Solitary Bone Metastasis and Oligometastatic Bone Disease in Breast Cancer: Are They Two Different Entities?

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Abstract

In this study, we planned to investigate the clinical course of breast cancer patients with oligometastatic bone disease (OMBD).

The patients were grouped according to the characteristics and the sites of metastases. Group I included 928 patients without metastasis. Group II, OMBD group, included 68 patients. Group III, widespread metastasis group, consisted of 185 patients with multiple bone metastases and/or solid organ metastases.

The mean overall survival of the groups were 16.7 ± 0.3 years in Group 1, and 7.8 ± 0.8 and 5.9 ± 0.4 years in Group 2 and 3, respectively (p<0.001 for the comparison of all three groups together; p <0.001 for Group 1 vs 2 & 3) and (p=0.037 for Group 2 vs. Group 3). In the subgroup survival analysis of patients in Group 2 (OMBD), the mean and median survival were 5.5 ± 0.8 and 4.0±0.8 years versus 9.2 ± 0.98 and 9.0 ±1.05 years in more than one bone metastasis and SBM patients, respectively (p = 0.019).

As a result; OMBD seems to be a different disease than breast cancer with isolated bone metastases. The high risk of developing OMBD especially following locoregional recurrences increases the importance of locoregional therapy in large T and N stage tumors.

Introduction

Breast carcinoma is a tumor with osteotropic potential and the most common cause of carcinoma-related deaths in women [1, 2]. Indeed, nearly 70% of the patients dying of breast cancer have evidence of metastatic bone disease at autopsy [3]. The models for predicting the effect of variables on breast cancer mortality have estimated a median of 19 percent reduction attributable to adjuvant therapy alone [4]. Besides, in a recently updated study, the addition of targeted therapies to a chemotherapeutic agent have improved median overall survival (OS) up to 56.5 months in patients with HER2-positive metastatic breast cancer [5]. The survival outcomes of stage IV breast cancer patients vary according to metastatic site and those with bone metastasis have the best survival [6]. In this context, oligometastatic breast cancer (OMBC) generally refers a special group of patients with less than five metastatic deposits in a single organ and is considering potentially curable stage IV disease [7]. However, the definition of OMBC in the literature varies according to the number and location of metastasis [8]. It is still uncertain whether OMBC corresponds to an intermediate stage between a localized disease and a widespread disease or a genetically unique entity rather than a transition point from primary tumor to metastasis [9].

In this study, with inspiration from the current literature and our previous publication about clinicopathologic features of single bone metastasis in breast cancer [10], we planned to investigate the clinical course of breast cancer patients with oligometastatic bone disease (OMBD). We evaluated demographic features of patients, histopathologic features with intrinsic subtypes of tumors and treatment-related factors on “survival outcomes” among non-metastatic group (Group I), OMBD group (Group II), and widespread metastatic group included patients with solid organ metastases with or
without bone metastasis (Group III). (Fig. 1) Also, we aimed to determine the common characteristics of the patients with solitary (only one) and oligo (more than 1 but less than or equal 5) bone metastasis in OMBD group by evaluating them in terms of clinico-pathological factors and survival outcomes. For this purpose, a sub-group analysis was conducted to compare two strata of the OMBD group (group II), comparing solitary bone metastatic patients (group IIa) with oligo bone metastatic patients (group IIb).

**Materials And Methods**

This retrospective cohort study was performed at the Izmir Bozyaka Health Practice and Research Center, University of Health Sciences Turkey and has been prepared for publication following the approval of the ethics committee on May 6, 2020. The study included patients with breast cancer operated between 2000 and 2020 at the Department of General Surgery. Those, who were between the ages of 23-92 years, have completed adjuvant therapy, had regular database and follow-ups, and followed up for at least 6 months were included.

There were a total of 1181 patients (1175 women, 6 men) in our series. The patients were grouped according to the characteristics and the sites of metastases. Group I included 928 patients without metastasis. Group II, OMBD group, included 68 patients. Group III, widespread metastasis group, consisted of 185 patients with multiple (more than six) bone metastases and/or solid organ metastases.

Between 2000 to 2015, we performed whole-body bone scintigraphy (B-scan) and/or magnetic resonance imaging (MRI) to determine bone metastases. After 2015, bone metastases were detected by B-scan and/or computed tomography and confirmed by 18-fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET)/CT method in all cases.

Beside radiological diagnoses, histopathological diagnoses of bone metastases were available in only 5 of 68 cases. Of these, two patients underwent bone biopsy, and three patients had had total excision of metastatic bone fragments of the pathological fractures.

The groups were compared in terms of demography, treatments applied, histopathological features and TNM stages of the American Joint Committee on Cancer (AJCC). In demographic factors, body mass index (BMI), smoking, family history, menopausal status, co-morbidity, hormone use were investigated. The history of hormone use described oral contraceptive (OC) drugs for pre-menopausal and estrogen-progesterone combinations in postmenopausal patients. Hormone replacement therapy (HRT) refers to regular hormone therapy taken at any time, up to the diagnosis of breast cancer. Co-morbidity in patients refers to hypertensive atherosclerotic heart disease, chronic obstructive pulmonary disease, congestive heart failure, cerebrovascular disease and autoimmune diseases. Treatment factors included the type of breast surgery (mastectomy-M, breast-conserving surgery-BCS), axillary intervention (axillary lymph node dissection-ALND, sentinel lymph-node biopsy-SLNB), neoadjuvant-CT (NACT), radiotherapy (RT) and hormone therapy (HT). Histopathological features and staging explain tumor localization, histological and nuclear grade, mitotic activity, perinodal involvement, receptor status, cerb2, e-cadherin, p53, Ki67,
lymph-vessel invasion, molecular classification (luminal A-B, triple negative, HER2(+), TNM staging and local recurrence.

Molecular subtypes of breast cancer are defined as follows:

Luminal A: Hormone-receptor positive (HR + / estrogen-receptor and / or progesterone-receptor positive), HER2 negative, low Ki-67 levels and nuclear grade (Grade I).

Luminal B: HR + and HER2 positive or HR + with high Ki-67 levels but HER2 negative. Nuclear grade is moderate or high (Grade II-III).

Triple-negative / basal-like: HR negative and HER2 negative. Nuclear grade is moderate or high (Grade II-III).

HER2-enriched: HR negative and HER2 positive. Nuclear grade is high (Grade-III).

STATISTICS

In univariate analyzes, the patients in three groups were compared using the chi-square test for categorical variables and the Student-t test for continuous variables. Two separate logistic regression models were developed using backward likelihood ratio method with variables found significant in univariate analyzes, one exploring independent factors associated with isolated and/or oligo-bone metastasis (group II), and the other predicting independent risk factors of multiple bone metastases and/or solid organ metastases (group III), both compared to the non-metastatic group (group I). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each possible determinant adjusted for other variables in the model. Survival times and survival curves were calculated and plotted using Kaplan-Meier analysis. Also, single bone metastatic patients were compared with more than one bone metastatic patients in terms of survival outcomes with chi-square, Student's T and Mann-Whitney U tests.

A p-value less than 0.05 was considered significant.

Results

There was no significant difference in the history and demographic parameters except for tumor markers (Table 1). CEA and CA 15 – 3 values were statistically significantly different between the groups.
### Table 1
Demographics and History

| DEMOGRAPHICS & HISTORY | Group 1 | Group 2 | Group 3 | p   |
|------------------------|---------|---------|---------|-----|
| Age                    | Median (Range) | 54 (23–92) | 51,5 (28–82) | 51 (24–84) | 0.086 |
| BMI                    | n (%)   | 5 (0.8) | 1 (2.3)  | 3 (2.9)   | 0.476 |
| Underweight            |         | 155 (25.3) | 10 (22.7)  | 23 (22.7) |       |
| Normal                 |         | 226 (36.9) | 17 (38.6)  | 44 (42.7) |       |
| Overweight             |         | 227 (37.0) | 16 (36.4)  | 33 (32.0) |       |
| Obese                  |         |         |         |         |       |
| BMI                    | Median (Range) | 28.3 (14.9–51.3) | 27.8 (18.3–44.3) | 27.8 (16.5–48.3) | 0.737 |
| Smoking                | n (%)   | 471 (65.1) | 38 (76.0)  | 82 (66.1) | 0.287 |
| No                     |         | 253 (34.9) | 12 (24.0)  | 42 (33.9) |       |
| Yes                    |         |         |         |         |       |
| Hormone Use            | n %     | 407 (52.9) | 30 (60.0)  | 80 (63.5) | 0.064 |
| No                     |         | 164 (21.3) | 15 (30.0)  | 24 (19.0) |       |
| OC or HRT              |         | 145 (18.9) | 4 (8.0)  | 17 (13.5) |       |
| OC                     |         | 31 (4.0)  | 0 (0)  | 5 (4.0)  |       |
| HRT                    |         | 22 (2.9)  | 1 (2.0)  | 0 (0)  |       |
| OC + HRT               |         |         |         |         |       |
| Diabetes               | n %     | 684 (84.4) | 51 (89.5)  | 116 (86.6) | 0.509 |
| No                     |         | 126 (15.6) | 6 (10.5)  | 18 (13.4) |       |
| Yes                    |         |         |         |         |       |
| Comorbid Disease       | n %     | 221 (47.5) | 15 (60.0)  | 30 (48.4) | 0.477 |
| No                     |         | 244 (52.5) | 10 (40.0)  | 32 (51.6) |       |
| Yes                    |         |         |         |         |       |
| Family History         | n %     | 607 (77.1) | 45 (83.3)  | 98 (76.0) | 0.531 |
| No                     |         | 180 (22.9) | 9 (16.7)  | 31 (24.0) |       |
| Yes                    |         |         |         |         |       |

Abbreviations: BMI: Body mass index, OC: oral contraceptives, HRT: hormone replacement therapy.
| DEMOGRAPHICS & HISTORY | Group 1 | Group 2 | Group 3 | p    |
|------------------------|---------|---------|---------|------|
| Menopausal Status      | n %     |         |         |      |
| Premenopausal          | 329 (36,3) | 27 (40,3) | 72 (41,4) | 0,161 |
| Postmenopausal         | 573 (63,3) | 40 (59,7) | 99 (56,9) |
| Male                   | 3 (0,4)  | 0 (0)   | 3 (1,7)  |
| CEA                    | Median (Range) | 1,7(0,2–56,2) | 2,0(0,4–26,1) | 2,2(0,2-312,1) | < 0,001 |
| CA15-3                 | Median (Range) | 15,1(0,5-333,7) | 18,2(4-127,1) | 20,1(5,8-698,5) | < 0,001 |

Abbreviations: BMI: Body mass index, OC: oral contraceptives, HRT: hormone replacement therapy.

The surgical treatment applied is presented comparatively in Table 2. Breast conserving surgery (BCS) was performed more frequently in patients in Group 1 (44.5%) than in group 2 (13.2%) and 3 (11.9%) (p < 0.001). Mastectomy was performed mostly on patients with OBMD. The proportion of patients who underwent SLNB was 36.6% in group 1, 13.2% in group 2 and 9.2% in group 3 (p < 0.001). ALND was applied mostly to patients with oligo-bone metastasis (Group 2) and SLNB to non-metastatic patients (Group 1).
Table 2
Surgical Treatment Methods

|                                | Group 1 | Group 2 | Group 3 | p      |
|--------------------------------|---------|---------|---------|--------|
| **Type of Breast Surgery**     | n (%)   |         |         |        |
| None                           | 8 (0,9) | 6 (8,8) | 36 (19,5) | < 0,001 |
| Mastectomy                     | 507 (54,6) | 53 (77,9) | 127 (68,6) |        |
| Breast-conserving surgery      | 413 (44,5) | 9 (13,2) | 22 (11,9) |        |
| **Axillary surgery**           | n (%)   |         |         |        |
| None                           | 16 (1,7) | 8 (11,8) | 39 (21,2) | < 0,001 |
| ALND                           | 433 (46,7) | 49 (72,1) | 112 (60,9) |        |
| SLNB                           | 339 (36,6) | 9 (13,2) | 17 (9,2) |        |
| SLNB + ALND                    | 139 (15,0) | 2 (2,9) | 16 (8,7) |        |
| **SLNB method**                | n (%)   |         |         |        |
| İsosulfan Blue                 | 67 (14,2) | 4 (30,8) | 6 (17,1) | 0,487 |
| Radiocolloid                   | 93 (19,7) | 3 (23,1) | 6 (17,1) |        |
| Combined                       | 312 (66,1) | 6 (46,2) | 23 (65,7) |        |
| **Tumor size (cm)**            | Median (Range) | 2,2 (0–16) | 3 (0–16) | 3 (0–14) | < 0,001 |
| **No. of positive SLNs**       | Median (Range) | 0 (0–11) | 0 (0–6) | 1 (0–7) | 0,049 |
| **Number of SLNs removed**     | Median (Range) | 4 (0–12) | 3 (0–8) | 4 (1–16) | 0,471 |
| **No. of lymph nodes removed by ALND** | Median (Range) | 15 (1–71) | 17 (1–53) | 18 (0–57) | 0,001 |
| **No. of positive nodes in ALND** | Median (Range) | 0 (0–44) | 6 (0–32) | 4 (0–51) | < 0,001 |
| **Perinodal Involvement**      | n (%)   |         |         |        |
| No                             | 514 (79,0) | 22 (47,8) | 52 (57,8) | < 0,001 |
| Yes                            | 137 (21,0) | 24 (52,2) | 38 (42,2) |        |

Abbreviations: ALND: Axillary Lymph Node Dissection, SLNB: Sentinel Lymph Node Dissection

After ALND, the number of metastatic lymph nodes was 0 (0–44) in group 1, 6.0 (0–32) in group 2, and 4 (0–51) in group 3 (p < 0.001).
The median tumor size was 2.2cm. (0–16) in Group 1, 3.0 cm. in Group 2 (0.7–16) and Group 3. (0–14) (p < 0.001).

The protocol and efficacy of adjuvant and neoadjuvant treatment on the groups are shown in Table 3.

| SYSTEMIC THERAPIES | Group 1 | Group 2 | Group 3 | p     |
|--------------------|---------|---------|---------|-------|
| Neoadjuvant Treatment (NAT) | n (%)   |         |         |       |
| No                 | 822 (88,6) | 61 (89,7) | 147 (79,5) | 0,003 |
| Yes                | 106 (11,4) | 7 (10,3)  | 38 (20,5)  |       |
| Response to NAT    | n (%)   |         |         |       |
| No                 | 8 (8,8)  | 4 (66,7) | 6 (17,6) | NA    |
| Partial            | 54 (59,3) | 2 (33,3) | 27 (79,4) |       |
| Almost Complete    | 14 (15,4) | 0 (0)    | 1 (2,9)  |       |
| Complete           | 15 (16,5) | 0 (0)    | 0 (0)    |       |
| Adjuvant CT        | n (%)   |         |         |       |
| No                 | 225 (29,6) | 16 (27,6) | 61 (38,9) | NA    |
| Taxane and/or AC   | 517 (67,9) | 41 (70,7) | 92 (58,6) |       |
| CMF                | 8 (1,1)  | 0 (0)    | 1 (0,6)  |       |
| Other              | 11 (1,4) | 1 (1,7)  | 3 (1,9)  |       |
| GCSF use           | n (%)   |         |         |       |
| No                 | 285 (62,9) | 29 (70,7) | 54 (62,1) | 0,588 |
| Yes                | 168 (37,1) | 12 (29,3) | 33 (37,9) |       |
| Radiotherapy       | n (%)   |         |         |       |
| No                 | 193 (22,6) | 16 (26,7) | 43 (30,9) | 0,088 |
| Yes                | 662 (77,4) | 44 (73,3) | 96 (69,1) |       |
| Hormonotherapy     | n (%)   |         |         |       |
| No                 | 175 (20,2) | 21 (31,8) | 72 (44,2) | < 0,001|
| Tmx                | 248 (28,7) | 17 (25,8) | 45 (27,6) |       |
| Aromatase Inh.     | 398 (46,0) | 25 (37,9) | 40 (24,5) |       |
| Switch             | 44 (5,1)  | 3 (4,5)  | 6 (3,7)  |       |

Abbreviations: NA: Not available, CT: Chemotherapy
Neoadjuvant chemotherapy (NACT) was applied mostly to patients in Group 3 ($p = 0.003$). The percentage of patients who received hormonotherapy after the operation was 79.8% in group 1, 68.2% in group 2 and 55.8% in group 3 ($p < 0.001$).

The histopathological features of the tumor are compared in Table 4.
| HISTOPATHOLOGICAL FEATURES | Group 1 | Group 2 | Group 3 | p       |
|---------------------------|---------|---------|---------|---------|
|                           | N (%)   | N (%)   | N %     |         |
| No. of tumor              |         |         |         |         |
| Single                    | 776 (89,7) | 48 (82,8) | 137 (81,5) | 0,019   |
| Multiple                  | 85 (9,8) | 9 (15,5) | 30 (17,9) |         |
| Inflammatory              | 4 (0,5) | 1 (1,7) | 1 (0,6) |         |
| Carcinoma In situ         | n (%)   |         |         |         |
| Yes                       | 346 (46,6) | 23 (44,2) | 42 (38,5) | 0,285   |
| No                        | 397 (53,4) | 29 (55,8) | 67 (61,5) |         |
| Histology                 | n (%)   |         |         |         |
| IDC                       | 722 (77,8) | 43 (63,2) | 151 (81,6) | <0,001  |
| ILC                       | 73 (7,9) | 10 (14,7) | 13 (7,0) |         |
| Mixed                     | 50 (5,4) | 12 (17,6) | 10 (5,4) |         |
| Other                     | 83 (8,9) | 3 (4,4) | 11 (5,9) |         |
| Histological Grade        | n (%)   |         |         |         |
| 1                         | 78 (10,6) | 2 (4,1) | 2 (1,6) | 0,004   |
| 2                         | 451 (61,0) | 31 (63,3) | 76 (59,4) |         |
| 3                         | 210 (28,4) | 16 (32,7) | 50 (39,1) |         |
| Nuclear Grade             | n (%)   |         |         |         |
| 1                         | 37 (6,0) | 2 (5,3) | 2 (2,2) | 0,274   |
| 2                         | 420 (67,7) | 23 (60,5) | 56 (62,9) |         |
| 3                         | 163 (26,3) | 13 (34,2) | 31 (34,8) |         |
| Mitosis                   | n (%)   |         |         |         |
| 1                         | 153 (25,5) | 14 (37,8) | 15 (17,0) | 0,006   |
| 2                         | 370 (61,8) | 17 (45,9) | 51 (58,0) |         |
| 3                         | 76 (12,7) | 6 (16,2) | 22 (25,0) |         |

Abbreviations: IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, ER: Estrogen Receptor, PR: Progesterone Receptor
| HISTOPATHOLOGICAL FEATURES | Group 1 N (%) | Group 2 N (%) | Group 3 N % | p |
|---------------------------|---------------|---------------|-------------|---|
| ER n (%)                  | 243 (27,0)    | 20 (30,3)     | 74 (41,3)   | 0,002 |
| Neg                       | 135 (15,0)    | 8 (12,1)      | 28 (15,6)   |     |
| 1+                        | 168 (18,7)    | 16 (24,2)     | 32 (17,9)   |     |
| 2++                       | 354 (39,3)    | 22 (33,3)     | 45 (25,1)   |     |
| 3+++                      |               |               |             |     |
| Percentage of ER Median (Min-Max) | 80 (1-100) | 70 (5-100) | 70 (2-100) | 0,139 |
| PR n (%)                  | 271 (30,3)    | 23 (34,3)     | 65 (37,1)   | 0,03 |
| Neg                       | 158 (17,7)    | 15 (22,4)     | 43 (24,6)   |     |
| 1+                        | 153 (17,1)    | 13 (19,4)     | 30 (17,1)   |     |
| 2++                       | 312 (34,9)    | 16 (23,9)     | 37 (21,1)   |     |
| 3+++                      |               |               |             |     |
| Percentage of PR Median (Min-Max) | 60 (0-100) | 50 (0-100) | 50 (1-100) | 0,003 |
| cerbB2 n (%)              | 569 (77,4)    | 40 (75,5)     | 94 (67,6)   | 0,047 |
| Negative                  | 166 (22,6)    | 13 (24,5)     | 45 (32,4)   |     |
| Positive                  |               |               |             |     |
| P53 n (%)                 | 312 (40,1)    | 27 (44,3)     | 74 (50,7)   | 0,053 |
| Negative                  | 467 (59,9)    | 34 (55,7)     | 72 (49,3)   |     |
| Positive                  |               |               |             |     |
| Ki67 n (%)                | 439 (58,1)    | 26 (49,1)     | 61 (44,9)   | 0,01 |
| ≤%14                      | 316 (41,9)    | 27 (50,9)     | 75 (55,1)   |     |
| >%14                      |               |               |             |     |
| Percentage of Ki67 Median (Min-Max) | 15 (1–90) | 15 (1–80) | 25 (1–90) | < 0,001 |
| e-cadherine n (%)         | 38 (9,9)      | 3 (13,0)      | 5 (8,5)     | 0,823 |
| Negative                  | 344 (90,1)    | 20 (87,0)     | 54 (91,5)   |     |
| Positive                  |               |               |             |     |

Abbreviations: IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, ER: Estrogen Receptor, PR: Progestrone Receptor
| HISTOPATHOLOGICAL FEATURES                      | Group 1 N (%) | Group 2 N (%) | Group 3 N % | p       |
|------------------------------------------------|---------------|---------------|------------|---------|
| Lymph vessel invasion                           | 515 (76,9)    | 19 (42,2)     | 47 (48,0)  | < 0,001 |
| No                                             | 155 (23,1)    | 26 (57,8)     | 51 (52,0)  |         |
| Yes                                            |               |               |            |         |
| Blood vessel invasion                           | 558 (83,3)    | 32 (69,6)     | 62 (67,4)  | < 0,001 |
| No                                             | 112 (16,7)    | 14 (30,4)     | 30 (32,6)  |         |
| Yes                                            |               |               |            |         |
| Molecular classification                        | 319 (37,2)    | 20 (31,3)     | 36 (21,4)  | 0,003   |
| Luminal A                                      | 364 (42,4)    | 30 (46,9)     | 79 (47,0)  |         |
| Luminal B                                      | 112 (13,1)    | 10 (15,6)     | 33 (19,6)  |         |
| Triple negative                                 | 63 (7,3)      | 4 (6,3)       | 20 (11,9)  |         |
| Her- 2 enriched                                 |               |               |            |         |

Abbreviations: IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, ER: Estrogen Receptor, PR: Progestrone Receptor

The percentage of mixed-type tumor histology was 5.4% in group 1 and 3 and, 17.6% in group 2. ILC and mixed type tumors were more common in patients with oligo-bone metastasis (p < 0.001).

ER-positivity was ≥ 70% in Group 1 and 2 but progressively decreased below 60% in Group 3 (p = 0.002). The percentage of progesterone receptor positivity was highest in Group 1 (60%) (p = 0.003). The median value of Ki67 was 25% in group 3 and was significantly higher compared to other groups (p < 0.001). The rate of lymphoid and blood vessel invasion was similar in Groups 2 and 3, and was significantly higher compared to Group 1 (p < 0.001).

In molecular classification; Luminal-A subtype was most common in non-metastatic patients (p = 0.003) with a rate of 37.2%, whereas the incidence of Luminal-B subtype was similar in all three groups.

The staging of T (tumor size), N (nodal involvement) and cancer (TNM) were statistically different between the groups (p < 0.001) (Table 5). T1-T2 tumor and N0-N1 lymph node were most common in non-metastatic patients (group 1), while T3-T4 tumor was most common in patients with oligo-bone metastases (group 2).
Table 5
Comparison of Cancer Stages According To TNM Classification

| STAGE (TNM) | Group 1 n (%) | Group 2 n (%) | Group 3 n % | P     |
|-------------|---------------|---------------|-------------|-------|
| T1          | 402 (46,5)    | 21 (36,2)     | 65 (47,4)   |       |
| T2          | 41 (4,7)      | 13 (22,4)     | 14 (10,2)   |       |
| T3          | 27 (3,1)      | 13 (22,4)     | 23 (16,8)   |       |
| T4          |               |               |             |       |
| N0          | 462 (51,5)    | 12 (20,3)     | 37 (25,9)   | < 0,001|
| N1          | 262 (29,2)    | 13 (22,0)     | 32 (22,4)   |       |
| N2          | 109 (12,2)    | 14 (23,7)     | 39 (27,3)   |       |
| N3          | 64 (7,1)      | 20 (33,9)     | 35 (24,5)   |       |
| Stage 1     | 259 (30,5)    | 7 (11,1)      | 12 (7,3)    | < 0,001|
| Stage 2     | 401 (47,2)    | 12 (19,0)     | 38 (23,2)   |       |
| Stage 3     | 189 (22,3)    | 29 (46,0)     | 62 (37,8)   |       |
| Stage 4     | 0 (0,0)       | 15 (23,9)     | 52 (31,7)   |       |

All demographic, treatment-specific, histopathological and molecular variables which have statistical significance in univariate analysis were re-evaluated in multivariate logistic regression analysis.

The parameters that were statistically significantly different between the patients in Group 1 and 3, were evaluated in the multiple regression analysis. (Table 6). Those with a negative impact on Group 1 patients were as follows:
Table 6
Multivariate Logistic Regression Analysis of Demographic, Therapeutic and Histopathological Parameters Between Group 1 & 3.

| Parameter                                | B   | Sig. | Exp(B)   | 95% C.I.for EXP(B) |
|------------------------------------------|-----|------|----------|--------------------|
| CEA (continuous)                         | .052| .006 | 1.053    | 1.015–1.093        |
| Tumor size (cm) (continuous)             | .155| .009 | 1.168    | 1.040–1.311        |
| No NACT (ref.)                           |     | .134 | 1        |                    |
| No Response to NACT                      | 22.897 | 1.000 | 8788932664.350 | 0.000-             |
| Partial response to NACT                 | .842| .021 | 2.320    | 1.137–4.734        |
| Complete response to NACT                | -.396| .707 | .673     | 0.086–5.296        |
| ER-negative (ref.)                       |     | .028 | 1        |                    |
| ER(+)                                    | -.632| .086 | .531     | 0.258–1.094        |
| ER(++)                                   | -.490| .154 | .613     | 0.312–1.202        |
| ER(+++)                                  | -.841| .004 | .431     | 0.245–0.759        |
| N0 (ref.)                                |     | .000 | 1        |                    |
| N1                                       | .200| .521 | 1.221    | 0.663–2.249        |
| N2                                       | 1.118| .001 | 3.058    | 1.591–5.878        |
| N3                                       | 1.291| .000 | 3.635    | 1.790–7.379        |
| No local recurrence (ref.)               |     | .052 | 1        |                    |
| Recurrence in the opposite breast        | .578| .316 | 1.782    | 0.575–5.519        |
| Locoregional recurrence                  | 1.283| .024 | 3.609    | 1.188–10.964       |
| Constant                                 | -2.736| .000 | .065     |                    |

Abbreviations: NACT: neoadjuvant chemotherapy, N: nodal involvement

Every 1 unit rise of CEA value and every 1 cm increase in tumor size enhances the risk of multimetastasis by 1.05 and 1.17 times. These significant increases in risk were independent from neoadjuvant therapy, ER, N, and local recurrence variables in the model. Also, for Group 1, the risk of multimetastatic disease increases 2.3 times in patients with partial response to neoadjuvant therapy, 3.1 and 3.64 times in patients with N2 and N3 nodal involvement, and 3.6 times in patients who develop loco-regional recurrence. On the other hand, Group 1 patients with ER (+++) positive tumors were protected 0.43 times from the risk of multimetastasis.

Multivariate logistic regression analysis of demographic, therapeutic and histopathological parameters between Group 1 & 2 is shown in Table 7. For the patients in Group 1; the risk of OMBD increased 7.7 and
5.4 times in patients with T3 and T4 tumors, and 2.7 times in those with perinodal invasion of the primary tumor. Also, every 1 unit rise of CEA value increased the risk of OMBD by 1.08 times. The most remarkable finding was the 68.3-fold increased risk of transition from nonmetastatic state to OMBD in patients who developed locoregional recurrence.

Table 7
Multivariate logistic regression analysis of demographic, therapeutic and histopathological parameters between Group 1 & 2

| Parameter                          | B    | Sig. | Exp(B) | 95% C.I. for EXP(B) |
|------------------------------------|------|------|--------|---------------------|
| CEA (continuous)                   | .077 | .014 | 1.081  | 1.016–1.149         |
| No HT (ref.)                       | .161 |      |        |                     |
| HT (Tamoxifen)                     | .121 | .859 | 1.129  | 0.297–4.288         |
| HT (Aromatase Inhitor)             | .164 | .791 | 1.179  | 0.350–3.965         |
| HT (Switch)                        | 2.224| .035 | 9.248  | 1.164–73.475        |
| Perinodal invasion (ref. none)     | .984 | .043 | 2.675  | 1.033–6.929         |
| Lymphovascular invasion (ref. none)| .768 | .113 | 2.156  | 0.834–5.571         |
| T1 (ref.)                          |      |      |        |                     |
| T2                                 | .334 | .557 | 1.396  | 0.458–4.258         |
| T3                                 | 2.037| .004 | 7.670  | 1.591–30.539        |
| T4                                 | 1.678| .046 | 5.357  | 1.033–27.778        |
| No local recurrence (ref.)         |      |      |        | .000                |
| Recurrence in the opposite breast  | -18.737| .998 | .000  | 0.000–.             |
| Locoregional recurrence            | 4.224| .000 | 68.292 | 10.441–446.667      |
| Constant                           | -4627| .000 | .010  |                     |

Abbreviations: HT: Hormone Therapy, T: T category

As a result; T3-T4 tumor, perinodal tumor invasion and high CEA levels in patients without metastasis (Group 1) are factors that trigger the development of OMBD. The risk of OMBD increases 68 times in patients who develop locoregional recurrence during follow-up.

In our series, we have 39 patients with single bone metastasis (SBM) and 29 patients with more than one bone metastasis. When these two strata of the OMBD group were compared, with the analysis being limited to the total number of patients (n: 68), no significant difference was found between them in terms of demographic, treatment-specific, histopathological and molecular variables.
The survival outcomes were statistically significantly different between the groups ($p < 0.001$). (Table 8)

| OVERALL SURVIVAL | Group 1  | Group 2  | Group 3  | $p$  |
|------------------|----------|----------|----------|------|
|                  | n (%)    | n (%)    | n %      |      |
| Deceased         | 136 (14.7) | 51 (75.0) | 141 (76.2) | $< 0.001$ |
| Alive            | 792 (85.3) | 17 (25.0) | 44 (23.8)  |      |

The mean and median follow-up for the whole study group were 14.1 ± 0.3 and 18.0 years. The mean overall survival of the groups were 16.7 ± 0.3 years in Group 1, and 7.8 ± 0.8 and 5.9 ± 0.4 years in Group 2 and 3, respectively ($p < 0.001$ for the comparison of all three groups together; $p < 0.001$ for Group 1 vs 2 & 3) and ($p = 0.037$ for Group 2 vs. Group 3). (Fig. 2)

In the subgroup survival analysis of patients in Group 2 (OMBD), the mean and median survival were 5.5 ± 0.8 and 4.0 ± 0.8 years versus 9.2 ± 0.98 and 9.0 ± 1.05 years in more than one bone metastasis and SBM patients, respectively ($p = 0.019$). (Fig. 3)

**Discussion**

In our previous study, we analyzed demographic, epidemiological, histopathological and intrinsic tumor subtype differences between 863 breast cancer (BC) patients without metastasis and 47 BC patients with single bone metastasis (SBM) ≥ 6 months after their first diagnosis. Among established risk factors, we studied twenty-nine variables and found that the risk of developing SBM was approximately 4.8 and 2.8 times higher in BC patients with TNM Stage III tumors and with mixed type (invasive ductal carcinoma + invasive lobular carcinoma) histology [10]. Following this study and again in our own patient series; we aimed to evaluate the patients without metastases and those with OMBD according to demographic, epidemiological, histopathological and intrinsic tumor subtypes. Thus, we planned to identify the common characteristics of patients with SBM and OMBD and to reveal whether OMBD is a different entity or a more aggressive form originating from isolated bone disease (SBM). Although ILC & mixed type tumors were found to be significantly higher in patients with OMBD (17.6% vs. 5.4%, $p < 0.001$) compared to other groups in univariate analysis, this feature lost its significance in multivariate regression analysis. In the present study study, the most important risk factors for the development of OMBD in the non-metastatic patient group were: T3-T4 tumor, perinodal tumor invasion, and particularly the postoperative locoregional recurrence. When we compare these results with our previous study [10]; the common feature in our patients with single bone metastasis and OMBD is the development of both following advanced stage tumors (Stage IIIA & B).

In 1995, Hellman and colleagues first described oligometastasis and suggested that at this stage the cancer has not yet reached its full metastatic potential and is restricted to certain regions [9]. In other
words; the concept of oligometastatic disease implies that few metastases, usually under five, may be present before tumor cells reach diffuse metastatic potential [11]. In this context, breast cancer patients with oligometastasis have so long been considered to have a disease with favorable course which should be treated with curative intent [12].

Herein, we examined the clinical course of oligometastatic patients in our large series of patients and compare the results with the literature. Our definition of OMBC is the presence of solitary or less than five detectable lesions limited to single organ amenable to local treatment with curative intent. Breast cancer patients with bone-only metastasis have pretty good prognosis with an average survival of 24–65 months after metastasis is detected [13–15]. In our study, the mean overall survival was 7.8 ± 0.8 years in the patient group with oligo-bone metastasis.

In our previous study on patients with isolated (single) bone metastases, the mean and median survival times were 9.9 and 7.0 years, respectively [10]. In the present study, the mean and median overall survival of patients with >1 bone metastasisi was 5.5 ± 0.8 and 4 years and is significantly lower than those with SBM (9.2 ± 0.98 and 9 years) (p = 0.019). This result indicates that BC patients with OMBD do not have similar outcome features and favourable prognosis as those with SBM.

Parkes et.al. achieved a similar result. They evaluated 1445 patients with bone-only metastasis followed for at least 6 months at MD Anderson Cancer Center from 1997 to 2015 and reported poorer overall survival (OS) in patients with multiple bone metastases (median OS, 4.80 years; 95% CI, 4.49–5.07) compared with single bone metastasis (median OS, 7.54 years; 95% CI, 6.28–10.10) [16]. In addition, in a systematic review examining prognostic factors upon survival in patients with oligometastatic breast cancer, solitary metastasis was associated with better overall survival [8]. Indeed, in a study of fifty patients with extracranial oligometastatic breast cancer, those with single metastasis were highly benefited from systemic chemotherapy and surgical resection and gained survival advantage with statistical significance [17].

Our study has several limitations. First of all, it is a single institute series. Although 43 prognostic and confounding factors were analyzed in depth in our study, the small number of patients with OMBD did not enable us to reveal the distinctive biological characteristics of these cases. With our own data, we were able to show that single bone metastatic disease and OMBD are not similar entities. However, we could not identify any molecular marker that would show whether a transition period existed between them.

**Conclusion**

As a result; OMBD seems to be a different disease than breast cancer with isolated bone metastases. The high risk of developing OMBD especially following locoregional recurrences increases the importance of locoregional therapy in large T and N stage tumors.
Larger case groups are needed to clarify whether these two subgroups, including patients with single and oligo-bone metastases, have different determinants.

**Declarations**

**Statements**

**Statement of Ethics**
Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (amended in October 2013).

The ethical approval for this study was obtained from University of Health Sciences Turkey, Izmir Bozyaka Health Practice and Research Center, Clinical Research Ethics Committee (Date: 12.05.2020 Decision no: 07).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Conflict of Interest Statement**

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

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**Author Contributions**

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**Final approval of manuscript:** All authors.

**Data Availability Statement**

The Data of all patients are kept by the corresponding author and are available through him.

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**Figures**
Figure 1

Patients Groups in This Study

GROUP I: non-metastatic group

- Non-metastatic pts. (n=928)

GROUP II: oligometastatic bone disease (OMBD) pts.

- Oligo-metastatic (1≤ and ≤5) bone disease (OMBD) pts. (n=68)
  - Group IIa: Solitary bone metastatic pts. (n=39)
  - Group IIb: Multiple (1< and ≤5) bone metastatic pts. (n=29)

GROUP III: Widespread metastatic pts.

- Widespread metastatic pts. (n=185)

GROUP III: Widespread metastatic disease = solid organ metastasis and/or multiple (more than five) bone metastasis group
Figure 2

The Overall Survival of Groups 1, 2 & 3.
Figure 3

Survival Outcomes of Patients with SBM and >1 Bone Metastasis.