stage IV disease are prolongation of survival, control of tumor burden, reduction of cancer-related symptoms, and preservation of the quality of life. Therefore, this study aims to describe the prognostic factors for overall survival in patients with extracranial oligometastatic breast cancer (OMBC).

Materials and Methods

We enrolled 130 patients with extracranial breast cancer who were evaluated at the University of Health Sciences Istanbul Training and Research Hospital Radiation Oncology clinic between 2013 and 2017. Exclusion criteria included patients who were under 18 years of age, male sex and those with another solid or hematological tumor or brain metastases. All patients underwent positron emission tomography-computed tomography to perform staging before diagnosis. The last patient follow-up was in December 2018. We conducted 6–8 cycles of chemotherapy or hormone therapy (if chemotherapy could not be used), administered bisphosphonates, and/or performed palliative radiotherapy (300 cGy/day doses in 10 fractions for bones). We didn't have a radiosurgery group. The response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines version 1.1.[8] Patients who had a complete response were operated by a surgeon. Radiotherapy was performed for the operated breast and then, according to hormone receptor status, adjuvant hormone therapy was initiated. Overall survival (OS) was defined as the time until death. Progression-free survival was defined as the time from the initiation of treatment to the point when disease progression was detected. This retrospective study was approved by the ethics committee of our hospital (number: 2019/1893).

Statistical Analysis

For descriptive statistics of the data, average, standard deviation, median, lowest, highest, frequency, and ratio values were used. The distribution of variables was measured using the Kolmogorov–Smirnov test. The Mann–Whitney U test was used for the analysis of quantitative independent data, whereas the chi-square test was used

for the analysis of qualitative independent data. Fischer's exact test was used when chi-square test conditions were not provided. Survival analysis was performed using the Kaplan–Meier (log-rank) test, Cox model for univariate and multivariate analysis. The SPSS 22.0 (IBM SPSS, Armonk, NY, USA) program was used for analyses. A p -value < 0.05 was considered significant.

Results

The median age of the patients was 52 (27–86 years). The most commonly observed histological type of breast cancer was invasive ductal carcinoma (80%, $n=104$). The mean diameter of the tumor was 3.8 cm (1–15 cm). Fifty-six percent ($n=72$) of the patients were postmenopausal, 44% ($n=58$) were premenopausal. Palliative radiotherapy was administered to 62% ($n=81$) of the patients. No statistical significance was observed between survival analysis groups concerning tumor diameter, histology, nuclear grade, progesterone receptor status, c-erbB2 receptor status, KI-67 ratio and T (tumor) or N (lymph node) stages. A second progression was observed in 14.6% of patients after an average of 6.7 months, and the next most common sites of metastases were bone ($n=7$; 5.4%), liver ($n=6$; 4.6%), brain ($n=5$; 3.8%), and lung ($n=1$; 0.8%) in patients ($p=0.007$). The general characteristics of the patients are shown in Table 1.

Seven patients who could not undergo chemotherapy were ≥ 80 years of age. Three of them were young and they only underwent palliative radiotherapy and hormone therapy. However, due to disease progression, they survived for < 6 months. Curative radiotherapy was applied to 28 patients with modified radical mastectomy (MRM) and 13 patients underwent breast-conserving surgery (BCS). There were 15 patients with MRM and only palliative radiotherapy was administered to them. Adjuvant radiotherapy was not applied to five patients who underwent MRM; they were > 70 age. One patient was dead in the early postoperative period. Nine postmenopausal patients had T1-2N1M1, ER(+), PR(+), CerbB2 (-) disease at initial diagnosis. Curative postmastectomy radiotherapy was not performed to these patients because of their good risk factors. Curative radiotherapy was not performed for any of the biopsy patients. Sixty-six (92%) patients performed palliative radiotherapy; six (8%) patients did not apply radiotherapy at all. Three of the patients without radiotherapy had only liver metastasis, while five patients had bone metastasis in painless, non-lytic, non-fracture risk localizations (e.g., ribs) (Table 2).

Table 1 General characteristics of the patients		
	Number of patients	%
Location of metastases		
Bone	109	84
Lung, liver	21	16
Histology		
IDC	104	80
ILC	18	14
IMPC	5	4
Apocrine	3	2
Operation type		
MRM/BCS	58	45
Biopsy	72	55
Nuclear grade		
I	5	4
II	71	55
III	54	41
T stage		
1-2	103	79
3-4	27	21
N stage		
1	37	28
2	71	55
3	22	17
Estrogen receptor		
Positive	96	74
Negative	34	26
Progesterone receptor		
Positive	111	86
Negative	19	14
CerbB2		
Positive	25	19
Negative	105	81
Chemotherapy		
Absent	10	8
CT+Trastuzumab	25	19
6 cycle FEC	59	45
4 AC+4 Docetaxel	27	21
6 cycle TAC	9	7
Radiotherapy		
Absent	8	6
50/60 Gy	41	32
30 Gy (palliative)	81	62
Hormonotherapy		
Absent	18	13
Present	112	87
Menopausal status		
Premenopause	58	44
Postmenopause	72	56
Number of metastases		
1-2	53	41
3-5	77	59

Table 1 Cont.		
	Number of patients	%
KI 67 ratio		
0-14	20	15
>15	110	85
Second metastases		
Absent	111	86
Present	19	14

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; IMPC: Invasive micropapillary carcinoma; MRM: Modified radical mastectomy; BCS: Breast-conserving surgery; CT: Chemotherapy; FEC: 5-Fluorouracil Epirubicine Cyclophosphamide; AC: Adriablastine Cyclophosphamide; TAC: Docetaxel Adriablastine Cyclophosphamide

According to palliative radiotherapy, the absence of radiotherapy was not found to be statistically significant ($p=0.672$). According to palliative radiotherapy, performed curative radiotherapy was found to be statistically significant ($p<0.001$). Lastly, estimated survival time was 55 (95 % CI: 43.29-66.70) and 30 (95 % CI: 20.41-39.58) months for radiotherapy application curative and palliative groups (Log-rank $p=0.001$). Radiotherapy absent group's survival time was 41 months. The 5-year OS for radiotherapy application groups is shown in Figure 1.

The estimated survival time was 55 and 13 months for the bone metastasis and organ metastasis groups (Log-rank $p<0.001$), respectively. The 5-year OS for the bone metastasis and organ metastasis groups are shown in Figure 2.

Age ≤ 50 , type of surgery, estrogen receptor (ER) status positivity, location of metastasis, number of metastases, premenopausal stage, radiotherapy and chemotherapy administration were the prognostic factors affecting OS in univariate analysis (Table 3).

Multivariate analysis revealed that age ≤ 50 ($p=0.047$), only bone metastasis ($p<0.001$), premenopausal status ($p=0.020$) and chemotherapy administration ($p=0.001$) were independent prognostic factors affecting OS (Table 4).

Table 2 Radiotherapy application according to operation types			
Radiotherapy	MRM/BCS number (%)	Biopsy number (%)	p
Curative (50/60Gy)	28/13 (71)	-	
Palliative (30 Gy)	15/0 (26)	66 (92)	<0.001
Absent	2 (3)	6 (8)	

MRM: Modified radical mastectomy; BCS: Breast-conserving surgery

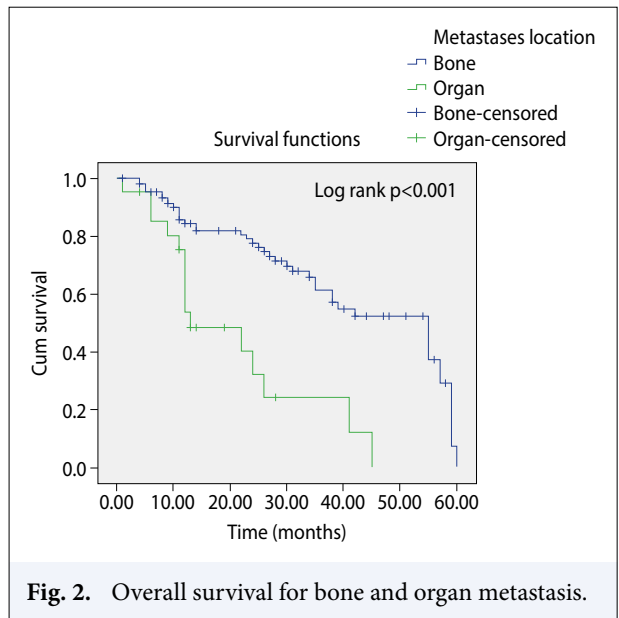
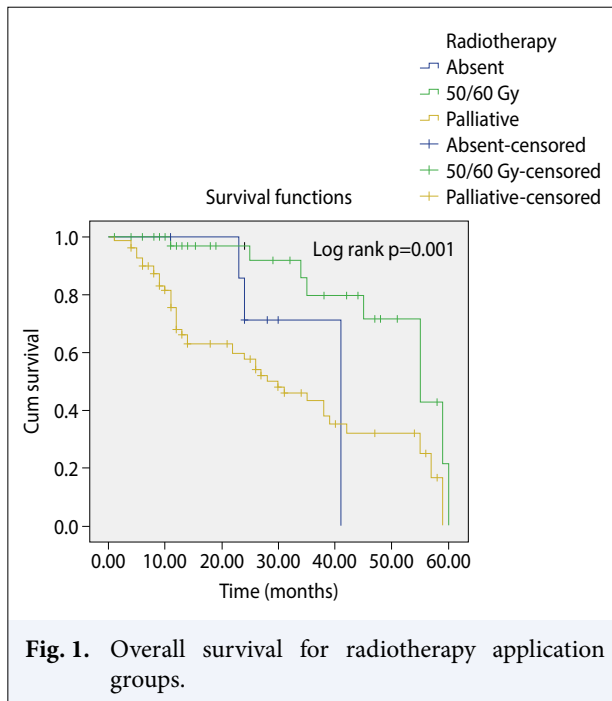
Table 3 Univariate Cox regression analysis

Univariate analysis	HR	95% CI	p
Age (≤50 vs. >50)	0.421	0.236-0.751	0.003
Operation type (MRM/BCS vs. biopsy)	0.368	0.205-0.661	<0.001
Estrogen receptor (positive vs. negative)	2.062	1.184-3.591	0.011
Location of metastasis (bone vs. organ)	0.281	0.150-0.526	<0.001
Number of metastases (1-2 vs. 3-5)	0.531	0.300-0.938	0.029
Menopausal status (premenopause vs. postmenopause)	0.374	0.204-0.684	0.001
Chemotherapy (present vs. absent)	4.538	2.267-9.084	<0.001
Radiotherapy (palliative vs. absent)	1.227	0.477-3.155	0.672
(palliative vs. curative)	0.122	0.044-0.337	<0.001

MRM: Modified radical mastectomy; BCS: Breast-conserving surgery

Table 4 Multivariate Cox regression analysis

Multivariate analysis	HR	95% CI	p
Age≤50	5.434	1.025-28.80	0.047
Location of metastasis (bone)	0.165	0.073-0.370	<0.001
Menopausal status (premenopausal)	0.125	0.022-0.723	0.020
Chemotherapy (present)	4.342	1.792-10.52	0.001



Discussion

Advances in imaging techniques have enabled the rapid detection of OMBC. Providing local treatment for OMBC is important to extend survival and control the disease.[9] In our study, the SBRT/SABR technique

was not used for radiotherapy because our linear accelerator devices were not suitable for this. Therefore, we used 3-dimensional conformal radiotherapy, intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy for radiotherapy. Furthermore, patients with liver and lung metastases were not eligible for metastasectomy because they had multiple organ metastases. For this group, only systemic chemo-

therapy was used. Anthracycline-based chemotherapy was administered to 92.3% of patients.

Some patients with OMBC may benefit from surgery of the primary tumor because it leads to the eradication of the source of metastatic seeding, regeneration of immune capacity, and reduction in chemoresistance by decreasing the number of clones.[2,10] Therefore, in some studies, surgical operation of the primary tumor is suggested for patients with OMBC who are less than 45 years of age.[11] The rate of operable patients was 44.6% in our study, and operation type was found to be a significant prognostic factor in univariate analysis.

Some researchers have suggested that OMBC may signify less aggressive tumor behavior and be potentially curable with aggressive treatment of the limited metastases.[12] Therefore, it should be treated using a multidisciplinary approach before the spread of cancer cells. We make decisions in the multidisciplinary breast council on the treatment of these patients in our hospital.

In breast cancer metastasis, the bone, lung, liver, and brain are considered the primary target sites. Bone metastasis occurs in approximately 75% of the metastatic sites, and the lung is the second-most common area of breast cancer metastasis.[13,14] Although the liver is a common metastatic region, only 4%–5% of patients have single liver metastases. Treatment options are usually palliative, and median survival is 4–33 months for patients with liver metastases.[15] A prospective study involving 81 patients has reported that R0 lung resection (81.5% of patients) was associated with the longer median OS than R1/R2 resections (103.4 vs. 23.6 vs. 20.2 months, respectively; $p < 0.001$). Size (>3 cm), R0 resection, number (>2), and hormone receptor positivity of metastases were shown to be independent prognostic factors for survival via multivariate analysis.[16] In our study, lung and liver metastases were observed in 16.2% of patients, and their 5-year OS was 13 months.

Some studies have reported that several patients who had attained complete remission after chemotherapy remained in this condition for extended periods of time, with some in remission for over 20 years in clinical practice.[17,18] These survivors are usually young, have good performance status, and have limited numbers of metastases; however, this describes a numerically small group of patients (1% and 3%). Furthermore, these findings challenge the commonly held belief that metastatic breast cancer is fatal. Age ≤ 50 , the number of metastatic lesions (1-2 metastases) and systemic chemotherapy administration were found to

be significant prognostic factors in univariate analysis in our study. Age ≤ 50 and systemic chemotherapy administration were found to be independent significant prognostic factors that positively influenced OS like that study.

Local radiotherapy should be administered to patients with good prognostic factors. Patients who may benefit from local radiotherapy include patients with young age, good performance status, ER (+) disease, and OMBC with <5 metastatic lesions.[19] In the present study, the number of metastatic lesions (1-2 metastases), estrogen receptor positivity, age ≤ 50 and perform radiotherapy to breast or chest wall after surgery was found to be a significant prognostic factor in univariate analysis. However, the multivariate analysis radiotherapy was not a prognostic factor. This is because the number of patients who do not receive radiotherapy is small. A recent study has reported fairly positive findings of a phase II study using SBRT or IMRT for oligometastases from breast cancer.[20] Their study included 23 cases of lymph node metastases that were treated without serious toxicity; however, the major region of metastatic disease was the bone, as in our study.

Local therapy, along with systemic therapy, contributes to OS in patients with OMBC. Providing long-term local control with radiotherapy to the metastatic region extends OS. A study has reported that with the addition of systemic treatment, approximately 73% of new metastases were prevented from growing.[21] Another study has demonstrated a superior prognosis for treatments using aggressive local therapies, achieving OS rates of 82% at 10 years and 53% at 20 years in patients with OMBC.[22] Furthermore, a study has demonstrated that high-dose radiotherapy for treating limited metastases is associated with better OS;[23] however, a limited number of patients with M1 breast cancer are suitable candidates for more aggressive systemic and locoregional treatments.[24] Our study has some limitations. First, this study was a retrospective study. Second, most of our patients had only bone metastases.

Conclusion

In conclusion, treatment for OMBC should not be the only palliative. The current treatment approach for patients with metastatic breast cancer is to achieve an asymptomatic extended life. Survival is prolonged via the use of systemic therapies, and local therapies are of importance. Our data present that in some groups of

patients with OMBC, an aggressive multidisciplinary approach involving both local and systemic treatment may provide long-term disease control and better OS.

Abbreviations:

OMBC: Oligometastatic Breast Cancer

OS: Overall Survival

MRM: Modified Radical Mastectomy

BCS: Breast-conserving Surgery

ER: Estrogen Receptor

PR: Progesterone Receptor

SBRT/SABR: Stereotactic Body Radiation Therapy/
Stereotactic Ablative Radiotherapy

IMRT: Intensity-modulated Radiation Therapy

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethics Committee Approval: This study was approved by the local ethics committee of the University of Health Science, Istanbul Training and Research Hospital, Turkey (approval number: 2019/1893).

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