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

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Research Article

Keywords: Breast Cancer, Oligometastasis, Bone Metastasis, Metastasis.

Posted Date: May 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-534885/v1

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, icluded 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 grup (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, icluded 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 fators 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 (22,3)	
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
Smokıng	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 %	329 (36,3)	27 (40,3)	72 (41,4)	0,161
Premenopausal		573 (63,3)	40 (59,7)	99 (56,9)	
Postmenopausal		3 (0,4)	0 (0)	3 (1,7)	
Male					
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 (%)	8 (0,9)	6 (8,8)	36 (19,5)	< 0,001
None		507 (54,6)	53 (77,9)	127 (68,6)	
Mastectomy		413 (44,5)	9 (13,2)	22 (11,9)	
Breast-conserving surgery					
Axillary surgery	n (%)	16 (1,7)	8 (11,8)	39 (21,2)	< 0,001
None		433 (46,7)	49 (72,1)	112 (60,9)	
ALND		339 (36,6)	9 (13,2)	17 (9,2)	
SLNB		139 (15,0)	2 (2,9)	16 (8,7)	
SLNB + ALND					
SLNB method	n (%)	67 (14,2)	4 (30,8)	6 (17,1)	0,487
İsosulfan Blue		93 (19,7)	3 (23,1)	6 (17,1)	
Radiocolloid		312 (66,1)	6 (46,2)	23 (65,7)	
Combined					
Tumor size (cm)	Median (Range)	2,2 (0–16)	3 (0,7–16)	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 (%)	514 (79,0)	22 (47,8)	52 (57,8)	< 0,001
No		137 (21,0)	24 (52,2)	38 (42,2)	
Yes					
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.

Table 3
Adjuvant and Neoadjuvant Treatment of The Groups

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

Table 4
The Histopathological Features of The Tumor

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

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
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	n (%)	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	n (%)	558 (83,3)	32 (69,6)	62 (67,4)	< 0,001
No		112 (16,7)	14 (30,4)	30 (32,6)	
Yes					
Molecular classification	n (%)	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	Group 1 n (%)	Group 2 n (%)	Group 3 n %	P
T (TNM)	395 (45,7)	11 (19,0)	35 (25,5)	< 0,001
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				
N (TNM)	462 (51,5)	12 (20,3)	37 (25,9)	< 0,001
N0	262 (29,2)	13 (22,0)	32 (22,4)	
N1	109 (12,2)	14 (23,7)	39 (27,3)	
N2	64 (7,1)	20 (33,9)	35 (24,5)	
N3				
Stage (TNM)	259 (30,5)	7 (11,1)	12 (7,3)	< 0,001
Stage 1	401 (47,2)	12 (19,0)	38 (23,2)	
Stage 2	189 (22,3)	29 (46,0)	62 (37,8)	
Stage 3	0 (0,0)	15 (23,9)	52 (31,7)	
Stage 4				

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.)*		.010		
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)

Table 8
Survival Outcomes

OVERALL SURVIVAL	Group 1 n (%)	Group 2 n (%)	Group 3 n %	p
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.

Funding Sources

The authors declared that this study has received no funding.

Author Contributions

Conception/design: B. Z., A. U., M. Kil.

Provision of study material or patients: B. Z., F. T., D. C.

Collection and/or assembly of data: B. Z., C. S., M. Kar.

Data analysis and interpretation: B. Z., R. D., F. T., O. O., A. U., K. K. B.

Manuscript writing: A. U., B. Z., M. Kil.

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

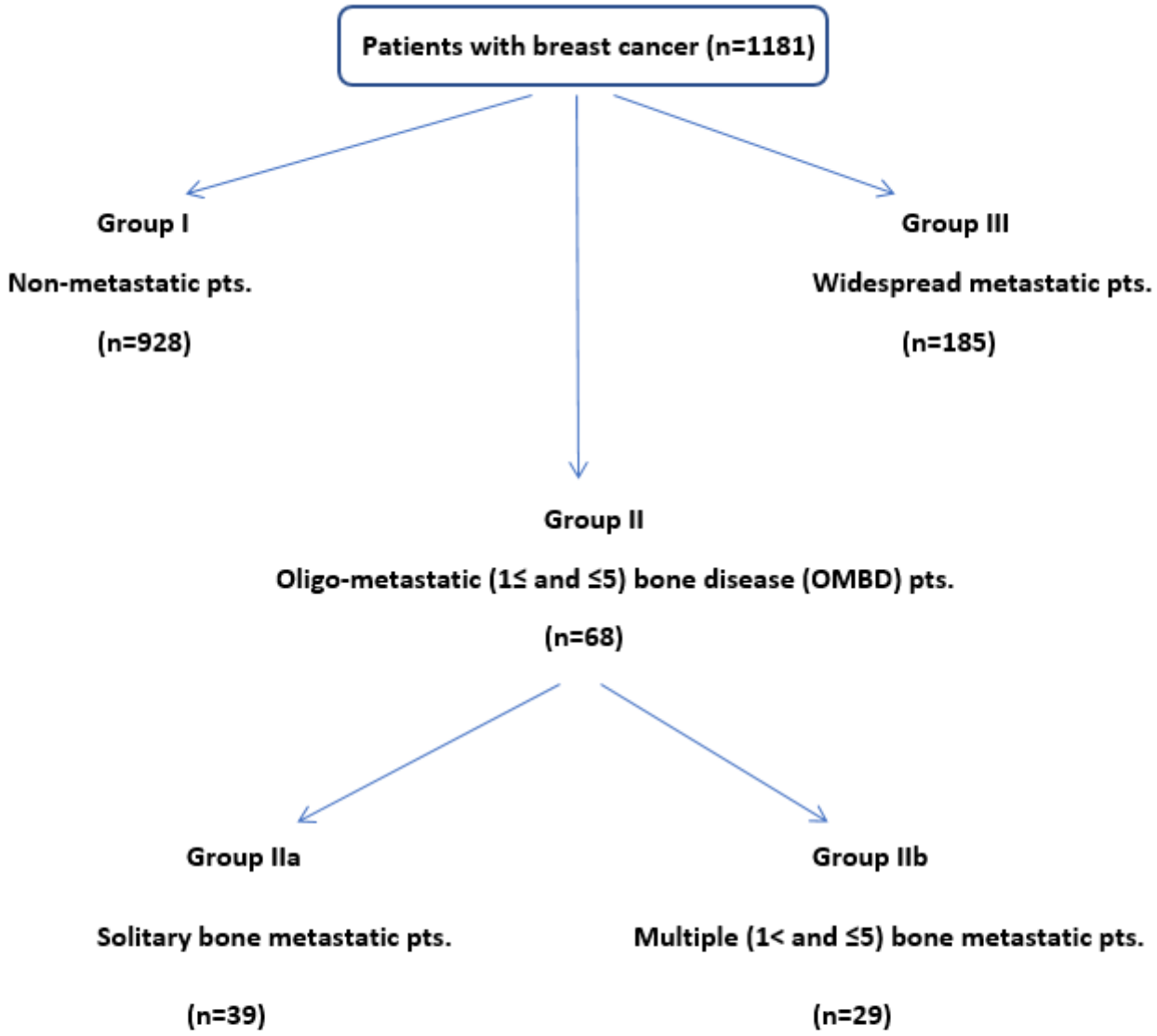

Figure 1

Patients Groups in This Study GROUP I: non-metastatic group GROUP II: oligometastatic bone disease (OMBD) = oligo-bone metastasis group = isolated bone metastases (IBM) IIa) Solitary bone metastatic patients = Only one bone met. IIb) Oligo bone met. patients = More than one but less than five bone met. GROUP III: Widespread metastatic disease = solid organ metastasis and/or multiple (more than five) bone metastasis group

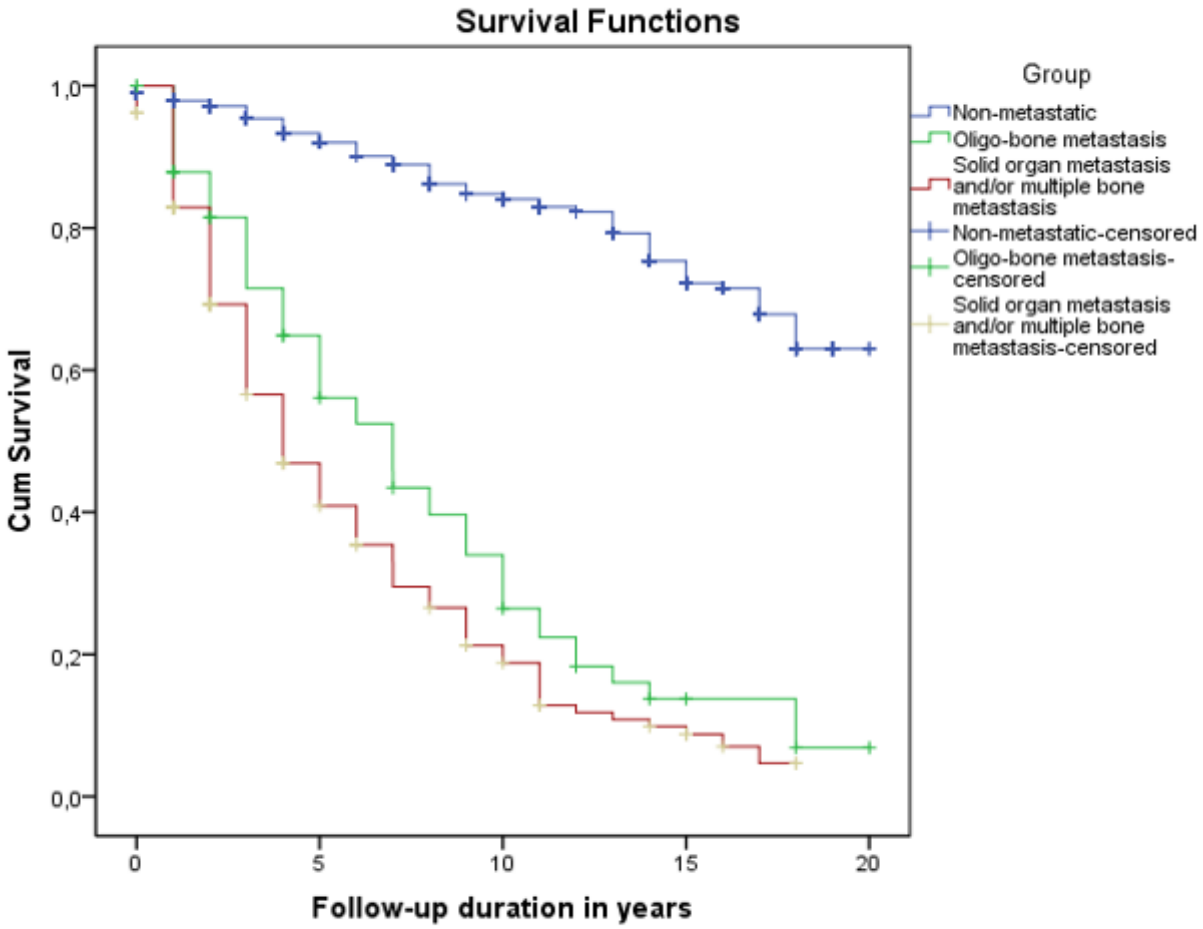

Figure 2

The Overall Survival of Groups 1, 2 & 3.

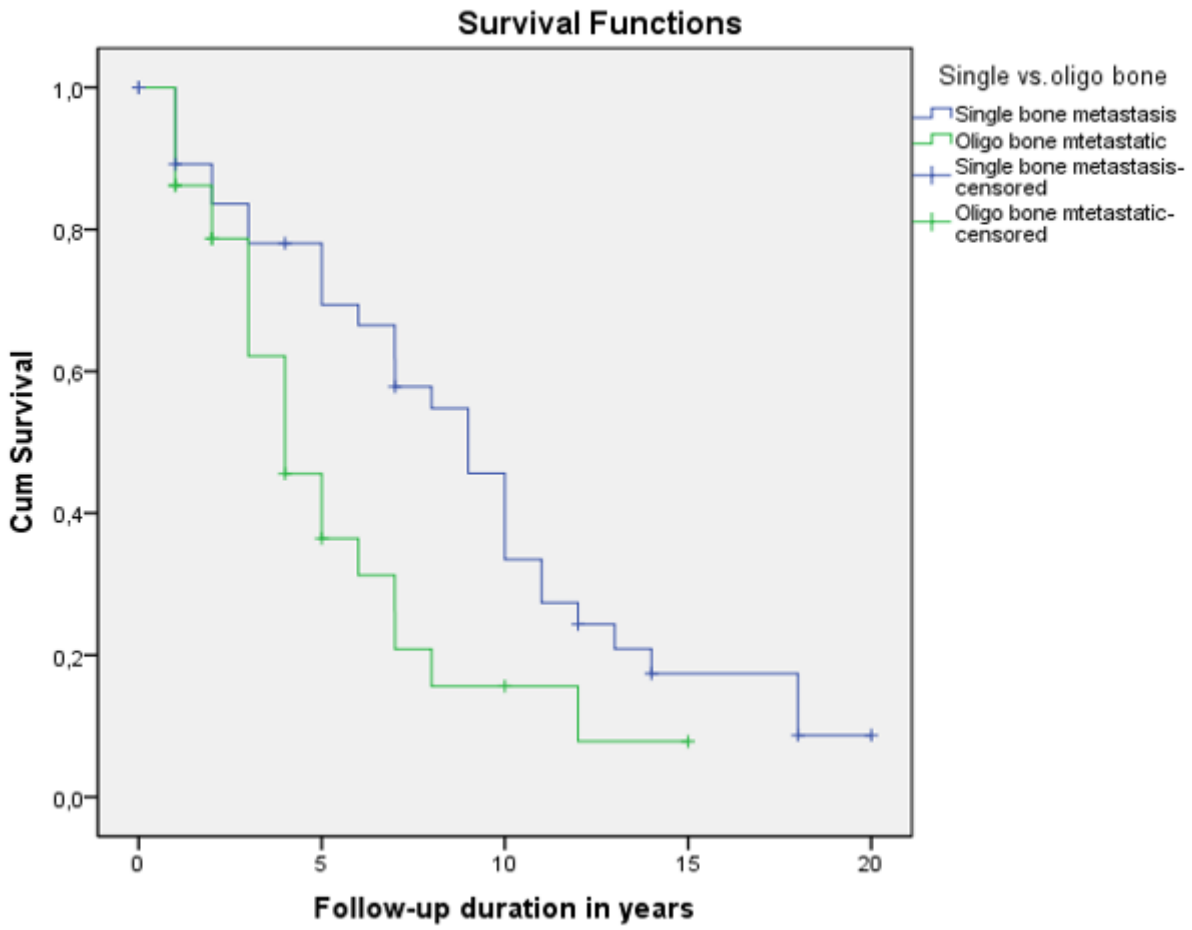

Figure 3

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