

## Multifocal/Multicentric versus Unifocal Breast Cancer: What is the Difference?

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### Abstract

**Background:** Although multifocal and multicentric breast cancers are a common entity, their clinical behavior is not well characterized. With the widespread use of mammographic screening and improved sensitivity of imaging modalities, the detection of multifocal and multicentric breast cancers is likely to continuously increase. Many studies have consistently shown a correlation between multifocality and multicentricity and the rate and extent of lymph node metastases. There is little clinical data on the impact of multifocal and multicentric breast cancers on survival outcomes. This study investigates the difference between multifocal and multicentric breast cancers and unifocal breast cancer regarding pathologic and clinical parameters. We have evaluated the impact of multifocal and multicentric breast cancers on disease-free and overall survival of breast cancer patients.

**Methods:** In this retrospective study, we reviewed the records of female patients newly diagnosed with breast cancer who presented to the department of Cancer Management and Research, Medical Research Institute, Alexandria University in the time period from January 2009 till December 2009. Patients with pathologically proven stages I-III invasive breast cancer were included in this study. Patients' clinical and pathological characteristics were compared between the two studied groups. The disease free and overall survivals were analyzed using the Kaplan–Meier method.

**Results:** Multifocal and multicentric breast cancers were associated with a number of known adverse prognostic factors such as higher clinical stage, larger tumor size and lymphovascular invasion. There was a significant correlation between multifocal and multicentric breast cancers and increased rate of axillary lymph node metastasis and higher N stage. Multifocal and multicentric breast cancer patients had shorter median 5-year disease free survival and overall survival compared to unifocal breast cancer patients. In multivariate analysis, after adjustment of other factors, only clinical stage and multifocality/multicentricity were independent predictors of poor disease free and overall survival.

**Conclusion:** There is an association between multifocal and multicentric breast cancers and known adverse prognostic factors such as increased incidence of regional lymph node metastases. This association may suggest that multifocal and multicentric breast cancers have an aggressive biology and more propensity for metastasis. Whether multifocal and multicentric breast cancer is an adverse prognostic factor in breast cancer remains controversial.

**Keywords:** Multifocal, Multicentric, Breast cancer, Prognostic factors, Survival outcomes

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## Introduction

Clinical multifocality and multicentricity are frequently used descriptors in the initial assessment of the extent of disease in patients that present with breast cancer. With the widespread use of mammographic screening and improved sensitivity of imaging modalities, clinical multifocal and multicentric breast cancer (MMBC) is more commonly diagnosed.<sup>1</sup>

Although multifocal (MF) and multicentric (MC) breast tumors are a common entity, their clinical behavior is not well characterized. Pathologists define MMBC as multiple, simultaneous, physically separate, primary lesions when there are two or more foci of tumors present in the same breast without intervening neoplastic tissue.<sup>2</sup>

For practical purposes, the distinction between MF and MC is based on topographic and histologic criteria. Multifocal tumors are defined as when only one breast quadrant is involved and MC tumors when two or more quadrants are involved.<sup>3</sup> Some authors also distinguish MF breast cancer and MC breast cancer based on the assumption that MF breast cancer arises within the same duct collecting system whereas MC breast cancers arise in different duct collecting systems.<sup>4</sup>

An exact radiological definition does not exist, but tumors are usually considered MF when the distance is less than or equal to 5 cm and MC when the distance is more than 5 cm between lesions.<sup>5</sup> Given the lack of anatomically distinct borders between the breast quadrants and the difficulty in radiologically evaluating the precise distance between lesions, most investigators have grouped MC and MF breast cancers together, as MMBC,<sup>6</sup> another reason is the fact that MF breast cancer is more common than MC breast cancer.<sup>7</sup>

The estimated prevalence of MMBC is between 9%–75% of all breast carcinomas; this variability is mainly due to lack of standardization in the gross examination and sampling of breast specimens.<sup>8,9</sup> The sensitivity of mammography and ultrasound for detecting multiple malignant foci have been reported.<sup>10</sup> Of patients clinically and mammographically suspected of having unifocal (UF) breast cancer, 30%–63% will have additional

malignant foci found in the ipsilateral breast at detailed serial sectioning of the mastectomy specimen.<sup>11</sup> The sensitivity of magnetic resonance imaging (MRI) is higher in detecting MMBC, reaching 94%–99% sensitivity for invasive ductal carcinoma (IDC).<sup>12</sup> In addition, breast MRI is reported to have superior sensitivity for diagnosing foci of MMBC breast cancer in dense breasts when compared to mammography.<sup>13</sup>

The current recommendation of the American Joint Committee on Cancer and the International Union against Cancer (AJCC/UICC) classification for staging MF/MC breast tumors is to use the diameter of the largest tumor nodule, regardless of the number or size of additional tumor nodules. As a result, these criteria underestimate the total tumor dimension because additional nodules, which are often sizable, are not included in the T classification.<sup>14</sup>

In the literature, few studies have investigated the prognosis of MF/MC cancers. Some authors have reported that MF/MC is associated with increased lymph node involvement compared with UF tumors.<sup>15</sup> Despite conflicting data, it is still controversial whether this reflects a larger tumor load or a different biologic behavior.<sup>16, 17</sup> In addition, the literatures are divided on the effect of MF/MC breast cancers on survival outcomes when compared with UF breast cancers.<sup>18</sup> The previous studies showed limited data about this issue. These studies have analyzed MF tumors by solely using the diameter of the largest nodule as a tumor size estimate and have not attempted to describe the relation between aggregate estimates of tumor volume and prognosis/metastasis.<sup>19</sup>

This study aimed to investigate the difference between MMBC and UF breast cancer regarding pathologic and clinical parameters. We evaluated the impact of multifocality on disease-free survival (DFS) and overall survival (OS) of breast cancer patients. In this paper we combined the two entities, MF and MC.

## Patients and Methods

In this study, we reviewed the records of female

patients newly diagnosed with breast cancer who presented to the department of Cancer Management and Research, Medical Research Institute, Alexandria University in the time period from January 2009 till December 2009. Clinical and pathological data of these patients were retrospectively collected.

We included patients with pathologically proven stages I-III invasive breast cancer in this study. Exclusion criteria included metastatic breast cancer at presentation, patients treated with neoadjuvant chemotherapy, and presence of diffuse breast involvement.

Patients were categorized into unifocal and multifocal/multicentric groups according to multiplicity of tumor nodules in the same breast. Multifocality/multicentricity was identified as cancers with multiple, clearly separated, and macroscopically measurable tumor nodules in the same breast. For each patient with MMBC breast cancer, the number of tumor nodules and the diameter of the largest nodule were collected. When available, three perpendicular diameters from each tumor nodule were recorded. Determinations were made based on the pathological review only; radiographic data were not considered. The pathological lymph nodes status was known for all patients.

Clinical and pathological data of the studied patients were included age, menopausal status, tumor size, nuclear grade, histological type, status and number of positive axillary lymph nodes, presence of lymphovascular invasion, status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2) expression. Breast cancer staging was defined according to the sixth edition of the Cancer Staging Manual of the AJCC.<sup>20</sup>

Surgical procedure was mastectomy or breast-conserving surgery with or without reconstruction. Adjuvant chemotherapy regimens included 3-6 anthracycline-based regimens with or without the addition of taxanes. Postoperative radiotherapy was administered according to our institutional guidelines. Adjuvant hormonal treatment was administered according to hormonal receptor status. Collected data also included the occurrence

of local or distant recurrence or death during the follow up period.

Patients were followed up with physical examination and laboratory testing that included tumor markers (carcinoembryonic antigen and CA 15.3) at least every 3 to 4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Mammograms of the breast along with ultrasonography, chest x-ray, abdominal ultrasound were obtained once a year in patients with high likelihood of recurrence. Bone scan was performed when indicated. Locoregional and distant metastasis were diagnosed by imaging techniques, biopsy, or both.

### *Statistical analysis*

Data were analyzed using the statistical package for social sciences (SPSS ver.20; SPSS Inc., Chicago, IL, USA). Quantitative data were described as mean  $\pm$  SD, whereas qualitative data were described by number and percent. For comparing quantitative variables between the two groups, we used the independent sample t-test. Patient clinical characteristics were compared between groups using the chi-square test. We calculated the 5-year DFS and OS from the date of diagnosis to the date of local or distant recurrence, death or last follow-up, respectively. The Kaplan–Meier product limit method was used to estimate the survival outcomes of all patients and groups were compared with the log-rank statistic. A multivariate analysis was performed by means of the Cox proportional hazards model in order to determine the association of MMBC with survival outcomes. *P*-values < 0.05 were considered statistically significant; all tests were two-sided.

### **Results**

In the current study, 140 patients had fulfilled the inclusion criteria. Among these, unilateral multiple cancers (MMBC) were observed in 60 patients (42.9%), while 80 patients had UF tumors (57.1%). Of 60 patients with MMBC tumors, 41 (68.3%) presented with 2 tumor nodules, 14 (23.3%) with 3 tumor nodules, and 5 (8.4%) with more than 3 tumor nodules. Patients with MMBC

**Table 1.** Comparison of clinicopathological data between multifocal/multicentric (MF/MC) and unifocal (UF) breast cancer patients.

	MF/MC (n=60)	UF (n=80)	P-value
<b>Age (years)</b>			
Mean $\pm$ SD	46.95 $\pm$ 8.64	54.33 $\pm$ 8.76	
Range	32 – 65	42 – 75	0.003*
<b>Menopausal status</b>			
Pre	39 (65%)	26 (32.5%)	
Post	21 (35%)	54 (67.5%)	0.009*
<b>Histological grade</b>			
I-II	42 (70%)	64 (80%)	
III	18 (30%)	16 (20%)	0.142
<b>Clinical stage</b>			
I-II	32 (53.4%)	55 (68.7%)	
III	28 (46.6%)	25 (31.3%)	0.037*
<b>ER status</b>			
Positive	38 (63.4%)	47 (58.7%)	
Negative	22 (36.6%)	33 (41.3%)	0.793
<b>PR status</b>			
Positive	35 (58.3%)	46 (57.5%)	
Negative	25 (41.7%)	34 (42.5%)	0.870
<b>Her-2/neu status</b>			
Positive	18 (30%)	23 (28.7%)	
Negative	42 (70%)	57 (71.3%)	0.343
<b>Tumor size (cm)</b>			
T1,T2	37 (61.7%)	70 (87.5%)	
T3	23 (38.3%)	10 (12.5%)	<0.001*
<b>Axillary lymph node involvement</b>			
Positive			
Negative	40 (66.7%)	45 (56.3%)	
	20 (33.3%)	35 (43.7%)	0.011*
<b>Axillary lymph nodes (N Stage)</b>			
N0	20 (33.3%)	35 (43.7%)	
N1	14 (23.3%)	22 (28.2%)	
N2	16 (26.7%)	14 (17.3%)	
N3	10 (16.7%)	9 (10.8%)	0.021*
<b>Lymphovascular invasion</b>			
Positive	48 (80%)	51 (63.7%)	
Negative	12 (20%)	29 (36.3%)	0.001*

Abbreviations: ER: Estrogen receptor, PR: Progesterone receptor.;\*, Statistically significant at  $P \leq 0.05$ .

breast cancer were compared to those with UF breast cancer in terms of clinical and pathological characteristics (Table 1).

There was a significant difference between MF/MC and UF breast cancer patients in terms of age, menopausal status, clinical stage, tumor size, lympho-vascular invasion and axillary lymph node involvement (positivity and number of involved nodes).

Compared with patients with UF disease, patients with MMBC breast cancer were younger ( $P=0.003$ ) and premenopausal ( $P=0.009$ ). Multifocality/multicentricity was associated with

higher clinical stage ( $P=0.037$ ) and larger tumor size ( $P<0.001$ ). Multifocal and MC breast tumors were also associated with an increased rate of axillary lymph node metastasis (66.7% versus 56.3%;  $P=0.011$ ) and higher N stage ( $P=0.021$ ), larger percentage of patients with N2 (26.7%) and N3 (16.7%) versus 17.3% and 10.8% respectively. On the other hand, insignificant difference existed between MF/MC and UF breast cancer patients as regard nuclear grade ( $P=0.142$ ), ER ( $P=0.793$ ) and PR status ( $P=0.870$ ), and Her-2/neu expression ( $P=0.343$ ).

In the term of treatment, patients with MMBC

**Table 2.** Multivariate Cox regression for disease-free (DFS) and overall survival (OS) in breast cancer patients.

Variables	DFS			OS		
	HR	95% CI	P-value	HR	95% CI	P-value
Age in years ( $\geq 50$ vs. $< 50$ )	1.006	0.968 – 1.046	0.760	1.003	0.955 – 1.054	0.911
ER (positive vs. negative)	0.729	0.242 – 2.192	0.574	0.733	0.319 – 1.377	0.335
PR (positive vs. negative)	0.854	0.414 – 1.763	0.669	0.957	0.251 – 3.650	0.949
LN (positive vs. negative)	1.365	0.990 – 1.648	0.530	0.874	0.292 – 2.616	0.810
Grade (III vs. II and I)	0.673	0.267– 1.696	0.401	0.730	0.236 – 2.256	0.585
Stage (III vs. II and I)	7.318	3.326 – 16.103	0.001*	6.267	2.471 – 15.894	0.004*
Her-2 (positive vs. negative)	0.972	0.761 – 1.242	0.821	0.995	0.750 – 1.318	0.969
MF/MC (yes versus no)	2.568	1.048 – 6.288	0.039*	3.105	1.821 – 9.004	0.011*
Adjuvant chemotherapy (yes versus no)	0.397	0.233-0.677	0.001*	0.550	0.404-0.733	0.003*

HR: Hazard ratio; CI: Confidence interval; ER: Estrogen receptor; PR: Progesterone receptor; LN: Lymph nodes; Her-2: Human epidermal growth factor receptor 2; MF/MC: Multifocal/multicentricity. \*Statistically significant at  $P \leq 0.05$

tumors more frequently had modified radical mastectomy where, 83.3% of patients with MMBC tumors underwent modified radical mastectomy compared to 62.3% of UF cases ( $P < 0.001$ ). No statistical significant difference existed between the two groups regarding the number of patients who had conservative breast surgery.

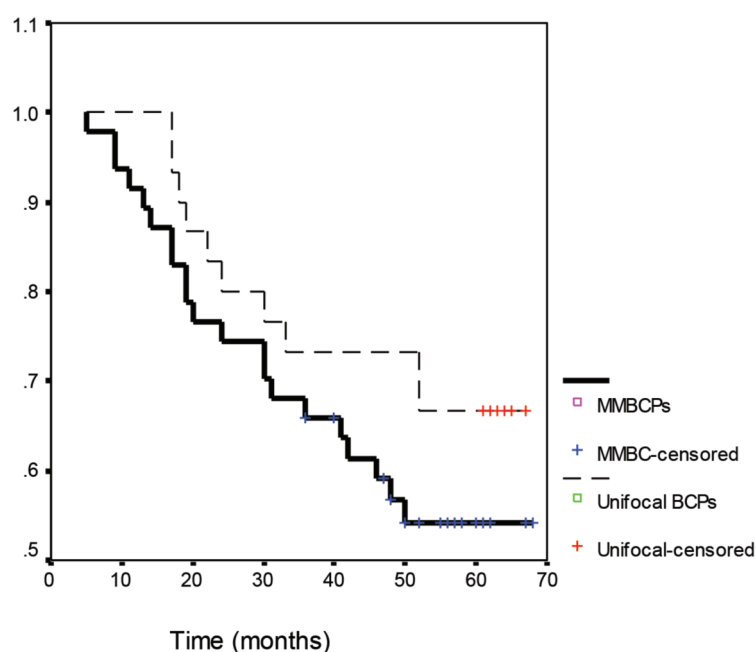
In addition, patients with MMBC (91.7%) were more likely to receive postmastectomy adjuvant chemotherapy compared to those with UF (75%) breast cancer ( $P < 0.001$ ). Based on their similar positive hormone receptor results, no significant difference could be found between patients with UF (58.1%) or MMBC (60.8%)

breast cancer as regards to hormonal therapy ( $P = 0.735$ ).

### Survival outcome

At a median follow-up of 50 months (range: 5-68 months), 14 (17.5%) patients in the UF group and 22 (36.7%) patients in the MMBC group had disease recurrence (locoregional or distant). There were 15 (25%) patients who died from breast cancer in the MMBC group and 8 (10%) died from breast cancer in the UF group.

A statistically significant difference existed in 5-year DFS time between the UF and MMBC groups as shown in Figure 1. Multifocal and MC



**Figure 1.** Disease free survival (DFS) estimates comparing multifocal and multicentric breast cancer (MMBC) with unifocal (UF) disease.



breast cancer patients had shorter median 5-year DFS time (48 months) compared to UF breast cancer patients (62 months;  $P=0.004$ ).

A statistically significant difference in 5-year OS time between UF and MMBC groups existed (Figure 2). Multifocal and MC breast cancer patients had shorter median 5-year OS (54 months) compared to UF breast cancer patients (63 months;  $P=0.002$ ).

### *Cox regression analysis for disease-free (DFS) and overall survival (OS) in breast cancer patients*

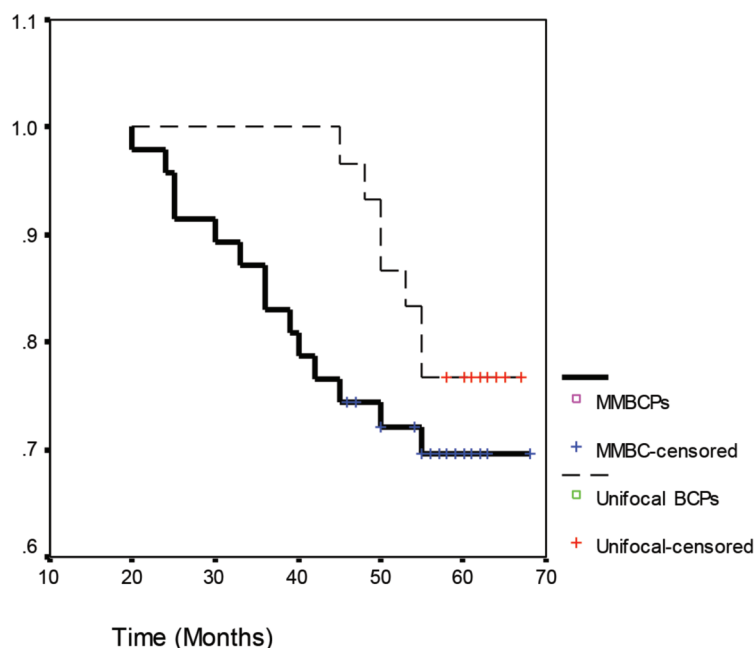
We performed a multivariate Cox regression analysis to evaluate the impact of MF/MC on survival outcomes (Table 2). We estimated the hazard ratios (HRs) to find the independent predictors of DFS in the study patients. In multivariate analysis, after adjustment for other factors, only clinical stage (HR: 7.318; 95% CI: 3.326-16.103;  $P=0.001$ ), adjuvant chemotherapy (HR: 0.397; 95% CI: 0.233-0.677,  $P=0.001$ ) and MF/MC (HR: 2.568; 95% CI: 1.048-6.288;  $P=0.039$ ) were independent predictors of poor DFS. On the other hand, age at presentation, ER and PR status, lymph node metastasis, tumor grade, and Her-2/neu expression showed no impact on breast cancer DFS in the studied patients.

In multivariate analysis we studied the risk factors that impacted OS. After adjustment for other factors, only clinical stage (HR: 6.267; 95% CI: 2.471-15.894;  $P=0.004$ ), adjuvant chemotherapy (HR: 0.550; 95% CI: 0.404-0.733;  $P=0.003$ ) and MF/MC (HR: 3.105; 95% CI: 1.821-9.004;  $P=0.011$ ) were independent predictors of poor OS. On the other hand, we found that other factors such as age at presentation, ER and PR status, lymph node metastasis, tumor grade and Her-2/neu expression showed no impact on breast cancer OS in the studied patients (Table 2).

### Discussion

The identification of MF or MC tumors is not uncommon. With widespread use of mammographic screening and increased accuracy of diagnostic imaging, the identification of multiple small tumor foci is increasing.<sup>1</sup> Multifocality/multicentricity is emerging as a practical issue in patient management.

Multifocal tumors are defined as two or more separate invasive tumors in the same quadrant of the breast while MC tumors are defined as two or more separate invasive tumors that occupy more than one quadrant of the same breast and are separated by normal breast tissue. Alternatively, some studies have used definitions based on the



**Figure 2.** Overall survival (OS) estimates comparing multifocal and multicentric breast cancer (MMBC) with unifocal (UF) disease.

distance of uninvolved tissue between lesions.<sup>18</sup>

The presence of simultaneous cancers can be missed either at preoperative evaluation by mammography and ultrasound<sup>11</sup> or at pathological examination.<sup>21</sup> Indeed, the reported prevalence of MMBC varies widely in the literature. This variation may be due to lack of standardization during the gross examination and definition of MMBC. Moreover, the extent of breast tissue sampling also plays an important role in the variability.<sup>22</sup> Most authors don't differentiate between Mf and MC tumors. In this study we grouped the two identities together.

Due to the retrospective nature of our study, we used the sixth edition AJCC/UICC T classification.<sup>20</sup> In classifying multiple simultaneous ipsilateral primary carcinomas (infiltrating, macroscopically measurable), this edition based on the assumption that the behavior of multifocal/ multicentric tumors is determined only by the size of the largest tumor and not to add the sizes together from the multiple foci.

The current AJCC/UICC T classification criteria did not differ from the previous one in defining the multiplicity. They used the code "m" to indicate "multiple" tumors. According to this system, the presence of additional foci is not taken into account in deciding adjuvant therapies.<sup>14</sup>

The majority of studies with MMBC cases had different methods of tumor size calculation such as the diameter of the largest tumor deposit versus the aggregate diameter of all tumor deposits.<sup>17, 23</sup> Due to variations in assessment of additional tumor aggregates; we used the size of the largest tumor nodule as an indicator of tumor size.

In the current study, patients with MMBC breast cancer were compared with patients with UF breast cancer in terms of pathological and clinical characteristics. In comparison to patients with UF disease, those with MMBC breast cancer were younger ( $P=0.003$ ) and premenopausal ( $P=0.009$ ). These results were similar to several previous studies.<sup>22, 24</sup>

In this study, MF/MC was associated with a number of known adverse prognostic factors such

as higher clinical stage ( $P=0.037$ ) and larger tumor size ( $P=0.001$ ). We also noted an increased incidence of lymphovascular invasion.

Similar to previous studies, we found a significant correlation between MMBC tumors with an increased rate of axillary lymph node metastasis (66.7%) compared to the UF group (56.3%;  $P=0.011$ ) and higher N stage ( $P=0.021$ ). A larger percentage of patients with MMBC tumors had N2 (26.7%) and N3 (16.7%) nodal status compared to 17.3% of UF tumor patients who were N2 and 10.8% of UF tumor patients who had N3 nodal status.

Lynch et al.<sup>25</sup> reported that MF as compared to UF tumors were associated with higher clinical stage ( $P<0.001$ ) and lymphovascular invasion ( $P<0.001$ ). They also found a significant association between MMBC tumors and the rate and extent of axillary lymph node involvement. In their study, MMBC tumors were associated with higher N stage disease. A larger percentage of patients had N2 and N3 stage disease ( $P<0.001$ ). These findings supported the current study results.

Andea et al.<sup>23</sup> found an increased risk of nodal involvement in MMBC compared to UF disease when the diameter of the largest deposit was used to record tumor size. However, when an aggregate diameter was used, UF breast cancer and MMBC showed a similar frequency of nodal involvement.

In a study by Cabioglu et al.<sup>15</sup>, patients with MF/MC were found to have a higher frequency of lymph node metastases when the largest diameter was used as a tumor size estimate for MF/MC cancer. Patients with UF T1 (35%) and T2 (49%) stage were compared to patients with MF/MC T1 (48%) and T2 (67%) stage. There was a significant association between MF/MC tumors and the frequency of axillary lymph node involvement ( $P=0.05$  for MF/MC T1 tumors and  $P=0.003$  for MF/MC T2 tumors). When the combined diameter assessment was used, the frequency of lymph node positivity was significantly higher in MF/MC patients versus UF patients. Those with UF T1 stage (35%) and T2 stage (49%) were compared to patients with MF/MC T1 stage (49%) and T2 stage (61%).

( $P=0.08$  for MF/MC T1 tumours and  $P=0.046$  for MF/MC T2 tumours).

On the other hand, we found an insignificant difference between MMBC and UF breast cancer patients with regards to nuclear grade ( $P=0.142$ ), ER ( $P=0.793$ ) and PR status, ( $P=0.870$ ) and Her-2/neu expression ( $P=0.343$ ). In contrast to our findings, Lynch et al.<sup>25</sup> found a significant association between MMBC tumors to increased grade 3 disease ( $P<0.001$ ) and Her2/neu positivity ( $P=0.001$ ).

In contrast to our results, Cabioglu et al.<sup>15</sup> found no statistically significant difference between two groups when patients with unifocal and multifocal breast cancer were compared as regard to age and lymphovascular invasion; although, as in the current study, they found no correlation between MF/MC and nuclear grade.

In the term of treatment, patients with MMBC tumors more frequently underwent modified radical mastectomy ( $P<0.001$ ). This issue was common because surgeons prefer mastectomy in patients with multiple foci as MF/MC may be a contraindication to breast preservation. In addition, pathological examination of the whole breast allows for discovery of additional foci of cancer. In addition, we have found that the patients with MMBC were more likely to receive adjuvant chemotherapy compared to those with UF breast cancer ( $P<0.001$ ). No significant difference could be found between the two groups with regards to hormone therapy ( $P=0.735$ ). These results were in accordance with the results of a study conducted by Lynch et al.<sup>25</sup>

We evaluated the impact of MF/MC on DFS and OS in the breast cancer study patients. At a median follow-up of 50 months (range: 5-68 months), 14 patients (17.5%) in the UF group and 22 patients (36.7%) in the MF group had disease recurrence (locoregional or distant). There were 15 patients who died from breast cancer in the MMBC group and 8 patients died from breast cancer in the UF group.

A statistically significant difference in 5-year DFS existed between the UF and MF groups. Multifocal/MC breast cancer patients had shorter median 5-year DFS (48 months) compared to UF

breast cancer patients (62 months;  $P=0.004$ ). There was also a statistically significant difference in 5-year OS between the two groups. Multifocal/MC breast cancer patients had shorter median 5-year OS (54 months) compared to UF breast cancer patients (63 months;  $P=0.002$ ).

Several trials studied the impact of MF/MC on survival outcome. In agreement with our findings, Boyages et al.<sup>26</sup> reported a similar finding in a study that included 94 patients with MF and MC breast cancers. They used the same definition as in the current study and grouped MF and MC tumors together. For patients with tumors larger than 2 cm, the 10-year survival was 54.7% for MMBC compared to the UF group (72.1%;  $P=0.008$ ), an impact that also persisted also on multivariate analysis. Pedersen et al.<sup>27</sup> analyzed 158 patients with more than one focus of tumor separated by normal breast tissue. They found worse OS for MF and MC tumors on univariate analysis.

On the other hand, Cabioglu et al.<sup>15</sup> reviewed 147 patients with MF and MC disease which was defined as at least two foci of invasive cancer more than 5 mm apart. At a median follow up of 55 months (range: 12 to 153 months), 5-year DFS rates were 88% for UF disease versus 82% for MF/MC cases ( $P=0.14$ ) and OS rates (UF: 92% versus MF/MC: 93%;  $P=0.43$ ) did not show any significant difference between the two groups.

Multivariate Cox regression analysis was performed to evaluate the impact of MF/MC on survival outcomes. After adjustment for other factors, only clinical stage, adjuvant chemotherapy and MF/MC were independent predictors of poor DFS and OS. On the other hand, we found that age at presentation, ER and PR status, lymph node metastasis, tumor grade and Her-2/neu expression showed no impact on breast cancer DFS or OS in the studied groups.

Joergensen et al.<sup>28</sup>, after conducting multivariate Cox analysis, concluded that MF was a significant prognostic factor for progression-free survival (PFS) but not for OS. In a study by Lynch et al.<sup>25</sup>, multivariate Cox regression analysis was applied in order to evaluate the risk factors



that were significant according to univariate analysis. Multifocality and multicentricity and the use of adjuvant chemotherapy were not independent predictors of survival which disagreed with our results.

The current study, along with numerous other studies, have shown an association between MMBC and known adverse prognostic factors such as increased incidence of regional lymph node metastases. This association might suggest that MMBC tumors have an aggressive biology and more propensity for metastasis.

The studies that have been conducted on MF breast cancer differ about whether the overall tumor burden in MMBC tumors is simply underestimated according to the current staging system. Andea et al.<sup>29</sup> have shown that using the sum of the largest diameters actually overestimates the total tumor burden, and that better measures of a tumor's propensity to metastasize are total tumor volume and surface area. However, MMBC tumors that have been reclassified according to this model still had an increased rate of lymph node involvement, which suggested that the difference was not due to understaging, but possibly due to more aggressive tumor biology.

Rezo et al.<sup>22</sup> performed a multivariate analysis with three different measurements of T staging (single largest diameter, aggregate diameter, and aggregate volume) and have found that the single largest diameter was the best predictor of DFS and OS. In routine clinical practice, these measurements require additional work and are unlikely to be practical or performed routinely. Therefore, tumor size should continue to be measured according to the current AJCC/UICC method for MMBC.

## Conclusion

The main finding of this study was the association between MMBC breast cancer and known adverse prognostic factors such as increased incidence of regional lymph node metastases. This association might suggest that MMBC tumors have an aggressive biology and more propensities for metastasis. Whether MMBC is an adverse prognostic factor in breast cancer has

remained controversial.

- We concluded that MF breast cancer patients had shorter median 5-year DFS and OS compared to UF breast cancer patients.

- In multivariate analysis, after adjustment for other factors, only clinical stage and multifocality were independent predictors of poor DFS and OS.

- A standardized method of classifying MF and MC breast cancers is required.

- Future studies are required to study the molecular profiles of MF breast cancer. This may provide clinically relevant information to guide treatment decisions.

- This study is retrospective in nature, and therefore subject to inherent biases. Further prospective studies are required to prove our findings.

- There was some variability in the treatments received by the two studied groups such as the type of surgical management and chemotherapy received. Moreover, the optimal local therapy for MF and MC tumors was not well defined.

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## Conflicts of interest

No conflict of interest is declared.

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