Survival, Recurrence, and Clinicopathological Characteristics in Multifocal and/or Multicentric versus Unifocal Locoregional Breast Cancers: Results of a Large Breast Cancer Registry

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Abstract

Background: Much is still unknown regarding the clinicopathology and prognosis of patients with multifocal/multicentric breast cancer (MMBC).

We herein compared the clinicopathology and prognosis of patients with unifocal and MMBCs.

Method: This cross-sectional research is a part of Shiraz Breast Cancer Registry (SBCR). We studied all the patients in the SBCR (n=6145). Ultrasound reports were used to differentiate between MMBCs and unifocal breast cancers (BCs). All the patients were examined with mammography and the diagnosis was confirmed postoperatively via pathology reports.

Results: After exclusion, 4045 patients entered the study (n=1072 and n=2973 for multifocal/multicentric and unifocal BCs, respectively). The mean follow-up period was 57.9 (0.27-275) months. Patients with MMBCs had higher rates of mastectomy (48% vs. 40.1%; $P < 0.001$) and higher rates of HER-2 overexpression (32.1% vs. 26%; $P = 0.001$) compared with those with unifocal BCs. Tumor size, lymph node involvement, type of axillary management, chemotherapy, radiotherapy, hormonal therapy, recurrence rates, histological grade, lymphovascular invasion, axillary node involvement, estrogen and progesterone receptor expression status, tumor, node, and metastasis staging were not significantly different between the groups. Five-year overall survival was 88.3% and 89% ($P = 0.8$) for unifocal and MMBCs, respectively; moreover, five-year disease-free survival was 80.2% and 81.2% ($P = 0.41$), respectively.

Conclusion: Despite the controversy regarding prognosis and surgical management in MMBCs, we found that MMBCs had similar clinicopathological features and prognosis compared to unifocal BCs. Survival, recurrence, and metastasis were similar among the two groups.

Keywords: Breast neoplasm, Staging, Survival, Multicentricity, Multifocality

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Introduction

Multifocal and multicentric breast tumors are defined as two or more neoplasms separated in one breast. In multifocal tumors, a quarter of the breast is involved while in multicentric tumors, two quarters or more are involved.[1] There is no exact radiological definition, but the distance between the multifocal tumors is less than or equal to 5 cm, whereas the distance between multicentric tumors is 5 cm, or more.[2] Considering the absence of distinct anatomical borders between the quadrants of the breast and difficult radiological evaluation of the distance between lesions, multifocal and multicentric tumors are generally defined as multifocal/multicentric breast cancer (MMBC).[1]

These definitions are mainly due to a lack of standardization in sampling of the breast tissue. Moreover, sampling may be limited to suspicious macroscopic areas. As a result, MMBCs are mostly (up to 40%-70%) reported in mastectomy specimens[3] and are generally considered as an obstacle to breast conservation surgery due to the increased risk of local recurrence.[4, 5]

The exact prevalence of MMBC is unclear since before surgery, simultaneous cancers can be missed by mammography or sonography or pathological assessments, unless these evaluations are thoroughly investigated with appropriate specimen analysis techniques.[6]

Some believe that radical surgery is more effective in local control of the disease and ultimately in survival, and suggest a worse prognosis and locoregional recurrence in patients undergoing breast conservation surgery.[7, 8] On the other hand, some studies have reported that breast conservation surgery can be safely performed for MMBC patients and can provide good cosmetic end results provided that enough excision is performed.[9, 10]
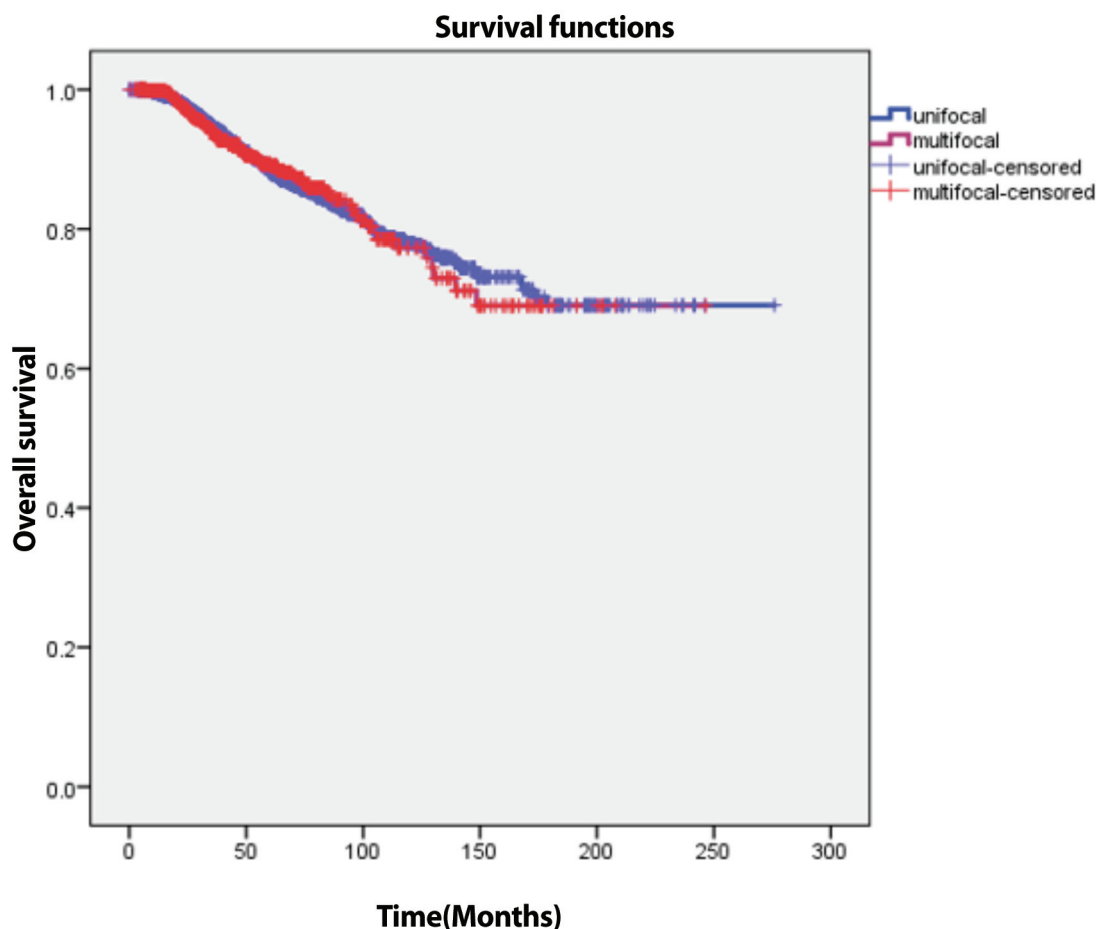
Figure 1. This figure shows the Kaplan–Meier estimator of the overall survival among the patients with unifocal and multifocal/multicentric

Table 1. Comparison of clinicopathology between the patients with unifocal and multifocal/multicentric breast cancers*

Variables	Unifocal (n = 2973)	Multifocal/multicentric (n = 1072)	*P*-value
Age (yrs.)	48.95 ± 11.91	46.85 ± 10.43	<0.001
Involved breast			
Right	1439 (48.7)	485 (45.4)	0.06
Left	1515 (51.3)	583 (54.3)	
Stage - no. (%)			
1	665 (25.6)	247 (26)	0.001
2	1325 (51)	451 (47.5)	
3	608 (23.4)	251 (26.4)	
Tumor size - cm	2.67 ± 1.41	2.68 ± 1.48	0.91
Histological grade - no. (%)			
I	514 (21.4)	173 (19.4)	0.403
II	1355 (56.5)	514 (57.5)	
III	529 (22.1)	207 (23.2)	
Lymphovascular invasion - no. (%)			
Yes	1406 (52.9)	516 (54.1)	0.49
No	1254 (47.1)	437 (45.9)	
Perineural invasion - no. (%)			
Yes	784 (29.6)	283 (29.7)	0.89
No	1876 (70.5)	670 (70.3)	
Estrogen receptor			
Positive	2119 (75.5)	738 (72.8)	0.08
Negative	687 (24.5)	276 (27.2)	
Progesterone receptor			
Positive	1962 (70.2)	690 (68.3)	0.26
Negative	833 (29.8)	320 (31.7)	
HER-2 overexpression			
Yes	605 (26)	280 (32.1)	0.001
No	1720 (74)	591 (67.9)	
Nodal involvement - no. (%)			
Yes	1363 (48.3)	527 (51)	0.89
No	1461 (51.7)	507 (49)	
Number of involved lymph nodes - no. (%)			
0	1461 (51.7)	507 (49)	0.065
1-3	745 (26.4)	280 (27.1)	
4-9	398 (14.1)	140 (13.5)	
≥10	220 (7.8)	107 (10.3)	
Molecular subtype			
HR+/HER2- (Luminal A)	1373 (59.4)	485 (56.1)	0.001
HR+/HER2+ (Luminal B)	395 (17.1)	159 (18.4)	
HR-/HER2+ (HER2 positive)	208 (9)	115 (13.3)	
Triple negative breast cancer	335 (14.5)	105 (12.2)	

HR: Hormone receptor; HER2: Human epidermal growth factor 2; *All plus-minus values are means and standard deviations unless stated otherwise

To date, much remains to be known regarding the exact clinicopathology and prognosis of patients with MMBCs. In this study, we compared the clinicopathology and prognosis of patients with MMBC and unifocal cancers using data from the largest breast cancer (BC) registry in Iran.

Patients and Methods
Study settings
This cross-sectional study is a part of the Shiraz Breast Cancer Registry (SBCR), the largest BC registry in Iran. The BC registry is a computer-based registry affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The registry includes data on more than 9000 BC patients

Table 2. Comparison of prognosis- and treatment-related variables between the patients with unifocal and multifocal/multicentric breast cancers*

Variables	Unifocal (n = 2973)	Multifocal/multicentric (n = 1072)	P-value
Operation - no. (%)			
Breast conserving therapy 1762 (59.9)		555 (52)	<0.001
Mastectomy	1181 (40.1)	513 (48)	
Hormonal therapy - no. (%)			
Yes	2079 (79.7)	746 (77.7)	0.18
No	528 (20.3)	214 (22.3)	
Radiotherapy - no. (%)			
Yes	2106 (81.8)	773(81.6)	0.87
No	467 (18.2)	174 (18.4)	
Chemotherapy - no. (%)			
Yes	2583 (96.2)	949 (96.8)	0.38
No	101(3.8)	31 (3.2)	
Axillary management - no. (%)			
Sentinel lymph node biopsy	768 (27)	285 (27.6)	0.26
Axillary node dissection	1703 (60)	634 (61.4)	
Sentinel lymph node biopsy + axillary node dissection	369 (13)	114 (11)	
Recurrence - no. (%)			
Yes	525 (18.1)	172 (16.3)	0.202
No	2378 (81.9)	881 (83.7)	
5-year overall survival	217.47 ± 3.81	202.55 ± 6.37	0.8
Percentage	88.3	89	
Disease-free survival	182.81 ± 5.89	169.72 ± 6.12	0.41
Percentage	80.2	81.2	

*All plus-minus values are means and standard deviations, unless stated otherwise

from 1993 up to this date and is still ongoing. The protocol of the registry has been described elsewhere.[11]

All the subjects in the SBCR, including 6145 patients, were considered for inclusion in the study. The exclusion criteria were male patients, those with distant metastases, those with tumors other than carcinomas, those with missing radiology data, and those with ductal carcinoma in situ without invasive cancer.

The Ethics Committee of Shiraz University of Medical Sciences approved the present work (ethics code: IR.SUMS.REC.1397.75). Written informed consent was obtained from the patients for participation in this study.

Study design

Considering the fact that all the patients suspected of BC were examined with ultrasound, ultrasound reports were used as the main pre-operation diagnostic tool for differentiating between MMBCs and unifocal BCs. All the patients were examined via mammography and the diagnosis was confirmed postoperatively by pathology report as two or more invasive cancers over 5 mm apart in the ipsilateral breast. The tumors that were not confirmed to be MMBC in pathology were excluded from the study.

In order to identify the molecular characteristics of the patients, immunohistochemistry testing was utilized to determine the status of estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth receptor -2 (HER-2) expression status.

In immunohistochemistry for HER-2 expression, based on the manufacturers guidelines, the scoring ranged from 0 as no staining or staining of less than 10%, 1+ as weak staining in 10% of the cells, 2+ as weak to moderate staining in all cell membranes among 10% of the cells, and 3+ as staining in all cell membranes in 10% of the cells.

Zero and 1+ results were considered negative and those with 3+ results were considered positive. Those with 2+ staining (or equivocal) results had

fluorescence in situ hybridization (FISH) (PathVision; Vysis, Downers Grove, IL) for confirmation and amplification of HER-2 gene.[12]

Staging of BC was done according to the tumor, node, and metastasis (TNM) staging system. Tumor size and lymph node involvement were further categorized according to the TNM staging system. Tumor size was classified as ≤ 2 cm, < 2, ≤ 5 cm, and > 5 cm, and the number of lymph nodes involved were classified as ≤ 3, < 3, < 10, and ≥ 10. The grade of BC, the grade of nucleus, in situ component, and tumor necrosis were assessed according to the pathology reports.

All the tumor specimens were examined by frozen sections and permanent pathology.

The size of MMBCs was defined according to the TNM classification. The current TNM classification criteria (AJCC/UICC) considers the diameter of the largest lesion mass in order to classify tumor size (T) of multifocal-multicentric carcinomas.[13]

Statistical analysis

For statistical analysis, we used the SPSS software version 20.00, for windows. The quantitative variables with normal distribution were compared between the two groups using the independent t-test and the qualitative ones were compared between the groups with the chi-square test.

Prognosis was assessed with the disease-free survival (DFS) and overall survival (OS). For OS and DFS, the Kaplan-Meier test was utilized.
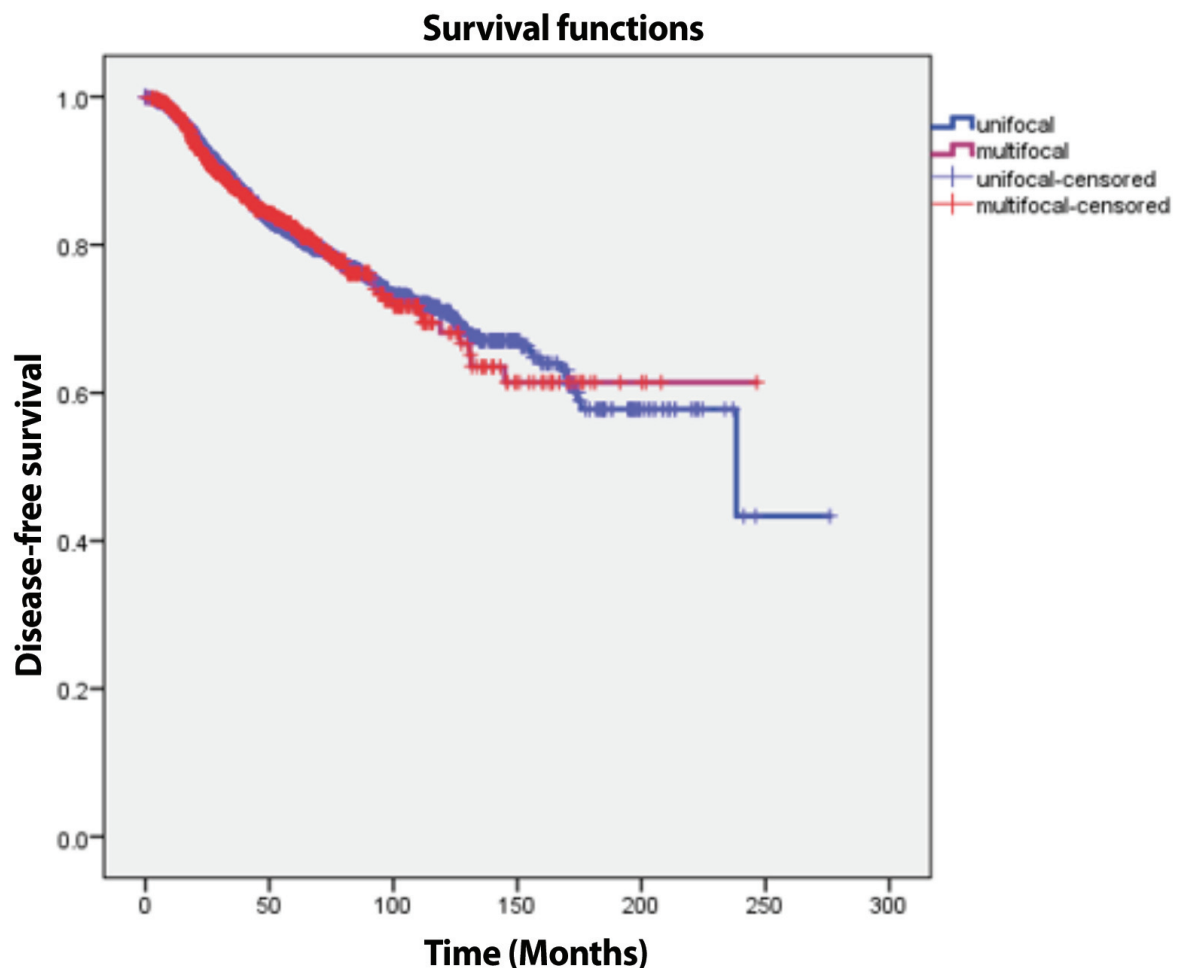
Figure 2. This figure shows the Kaplan–Meier estimator of disease-free survival among the patients with unifocal and multifocal/multicentric breast tumors.

P-value below 0.05 was considered to be statistically significant.

Results

After exclusion, a total of 4045 patients entered the study. The number of multifocal/multicentric and unifocal BCs in our population was 1072 and 2973, respectively. The mean follow-up period was 57.9 months (ranging from 0.27 to 275 months).

Those in the MMBC group were significantly younger compared with the unifocal BC group (46.85 ± 10.43 vs. 48.95 ± 11.91 years old; *P* < 0.001) (Table1).

A bigger proportion of patients with unifocal BC had stage 3 BC (23.4% vs. 26.4%; *P* = 0.001). The patients with MMBCs had higher rates of mastectomy (48% vs. 40.1%; *P* < 0.001) and higher rates of HER-2 overexpression (32.1% vs. 26%; *P* = 0.001) compared with those with unifocal BCs. Accordingly, triple negative rates were lower among those with MMBCs (12.2% vs. 14.5%, *P* = 0.001). Tumor size, lymph node involvement, type of axillary management, chemotherapy, radiotherapy, hormonal therapy, recurrence rates, histological grade, lymphovascular invasion, axillary node involvement, ER and PR expression status, and TNM staging were not significantly different between the two groups (Table 2).

Regarding prognosis, the mean OS was 217.47 ± 3.81 and 202.55 ± 6.37 months for unifocal and MMBCs, respectively (Figure 1).

The mean DFS was 182.81 ± 5.89 and 169.72 ± 6.12 months for unifocal and MMBCs, respectively (Figure 2).

The five-year OS rates were 88.3% and 89%, respectively, for unifocal and MMBCs. The results of the Kaplan–Meier analysis showed no significant difference between the unifocal and MMBCs with respect to the OS rate (*P* = 0.8) (Figure 1).

The five-year DFS rates were 80.2% and 81.2% for unifocal and MMBCs, respectively. Moreover, no difference was seen between the two groups regarding DFS rates (*P* = 0.41) (Figure 2).

Discussion

Herein, we aimed to compare clinicopathology and prognosis of multifocal/multicentric breast tumors with those of unifocal tumors. Our results showed that a total of 26.5% of our patients had either multifocal or multicentric BCs. These individuals had higher rates of mastectomy (than quadrantectomy) and higher rates of HER-2 expression. Regarding prognosis, the two groups were similar concerning OS and DFS.

The clinical significance of MMBCs and their impact on prognosis is still highly controversial. The presence of MMBCs is frequently considered to be an indication for extended operations or mastectomies.[7]

The prevalence of MMBCs has been reported to be highly variable in different regions of the world.[2, 3, 6] In this report, we found that the prevalence of MMBCs among the Iranian population was 26.5%.

A number of studies have concluded that MMBCs are associated with poor prognosis and outcomes, and depicted features that make these cancers more aggressive in nature. Neri et al. in 2015 reported on a series of 1158 of patients with BC during a 14-year study period. They reported that 191 of their patients had MMBCs (16.5%). In their report, 81.2% of their MMBC patients were treated with mastectomy. They found that patients with MMBCs had a DFS of 154 months (95% confidence interval (CI): 139 – 169 months), while patients with unifocal tumors had a DFS of 204 months (95% CI: 194 – 214 months). They also reported that MMBC patients had lower survival with higher rates of metastatic axillary lymph nodes and lower ER expression. In their cox regression analysis, an absent ER receptor status (hazard ratio (HR) = 1.89, 95% CI: 1.2 - 2.98; *P* = 0.005), nodal status as N3 (HR = 9, 95% CI: 4.95 - 16.4; *P* < 0.001), and MMBCs compared to unifocal BCs (HR = 1.64, 95% CI: 1.05 - 2.57; *P* = 0.029) were predictors of poor survival among the patients with BC.[7]

Their findings were incoherent with ours, which could be due to multiple reasons; primarily, the different sample sizes between the two studies could be mentioned, as our study sample size

with MMBCs was significantly larger than that of the mentioned study; the reported risk factors in their regression model may have been due to the small sample size within the MMBC group (n = 131). More importantly, certain factors which were significantly different within the MMBC group, such as HER2 status, which was not considered in their multivariate analysis and may have affected their results.

Our findings were similar to those reported by Karakas et al.[14] who evaluated a total of 3890 cases of BC. They found that among the overall 323 (8%) patients who showed MMBCs, a 10-year survival (75% vs. 74% for the unifocal and MMBC groups, respectively; $P = 0.965$) and DFS (66% vs. 61% for the unifocal and MMBC groups, respectively; $P = 0.817$) were similar to the group of patients with unifocal BCs. Similar to the mentioned report, we did not find any significant difference between the two groups of patients regarding prognosis. Similar results were also seen in other reports.[15]

Despite the controversy concerning the application of a more aggressive treatment approach among patients with MMBCs, this study supports the notion that MMBCs are not associated with a worse prognosis; this denotes that breast conserving surgery should be considered for these patients similar to those who have unifocal breast tumors. In other words, the multifocal nature of a breast tumor alone should not be considered a reason to perform mastectomy. Similarly, regarding axillary management, SLNB should be considered with the same criteria for patients with MMBCs as those for patients with unifocal BCs since these patients are not prone to the increased risk of locoregional or distant recurrence. This indicates that other factors, except multiple focis of breast tumors, play a role in prognosis of BCs.

From another perspective, our results do not support the idea of adjuvant therapy for BCs with multiple foci as these alone do not display a worse biological behavior. This was further supported by our univariate analysis as none of the risk factors, such as triple negativity, higher grade or stage, or hormone receptor negativity, were seen at a higher rate among our patients with MMBCs.

This study was not without limitations. Our primary analysis did not show a worse prognosis for MMBCs; a separate analysis that would preclude the role of surgery type, as mastectomy rates were slightly higher among these patients, may have provided more valuable results, although no other risk factors for a worse prognosis were seen among the patients with MMBCs. Additionally, we did not investigate some other biological markers, such as Ki-67, or compare them between the two groups of BC patients.

Our research was a prospective study as part of one of the largest BC registries in our region. Moreover, it included one of the largest reports on multifocal or multicentric BCs in literature.

Conclusion

Despite the existing controversy regarding prognosis and surgical management in MMBCs, we found that MMBCs have similar clinicopathological features and prognosis as unifocal BCs. Survival and recurrence, both distant and locoregional metastasis, were similar among the patients with MMBC and those with unifocal BCs.

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Conflict of Interest

None declared.

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