The Importance of Multifocal/Multicentric Tumor on the Disease-Free Survival of Breast Cancer Patients

Single Center Experience

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Objectives: Multifocal/multicentric breast cancers have been comprehensively studied and their outcomes have been compared with unifocal tumors. We evaluated the impact of multifocality and multicentricity on the disease-free survival (DFS) and overall survival of breast cancer patients and tried to analyze the correlation between multifocality/multicentricity (M/M) and other prognostic factors.

Material and Methods: Between 1994 and 2009, we analyzed retrospectively 697 breast cancer patients. Multicentric and multifocal breast cancer were defined as the presence of 2 or more invasive tumor foci within the different quadrants of the same breast or within a same quadrant of the breast, respectively. M/M and other prognostic factors were evaluated using univariate and multivariate analyses.

Results: Multifocal/multicentric tumors were seen in 107 (15.4%) of the 697 breast cancer patients. pT and pN stage were related with the presence of multifocal/multicentric tumors. As tumor size increased and the number of axillary lymph nodes metastasis increased, the incidence of M/M increased significantly ($P=0.003$ vs. $P=0.02$, respectively). Overall, the median DFS time of patients with multifocal/multicentric tumors was significantly worse than that of the unifocal tumors (55 vs. 137 mo, $P<0.001$). Multivariate analysis showed that the presence of M/M was the most important prognostic factor for DFS ($P=0.001$, hazard ratio (HR): 0.33; 95% confidence interval (CI), 0.18-0.58), as were pN stage and extracapsular extension of the tumor ($P=0.01$, HR: 1.74; 95% CI, 1.13-2.69) ($P=0.03$, HR: 1.9; 95% CI, 1.04-3.47, respectively). M/M were not also statistically significant prognostic factors in breast cancer for overall survival ($P=0.06$).

Conclusions: M/M imparts an unfavorable prognosis on the DFS of breast cancer patients in comparison to unifocal tumors and the presence of multifocal/multicentric tumors were associated with advanced pT and pN stages.

Key Words: multicentricity, multifocality, breast cancer, disease-free survival

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Breast cancer is the leading cause of cancer-related death for women.[1] Tumor size, axillary lymph node (ALN) involvement, hormone receptor status, and histologic grade have all been reported as important prognostic factors for overall survival (OS) in breast cancer.[2–5] In unifocal breast cancer, the largest diameter of an invasive tumor has been considered in the pT staging.[6] Currently the American Joint Committee on Cancer recommends using the diameter of the largest tumor only when more than 1 tumor is present in the same breast.[6] Although multifocality/multicentricity (M/M) have been described as independent prognostic factors for breast cancer in several studies, the significance of this phenomenon is uncertain.[7,8] Multicentricity is accepted as more than 1 invasive tumor in different quadrant of the same breast, whereas multifocality has been defined as more than 1 invasive tumors located in the same quadrant of the breast.[9,10] In several reports, M/M breast tumors had a higher frequency of lymph node metastasis than unifocal tumors; therefore M/M tumors might show more aggressive behavior.[1,7]. The incidence of M/M tumors has been reported as 30% to 60%.[10,11] The aims of this study are to determine whether M/M influences disease-free survival (DFS) or OS of breast cancer patients and evaluate the relationship between prognostic factors and M/M tumors.

MATERIALS AND METHODS

From May 1994 to March 2009, 697 breast cancer patients followed in our oncology department at Dr Lutfi Kirdar Kartal Education and Research Hospital, were evaluated retrospectively. Breast cancer was diagnosed clinically in approximately 60% of the patients, whereas the others were diagnosed during screening. Breast ultrasonography and magnetic resonance imaging were performed for all patients preoperatively. Perioperative breast ultrasonography or mamography were not performed because these methods are not carried out routinely in our institution. All pathologic specimens that were sliced in 3 mm thickness were reevaluated by the same pathologist who was an expert in matters of breast cancer. All pT-stages were included. Patients with distant metastasis at diagnosis were excluded from the study. All patients included were surgically treated with modified radical mastectomy or breast conserving surgery (BCS) with ALN dissection or sentinel lymph node (SLN) sampling. In patients with SLN metastasis, ALN dissection was also performed. All patients were staged according to the American Joint Committee on Cancer (6th edition) tumor node metastasis staging manual.[6] The diameter of the largest tumor was also obtained for the pT stage of M/M tumors. Multicentric tumors were defined as 2 or more separate invasive tumors in different quadrant of the breast with a distance of at least 5 cm. Multifocal tumors were defined as more than 1 invasive tumors located in the same quadrant of the breast.[10] The minimum distance between the 2 tumors in multifocal tumors was

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accepted as 1 mm and ductal carcinoma in situ between the 2 tumors was not accepted as a bridge and ductal carcinoma in situ was excluded from the study. Because breast quadrants cannot always be distinctly separated on histologic grounds alone, M/M was used without distinction.

This study is a retrospective, observational, and review-based study of medical records of patients in our institution. Clinical information regarding age, operation type, tumor location, histopathology, tumor stage, tumor size, histologic grade, M/M, necrosis, lymph node involvement, extracapsular invasion of lymph nodes, perineural and lymphovascular invasion, hormone receptor status, c-erb-B overexpression, adjuvant chemotherapy, radiation therapy, hormonotherapy, trastuzumab therapy, responses to treatment, and survival were obtained from patient charts. Patients received adjuvant radiotherapy if they had undergone BCS or if they had ALN metastasis. In addition, patients with positive hormone receptors and c-erb-B overexpression received adjuvant hormonotherapy and trastuzumab therapy, respectively.

The patients with M/M tumors (n = 107) were compared with patients with unifocal tumors (n = 590) regarding known prognostic factors such as pT stage, pN stage, extracapsular invasion of lymph nodes, pathologic stage, menopausal status, necrosis, hormonal status, perineural, lymphovascular invasion. In addition, pT stage according to both the diameter of the largest tumor and the sum of the diameter of the all tumors were analyzed with respect to their OS and DFS, respectively.

Statistical Analysis

Statistical analyses were carried out using SPSS 17.0 (SPSS Inc., Chicago, IL) software. The relationship between M/M and the other clinicopathological features were analyzed using the χ^2 and Fisher exact tests. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. Median follow-up time was calculated as the median observation interval for all patients as the time from surgery to the last follow-up. DFS was defined as the time since surgery to the first evidence of relapse. In addition, OS was described as the time from diagnosis to the date of the patient's death or last known contact. Prognostic factors analyzed by univariate analysis were also evaluated with multivariate analysis using the Cox proportional hazards model to predict the risk factors for relapse. Multivariate P values were used to characterize the independence of these factors. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All P values were 2-sided in tests and P values $\leq$ to 0.05 were considered significant.

RESULTS

A total of 697 breast cancer patients were evaluated. The median age of patients was 49 years, ranging from 22 to 82 years, and 48.1% were premenopausal, whereas the remaining 51.9% were postmenopausal. Tumors of 341 patients were localized in the right breast (48.9%), tumors of 336 patients (48.2%) were in the left breast. Other 20 patients (2.9%) had bilateral tumor. While 418 patients underwent modified radical mastectomy (60.1%), BCS was performed in 278 patients (39.9%). ALN dissection was carried out for the majority of patients (86%), however the remaining 14% underwent SLN biopsy. Only 14 multicentric breast cancer patients underwent SLN dissection without any caveates. All patients had a histologically proven breast carcinoma. Almost 88.5% of patients had an invasive ductal carcinoma, and the remaining of them had invasive lobular (4.9%), mixed type (2.6%) and other types. The distribution of the patients according to the T stage was 35%, 51.5% 9.6%, and 3.9% for pT1, pT2, pT3, and pT4 respectively. Based on the ALN metastasis, 275 patients were pN0 (39.5%), 192 pN1 (27.5%), 151 pN2 (21.7%), and 76 pN3 (10.9%). The majority of the patients were staged pathologically as stage II (43.9%, 306 patients), followed by stage III (36%) and stage I (20.1%).

M/M tumors were detected in 107 patients (15.4%) following histopathological examination. Advanced pT and pN stages were closely associated with the presence of M/M tumors. As the size of the tumors and the number of positive ALNs increased, the presence of M/M tumors also increased ($P = 0.04$, $P<0.001$, respectively). Although, M/M tumors were seen more often in advanced stages of breast cancer (10.2% for stage I, 12.8% for stage II, 17.7% for stage III), this difference was not significant ($P = 0.1$).By contrast, no relationship between M/M tumors and menopausal status, operation type, histologic grade, lymphovascular, perineural or extracapsular invasion, necrosis, hormone receptor status, c-erb-B over-expression, and the presence of inflammatory breast cancer was detected. The associations between M/M tumors and other clinicopathological characteristics are shown in Table 1.

When using the aggregate size of the multifocal tumors, the pT stage of 33 of the 107 patients with M/M tumors changed. Thirteen became pT2 from pT1, whereas 20 of the 33 patients became pT3 from pT2. After univariate analysis was carried out for the subgroup of patients with M/M tumors only, the largest tumor diameter was shown to be a weak prognosticator for OS ($P = 0.05$), whereas aggregate tumor diameter was also mildly correlated with DFS ($P = 0.05$).

At a median follow-up of 26 months (range, 4 to 154 mo), 5-year DFS and OS were 73.6% and 94.1%, respectively. The median DFS time was 117.9 months (SD: 19.8, 95% CI, 78.9-156.8). Five-year DFS rate was 48.4% for patients with M/M tumors and, 77.5% for unifocal tumors. The median DFS interval for M/M and unifocal tumors were 55 months and 137.3 months, respectively ($P<0.001$) (Fig. 1). One hundred four patients had recurrent disease during follow-up, whereas 22 of them had local recurrence, 3 of them had contralateral breast cancer recurrence. Although the median OS time was not reached, the 5-year OS rate were 90.2% and 94.5% for M/M tumors and unifocal tumors, respectively ($P = 0.1$). In our study, patients who had received neoadjuvant chemotherapy were not excluded. Totally 52 patients received neoadjuvant chemotherapy and 11 of them had M/M tumor. Although the median DFS was 21.6 months for patients who did not receive neoadjuvant chemotherapy, patients treated with neoadjuvant chemotherapy displayed a median DFS of 7.9 months in M/M tumor groups ($P<0.001$). The median OS time was also significantly better in the patients who were not treated with neoadjuvant chemotherapy (2 y OS rate; 88.9% vs. 98.9%, respectively) ($P = 0.03$).

The presence of M/M was closely related with DFS ($P<0.001$). In addition, operation type ($P = 0.02$), histologic grade ($P = 0.007$), the presence of necrosis ($P = 0.03$), pT stage ($P<0.001$), pN stage ($P<0.001$), pathologic stage ($P<0.001$), the positivity of the estrogen ($P = 0.01$) and progesterone ($P<0.001$) receptors, and the presence of inflammatory breast cancer ($P<0.001$) were also found to be the important factors for predicting DFS. Histologic grade ($P = 0.01$), pT stage ($P<0.001$), pN stage ($P = 0.009$), pathologic stage ($P = 0.002$), and the presence of inflammatory breast cancer ($P = 0.01$), were also related with OS. The results of univariate analyses are shown in Tables 2 and 3. The presence of adjuvant

TABLE 1. The Correlation Between the Multicentricity/Multifocallity and Clinicopathological Characteristics

	Multicentricity/Multifocality		
Characteristics	**Present, n (%)**	**Absent, n (%)**	***P***
Menapousal status			
Premenapouse	55 (51.4)	280 (47.4)	
Postmenapouse	52 (48.6)	310 (52.6)	0.2
Operation type			
MRM	69 (65)	349 (59.1)	
BCS	37 (35)	241 (30.9)	0.2
Histologic grade			
1	9 (9.2)	57 (9.6)	
2	59 (60.8)	352 (59.7)	
3	29 (30)	180 (30.7)	0.9
pT stage			
1	32 (29.9)	212 (35.9)	
2	52 (48.5)	307 (52)	
3	15 (14)	52 (8.8)	
4	8 (7.6)	19 (3.1)	0.04
pN stage			
0	34 (32.6)	241 (40.8)	
1	25 (24)	167 (28.3)	
2	25 (24)	126 (21.3)	
3	20 (19.4)	56 (9.6)	<0.001
Stage			
I	18 (16.8)	122 (20.7)	
II	42 (39.3)	264 (44.8)	
III	47 (43.9)	204 (34.5)	0.1
Lymphovascular invasion			
Present	56 (65.1)	253 (52.5)	
Absent	30 (34.9)	228 (47.5)	0.1
Perineural invasion			
Present	32 (42.1)	188 (42.9)	
Absent	44 (57.9)	250 (57.1)	0.5
Extracapsular invasion			
Present	21 (22.5)	152 (28.3)	
Absent	72 (77.5)	385 (71.7)	0.07
Necrosis			
Present	22 (52.3)	179 (42.5)	
Absent	40 (47.7)	242 (57.5)	0.04
ER			
Positive	73 (72.2)	391 (70.5)	
Negative	28 (27.8)	163 (29.5)	0.7
PR			
Positive	70 (69.3)	394 (71.1)	
Negative	31 (30.7)	160 (28.9)	0.7
c-erb-B			
Positive	20 (24)	117 (23.8)	
Negative	63 (76)	374 (76.2)	0.4
Inflammatory breast Ca			
Present	5 (4.7)	29 (4.9)	
Absent	101 (95.3)	560 (95.1)	0.1

BCS indicates breast conserving surgery; Ca, cancer; ER, estrogen receptor; MNM, modified radical mastectomy; PR, progesterone receptor.

chemotherapy and radiotherapy and chemotherapy type such as taxanes or antracycline-based regimen were not related with DFS both in M/M tumors or unifocal tumors. The results of univariate analysis regarding the relationship between adjuvant treatment and DFS and OS are indicated in Table 4. We then carried out multivariate analyses with the Cox proportional hazards model to further evaluate the prognostic significance of M/M tumors for both DFS and OS. It indicated that the presence of M/M ($P=0.001$, HR: 0.33; 95% CI, 0.18-0.58) was an independent prognostic factor for DFS, as were pN stage ($P=0.01$, HR: 1.74; 95% CI, 1.13-2.69), and extra-

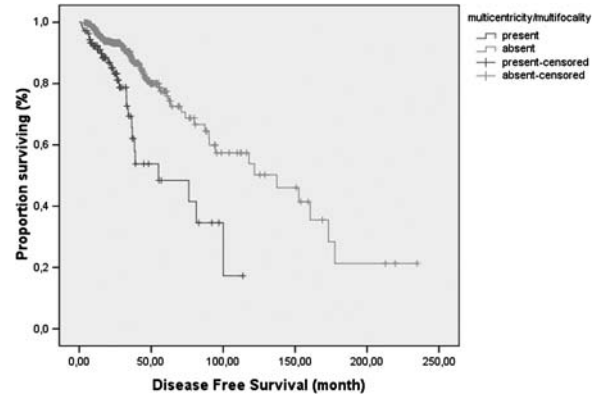

FIGURE 1. The comparison of the disease-free survival of the multicentricity/multifocallity tumors and unifocal tumors.

capsular invasion of lymph nodes ($P=0.03$, HR: 1.9; 95% CI, 1.04-3.47). Table 5 shows the results of the multivariate analyses for DFS. However, the presence of M/M tumor was not statistically significant for OS ($P=0.06$, HR: 0.31 95% CI, 0.04-1.07) (Table 6).

DISCUSSION

The incidence of M/M tumors has been reported between 2% and 60%.[5,10,11] because of the different definitions of M/M tumors in several studies. Egan[7] defined M/M tumors as a wide separation of cancerous areas with noncancerous areas. Katz et al[12] defined M/M tumors as more than 1 quadrant of the breast and separated by at least 4 cm or in different quadrant. Vlastos et al[13] defined M/M tumors as more than 1 tumor in the same breast. There is no distinct border between the quadrants of the breasts and evaluating the actual borders radiologically between the tumor foci is difficult. Therefore, we considered M/M as 1 entity and defined M/M tumors as more than 1 tumor foci in the same breast histopathologically. Using this definition, we found that 15.4% of breast cancer patients had M/M tumors as compatible with the literature. Holland et al[10] reported higher incidence of M/M tumors than our study. This may be attributed that the incidence of M/M tumor are low in our population.

In another study, 97 patients with M/M tumors had similar DFS and OS after treatment with neoadjuvant chemotherapy followed by locoregional therapy, compared with 706 patients with unifocal tumors.[14] In our study 11 of 52 breast cancer patients who had received neoadjuvant chemotherapy had M/M tumor. The median DFS was better for patients who had not received neoadjuvant chemotherapy in M/M tumor groups (21.6 vs. 7.9 mo) ($P<0.001$). It was usual that bigger tumor which had worse prognosis had received neoadjuvant therapy and they had worse DFS than the patients who did not receive neoadjuvant chemotherapy. Although significant differences were present between the group of patients with M/M tumors receiving neoadjuvant chemotherapy, the sample size of the former group in our population is so small compared with the literature that caution must be used in interpreting the results.

In our study, we found that patients with M/M tumors had larger tumors ($P=0.04$) and more lymph node positivity ($P<0.001$). Moreover, more necrosis was seen in M/M tumors ($P=0.04$) than unifocal tumors. The association of M/M tumors with lymph node metastasis has been studied in several

TABLE 2. The Results of Univariate Analysis for DFS

Characteristics	n (%)	3-year DFS rate (%)	Median DFS (mo)	95% CI	*P*
Menapousal state					
Premenapouse	335 (48.1)	88.6	100.1	70.6-129.6	
Postmenapouse	362 (51.9)	83.6	117.9	72.8-162.9	0.2
Tumor localization					
Right	339 (48.9)	83.9	121.7	74.4-169	
Left	334 (48.2)	88 .2	90.3	55.5-125.1	
Bilateral	20 (2.9)	75	90.1	na	0.8
Operation type					
MRM	418 (60.1)	84.2	64.5-124.6	67.4-132.7	
BCS	278 (39.9)	89.2	na	na	0.02
Multicentricity/multifocality					
Present	107 (15.4)	69	55	13.1-96.9	
Absent	590 (84.6)	88.7	137.3	82.7-191.8	<0.001
Histological grade					
1	67 (9.6)	97.7			
2	416 (59.7)	86			
3	217 (30.7)	82.6	na	na	0.007
pT stage					
1	244 (35)	89.9	160.5	66.3-254.6	
2	359(51.5)	87.1	117.9	70.7-165	
3	67 (9.6)	66	63.3	35-91.5	
4	27 (3.9)	60	44	17.1-70.8	<0.001
pN stage					
0	275 (39.5)	92.7	160.5	103.2-217.7	
1	192 (27.5)	89.1	94.6	71.6-117.5	
2	151 (21.7)	81.4	na	na	
3	76 (10.9)	65.8	61.9	29.5-94.4	<0.001
Stage					
I	140 (20.1)	95.8	160.5	79.4-241.5	<0.001
II	306 (43.9)	90.1	117.9	63.4-172.3	
III	251 (36)	76	79.9	55.9-103.8	
Lymphovascular invasion					
Present	309 (44.3)	81.6	121.7	60.1-139.5	
Absent	258 (37)	85.9	137	41.4-263.7	0.02
Perineural invasion					
Present	220 (31.6)	79.8	121.7	64.8-178.5	
Absent	294 (42.2)	85	100.1	57.5-142.7	0.2
Extracapsular invasion					
Present	173 (27.3)	86.5	137.31	63.3-211.2	
Absent	454 (71)	87.7	17.9	81.3-154.4	0.5
Necrosis					
Present	201 (28.8)	78.2	na	na	
Absent	282 (40.5)	88			0.03
ER					
Positive	464 (70.9)	87	na	na	
Negative	191 (29)	81.2			0.01
PR					
Positive	464 (70.5)	89.5	117.9	54.3-181.4	
Negative	191 (29)	76.1	70.9	57.4-84.4	<0.001
c-erb-B					
Pozitive	139 (22.1)	76.7	73.7	42.1-105.2	
Negative	437 (71)	85.5	94.6	59.7-129.4	0.07
İnflammatory breast Ca					
Present	34 (4.9)	66.6	70.9	31.9-109.9	
Absent	651 (95.1)	87	117.9	77-158.7	<0.001

BCS indicates breast conserving surgery; Ca, cancer; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; MRM, modified radical mastectomy; na, not available; PR, progesterone receptor.

studies.[5,9,13,15,16] Andea et al[9] reported that M/M tumors had showed a higher incidence of positive lymph nodes than unifocal tumors. They used the largest diameter of the tumor as pT stage and showed that multifocal cases had a higher incidence of pT1 than pT2 and pT3 (49.5%, 45.5%, and 5%, respectively) compared with unifocal tumors (33.9%, 48%, and 18.1%, respectively) ($P<0.001$). Fish et al[15] also indicated that the mean size of unifocal tumors (n = 557) was smaller than multifocal tumors (n = 37) ($P = 0.02$). In our study, the values for pT1, pT2, pT3, and pT4 were 29.9%, 48.5%, 14%, and 7.6% for M/M tumors and 35.9%, 52%, 8.8%, and 3.1% for unifocal tumors ($P = 0.04$). Although the incidence of pT3 and pT4 was higher in multifocal tumors, the incidence of pT1, pT2 was also higher in unifocal tumors in contrast to the

TABLE 3. The Results of OS Univariate Analysis

Characteristics	5-y OS Rate (%)	Median OS (mo)	95% CI	*P*
Menapousal state				0.5
Premenapouse	91.9	na	na	
Postmenapouse	95			
Tumor localization				0.2
Right	91			
Left	97.8	na	na	
Bilateral	na			
Operation type				0.3
MRM	92.8	na	na	
BCS	97.7			
Multicentricity				0.2
Present	91.1	na	na	
Absent	94.5			
Histological grade				0.01
1	na			
2	96.8	na	na	
3	85.1			
pT stage				<0.001
1	98			
2	93.9	na	na	
3	92.9			
4	79.3			
pN stage				0.009
0	99.6			
1	97.5	na	na	
2	90			
3	85.2			
Stage				0.002
I	99.3			
II	98.5	na	na	
III	87.4			
Lymphovascular				0.02
İnvasion				
Present	92.4			
Absent	94.2	na	na	
Perineural invasion				0.2
Present	94.9	na	na	
Absent	90.6			
Extracapsular invasion				0.5
Present	91.4	na	na	
Absent necrosis	98.4			
Present	94.7	na	na	0.8
Absent	91.6			
ER				0.2
Positive	94.9	na	na	
Negative	93.4			
PR				0.08
Positive	96.4			
Negative	89.2	na	na	
c-erb-B				0.6
Pozitive	94.1	na	na	
Negative	94.4			
İnflammatory breast cancer				0.01
Present	86.5	na	na	
Absent	94.5			

BCS indicates breast conserving surgery; CI, confidence interval; ER, estrogen receptor; MRM, modified radical mastectomy; na, not available; OS, overall survival; PR, progesterone receptor.

Andea study.[9] Coombs and Boyages[8] reported that patients with multifocal tumors had an ALN positivity rate of 52.1% compared with 37.5% for patients with unifocal tumors ($P = 0.009$). The authors used the largest multifocal tumor diameter and showed that multifocality was a significant predictor of lymph node positivity. Cabioglu et al[16] showed a higher frequency of lymph node metastasis in M/M tumors but found a similar pT stage between 1175 unifocal and 147 multifocal tumors in breast cancer patients. In this study, both advanced pT stage and lymph node metastasis were lower in the M/M group. We evaluated M/M tumors and related prognostic factors regarding OS and DFS but we did not undertake a multivariate analysis to evaluate the importance of lymph node positivity.

TABLE 4. The Univariate Analysis Showing the Relationship Between Adjuvant Treatment and DFS and OS

	Multifocal					Unifocal				
	n (%)	DFS Log-rank χ^2	*P*	OS Log-rank χ^2	*P*	n (%)	DFS Log-rank χ^2	*P*	OS Log-rank χ^2	*P*
Adjuvant RT										
Present	69 (69.7)					372 (65.2)				
Absent	33 (30.3)	0.09	0.7	0.02	0.9	199 (34.8)	10.01	0.05	0.15	0.9
Adjuvant CT										
Present	93 (88.5)					464 (82.1)				
Absent	12 (11.5)	0.18	0.6	0.46	0.4	101 (17.9)	1.9	0.1	1.9	0.1
CT type										
Taxane based	47 (50.5)					235 (43.9)				
Antracycline based	45 (48.3)					228 (42.6)				
Absent	1 (1.2)	1.34	0.5	0.58	0.4	72 (13.4)	2.77	0.2	2.57	0.2

CT indicates chemotherapy; DFS, disease-free survival; OS, overall survival; RT, radiotherapy.

Rakowsky et al [17] analyzed 214 ALN-positive breast cancers and found no relationship between the multifocal breast cancers and DFS. Vlastos et al[13] also could find similar DFS rate for both in multifocal and unifocal breast cancer patients. Although Egan[7] stated that the presence of M/M tumors indicated a worse prognosis, they did not provide a multivariate analyses to show the significance of M/M tumors for OS. Pedersen et al[5] reported that patients with M/M tumors had a worse OS compared with unifocal tumors. They evaluated relationship between M/M tumors with other known prognostic factors; they did not show M/M tumors as an independent prognostic factor by using multivariate analysis. Although in the largest study (23.766 unifocal, 1554 multifocal tumors) carried out by Yerushalmi et al,[18] was reported that breast cancer-specific survival rate was worse in M/M tumors compared with unifocal tumors (3.4% difference in breast cancer-specific survival in favor of the unifocal group),but OS was not different. Our study is noteworthy due to the new results in respect to previously published studies; we found that M/M tumors had a worse DFS for breast cancer compared with unifocal tumors. Moreover, the presence of M/M was the most important independent prognostic factor for DFS in breast cancer patients ($P = 0.001$) and M/M might have an additional aggressiveness to tumor biology or a worse outcome related with larger tumor or greater lymph nodes-positivity .Thus, it says that, more aggressive local and systemic treatments might be needed in the M/M breast cancer.

TABLE 5. The Results of the Multivariate Analysis for Disease-Free Survival

Characterisitcs	Wald*	*P*	HR	95% CI
Multicentricite	14.2	0.001	0.33	0.18-0.58
Histologic grade	0.51	0.4	1.2	0.72-2.00
Operation type	0.38	0.5	0.82	0.45-1.58
pT stage	0.33	0.5	089	0.62-1.29
pN stage	6.33	0.01	1.74	1.13-2.69
Stage	0.11	0.7	0.87	0.41-1.85
Lymphovascular invasion	0.05	0.8	0.78	0.11-5.56
Extracapsular invasion	4.42	0.03	1.9	1.04-3.47
Necrosis	1.32	0.2	1.91	0.63-5.77
ER	0.04	0.98	0.99	0.54-1.83
PR	1.03	0.3	1.33	0.76-2.33
İnflammatory breast cancer	0.04	0.8	1.12	0.1-0.59

CI indicates confidence interval; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.
*Wald: multivariate χ^2 value.

TABLE 6. The Results of the Multivariate Analysis for Overall Survival

Characterisitcs	Wald*	*P*	HR	95% CI
Multicentricite	3.5	0.06	0.21	0.04-1.07
Histologic grade	3.03	0.08	3.08	0.86-10.96
pT stage	0.59	0.8	0.89	0.02-32.02
pN stage	0.002	0.9	72.9	0.24-4.10
Stage	0.13	0.7	0.16	0-23
Perineural invasion	2.6	0.1	0.01	0-2.3
Extracapsular invasion	0.01	0.9	0.9	0.2-4
ER	0.6	0.4	1.9	0.3-10.8
PR	0.6	0.4	2.1	0.3-15.4
İnflammatory breast cancer	0.04	0.8	0.75	0.04-1.20

CI indicates confidence interval; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.
*Wald: multivariate analysis χ^2 value.

As our patients with M/M tumors had more aggressive features such as more lymph node metastasis and greater tumor size, these features might have acted independently in the M/M tumors to worsen DFS. If we had separated M/M tumors, the results might change. The major limitation of our study was its small sample size and short follow-up time. Although our findings must be confirmed with larger prospective studies, we conclude that our results contribute to the existing literature because it suggests that M/M might be an independent prognostic factor for DFS of the breast cancer patients. On the basis of this data M/M breast cancer may be used in the tumor node metastasis staging.

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