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Characteristics of multifocality/multicentricity in breast cancer and its effect on axillary lymph node metastasis

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Abstract

Multifocal (MF) and multicentric (MC) breast cancers are seen with increasing frequency with advances in imaging methods. However, there is no consensus on the behavior and management of these tumors. In this study, we aimed to investigate the characteristics of MF/MC breast cancers and their relationship with axillary lymph node metastasis (ALNM). Patients who underwent surgery for breast cancer between January 2015 and January 2023 were retrospectively scanned. Exclusion criteria were as follows; male breast cancer, second primary cancer diagnosis, previous breast cancer history, previous excisional/incisional breast biopsy, neoadjuvant chemotherapy, and occult breast cancer. Multiple tumors that were closer than 5 cm to each other were defined as MF, and the others were defined as MC. T stage was determined in two different ways, using the largest tumor diameter (T_{max}) and the aggregate tumor diameter (T_{sum}), and two different multivariate analysis models were applied. A total of 156 patients were enrolled in the study, including 130 unifocal (UF), 17 MF and 9 MC. Lymphovascular invasion (LVI) (p=0.43), ALNM (p=0.23), younger age (<50) (p=0.41) and invasive lobular carcinoma (ILC) (p<0.001) were higher in MF/MC tumors than in UFs. When comparing MF and MC, no difference was seen except progesterone receptor positivity (p=0.017). In both multivariate analyses, LVI and ILC had an effect on ALNM, while no effect of MF/MC was seen. In addition, while T stage had a significant effect on ALNM in the model using T_{sum}, it did not have a significant effect in the T_{max} model. Our retrospective data supports that MF/MC is not a direct risk factor for ALNM and that the main factor affecting ALNM is the total tumor burden.

Keywords: Breast cancer, multifocality, multicentricity, axillary lymph node metastasis, aggregate tumor diameter

Introduction

Breast cancer is the most common cancer and the leading cause of cancer-related deaths in women worldwide [1]. Although breast cancer is often unifocal, multiple foci may be found synchronously in the ipsilateral breast. Ipsilateral multiple breast cancers are divided into two group as multifocal (MF) and multicentric (MC). MF tumors are considered as multiple tumoral lesions formed by the spread of a single focus through the ductal complex, whereas in MC tumors there are multiple independent foci [2]. Definitions of MC and MF vary in the literature. In general, if the distance between lesions is less than 5 cm, it is defined as MF, and if it is more than 5 cm, it is defined as MC [3]. Another method is to directly divide the breast into four quadrants (3:00, 6:00, 9:00 and12:00 clock positions) and define lesions located in different quadrants as MC, and lesions located in the same quadrant as MF [4]. However, in this method, ambiguity may occur because lesions in different quadrants may be very close to each other. For this reason, some authors use the definition of MC if there is a 90° angle between the lesions and the nipple [5]. With the increased use of magnetic resonance imaging, the frequency of MF/MC tumors has increased [6,7]. In the literature, the frequency of MF/MC tumors varies between 20-75% [8,9].

In recent years, there have been significant developments in breast cancer treatment modalities, and it has been shown that successful survival results can be achieved by using less radical

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surgeries and combinations of radiotherapy, chemotherapy and hormonotherapy compared to the past [10-12]. However, in most of these studies, MF and MC tumors were excluded. In addition to the relatively few studies on this subject, the designs of the studies are also different. In some studies, MF and MC tumors were examined in the same group. On the other hand, while some studies required at least two invasive foci for the definition of MF/MC, in others, the same definitions were used for DCIS foci accompanying a single invasive focus. This makes the studies in the literature heterogeneous [13-14]. Therefore, information about the behavior of multiple tumors is quite narrow compared to unifocal tumors. There is no full consensus on the approach to MF/MC tumors [5]. In this study, we aimed to compare the clinical characteristics of MF and MC tumors, and especially their tendency to lymph node metastasis, among themselves and with UF tumors.

Material and Methods

Patients who underwent surgery for breast cancer between January 2015 and January 2023 were retrospectively examined. Male breast cancer, second primary cancer diagnosis, previous breast cancer history, previous excisional/incisional breast biopsy, neoadjuvant chemotherapy and occult breast cancer were determined as exclusion criteria. Patients were classified as MF, MC and unifocal (UF). Patients with at least two invasive foci were defined as MF or MC. Patients with a ductal carcinoma in situ (DCIS) focus in addition to a single invasive focus were considered UF. In the ipsilateral breast, invasive tumors with a distance of 5 cm or more were considered MC, and those closer than 5 cm were considered MF.

Patients' age, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki-67 index, molecular subtypes, histological grade, the largest tumor diameter, aggregate tumor diameter, presence of DCIS, axillary lymph node metastasis (ALNM), extranodal involvement, lymphovascular invasion (LVI), perineural invasion (PNI), pathological type, surgical procedure data were searched.

Patients with a HER2 score of 3+ were considered positive, and those with a HER2 score of 0 and 1+ were considered negative. Those with 2+ were determined according to the FISH result. A 1% staining threshold was used to define ER or PR positivity. Patients with Ki-67 staining ≤14% were classified as low proliferation, and those with >14% were classified as high proliferation. Molecular subtypes were classified as follows, Luminal A (ER and/or PR positive, HER2 negative, Ki-67 <14%), Luminal B (ER and/or PR positive, HER2 positive and/or Ki-67 ≥14%), HER2 (HER2 positive, ER and PR negative), Triple negative (ER, PR and HER2 negative).

Since neoadjuvant treatment is applied to tumors with skin or chest wall invasion in our clinic, T4 tumors were not included in the study. Two different methods were followed when determining the T stage. T_{max} values were determined according to the largest tumor diameter and T_{sum} values were determined according to the aggregate tumor diameter. T stages were determined according to tumor diameters as follows; ≤2 cm T1, 2-5 cm T2 and >5 cm T3.

Chi-square test was used to compare categorical variables according to paired groups. The independent samples t-test was used to compare the normally distributed data according to the paired groups. Factors significantly associated with lymph node positivity were evaluated using univariate and multivariate logistic regression analyses. Analysis results were presented as mean±standard deviation for quantitative data, and frequency (percent) for categorical data. Data were analyzed with IBM SPSS V25. All P values lower than 0.05 were considered statistically significant. This study was approved by the Institutional Review Board of Sivas Cumhuriyet University (Approval Number: 2022-10/07, Date: 19.10.2023).

Results

A total of 156 patients were enrolled in the study, including 130 UF, 17 MF (2 foci in 15 patients, 3 foci in 1 patient, and 4 foci in 1 patient) and 9 MC (2 foci in 8 patients, 4 foci in 1 patient). The clinical and pathological characteristics of the patients are summarized in tables 1 and 2. There were 126 invasive ductal carcinomas (IDC), 3 invasive lobular carcinomas (ILC) and 27 other types of breast cancer (5 cribriform, 9 papillary, 3 mucinous, 7 medullary, 2 neuroendocrine carcinomas, 1 signet ring cell carcinoma).

Patients with MF/MC tumors were younger (<50 vs ≥50) than UF and had a significantly higher frequency of mastectomy, LVI, ALNM, and IDC (Table 1). There was no difference between the groups in terms of T_{max} and the largest tumor diameter, while T_{sum} and aggregate tumor diameter were significantly higher in patients with MF/MC tumors, as would be expected, compared to the UF group (Table 1).

When patients with MF and MC breast cancer were compared among themselves, no significant difference was found except that PR positivity was more frequent in the MF group (Table 2). When T stage was determined with T_{sum} instead of T_{max}, three patients in the MC group had T1 to T2 upstage and three had T2 to T3 upstage. T1 to T2 upstage was observed in four of the patients in the MF group, and from T1 to T3 in five (Table 2).

In addition, factors affecting ALNM were also investigated. In univariate analysis, multiplicity (MF/MC vs UF), T_{sum}, T_{max}, LVI, PNI and pathological type (ILC vs IDC) were found to be effective on lymph node metastasis (Table 3). Multivariable analysis was applied through two different models depending on how T stage was calculated. When T stage was calculated according to T_{max}, only LVI and pathological type (ILC vs IDC) had an effect on ALNM, while T_{max} had no significant effect. In the second model, T stage was calculated according to T_{sum}. Similar to the other model, LVI and pathological type (ILC vs IDC) were significant. In addition, a significant effect of T_{sum} (T3 vs T1) was found on ALNM. No effect of multiplicity (MF/MC vs UF) was found in both multivariable analyzes (Table 4).

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Table 1. Clinical and pathological characteristics of patients with unifocal and ipsilateral multiple breast cancers

		Unifocal n (%)	Multifocal/Multicentric n (%)	p value
Age	**<50**	34 (26)	12 (46)	0.041
	≥50	96 (74)	14 (54)	
ER status	**Positive**	103 (79)	22 (85)	0.530
	Negative	27 (21)	4 (15)	
PR status	**Positive**	96 (74)	19 (73)	0.935
	Negative	34 (26)	8 (27)	
HER2 status	**Positive**	31 (24)	11 (42)	0.053
	Negative	99 (76)	15 (58)	
Ki-67	**Low (<14)**	41 (32)	8 (31)	0.939
	High (≥14)	89 (68)	18 (59)	
Molecular subtypes	**Luminal A**	33 (25)	6 (24)	0.630
	Luminal B	70 (54)	16 (61)	
	HER-2	6 (5)	2 (8)	
	TNBC	21 (16)	2 (8)	
Histological grade	**I-II**	100 (77)	21 (81)	0.668
	III	30 (23)	5 (19)	
T_{max}	**T1**	35 (27)	9 (35)	0.356
	T2	78 (60)	16 (61)	
	T3	17 (13)	1 (4)	
Tumor diameter (The largest tumor) (mm)*		31.2±18.5	27.2±13.1	0.382
T_{sum}	**T1**	35 (27)	2 (8)	**0.009**
	T2	78 (60)	15 (58)	
	T3	17 (13)	9 (34)	
Tumor diameter (Sum) (mm)*		31.2±18.5	43.08±19.7	**0.004**
Ductal carcinoma in situ	**Presence**	87 (33)	19 (73)	0.539
	Absence	43 (67)	7 (27)	
Axillary lymph node metastasis	**Presence**	74 (57)	21 (81)	**0.023**
	Absence	56 (43)	5 (19)	
Extranodal involvement	**Presence**	51 (68)	16 (76)	0.519
	Absence	23 (32)	5 (24)	
Lymphovascular invasion	**Presence**	52 (40)	16(62)	**0.043**
	Absence	78 (60)	10 (38)	
Perineural invasion	**Presence**	35 (29)	11 (48)	0.07
	Absence	87 (71)	12 (52)	
Pathological type	**IDC**	107 (82)	19 (73)	**<0.001**
	ILC	0	3 (12)	
	Other Types	23 (18)	4 (15)	
Surgical procedure	**Mastectomy**	56 (43)	23 (88)	**<0.001**
	BCS	74 (57)	3 (12)	

*Mean Value±Standard Deviation, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, TNBC: triple-negative breast cancer, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, BCS: breast conserving surgery

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Table 2. Comparison of clinical and pathological characteristics of patients with multifocal and multicentric breast cancer

		Multifocal n (%)	Multicentric n (%)	p value
Age	**< 50**	9 (53)	3 (33)	0.340
	≥ 50	8 (47)	6 (67)	
ER status	**Positive**	16 (94)	6 (67)	0.065
	Negative	1 (6)	3 (33)	
PR status	**Positive**	15 (88)	4 (44)	**0.017**
	Negative	2 (12)	5 (56)	
HER2 status	**Positive**	6 (35)	5 (56)	0.329
	Negative	11 (65)	4 (44)	
Ki-67	**Low (<14)**	6 (35)	2 (22)	0.492
	High (≥14)	11 (65)	7 (78)	
Molecular subtypes	**Luminal A**	4 (23)	2 (22)	0.200
	Luminal B	12 (71)	4 (45)	
	HER-2	0	2 (22)	
	TNBC	1 (6)	1 (11)	
Histological grade	**I-II**	14 (82)	7 (78)	0.778
	III	3 (18)	2 (22)	
T_{max}	**T1**	6 (35)	3 (33)	0.743
	T2	10 (59)	6 (67)	
	T3	1 (6)	0	
Tumor diameter (The largest tumor) (mm)*		28.35±14.11	27.11±11.86	0.824
T_{sum}	**T1**	2 (12)	0	0.533
	T2	9 (53)	6 (67)	
	T3	6 (35)	3 (33)	
Tumor diameter (Sum) (mm)*		41.53±18.44	46±23.02	
Ductal carcinoma in situ	**Presence**	14 (82)	5 (56)	0.143
	Absence	3 (18)	4 (44)	
Axillary lymph node metastasis	**Presence**	14 (82)	7 (78)	0.778
	Absence	3 (18)	2 (22)	
Extranodal involvement	**Presence**	10 (71)	6 (86)	0.469
	Absence	4 (29)	1 (14)	
Lymphovascular invasion	**Presence**	11 (65)	5 (56)	0.648
	Absence	6 (35)	4 (44)	
Perineural invasion	**Presence**	6 (40)	5 (62)	0.304
	Absence	9 (60)	3 (38)	
Pathological type	**IDC**	12 (70)	7 (78)	0.902
	ILC	2 (12)	1 (11)	
	Other Types	3 (18)	1 (11)	
Number of tumor foci*		2.18±0.53		0.849
Surgical procedure	**Mastectomy**	14(82)	9 (100)	0.180
	BCS	3 (18)	0	

*Mean Value±Standard Deviation, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, TNBC: triple-negative breast cancer, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, BCS: breast conserving surgery

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Table 3. Univariate analysis of lymph node positivity

		Lymph node positivity/n (%)	Univariable analysis		
			Odds ratio	95% CI for odds ratio	p value
Age	**< 50**	29/46 (63)	Referent		
	≥ 50	66/110 (60)	0.879	0.432-1.788	0.723
Multiplicity	**Unifocal**		74/130 (57)	Referent	
	Multifocal/multicentric	21/26 (81)	0.315	1.129-8.950	**0.029**
T_{sum}	**T1**	18/37 (49)	Referent		
	T2	54/93 (58)	5.537	1.552-19.750	**0.008**
	T3	23/26 (89)	8.093	2.067-31.687	**0.003**
T_{max}	**T1**	23/44 (52)	Referent		
	T2	56/94 (60)	5.429	1.179-24.985	**0.030**
	T3	16/18 (90)	7.304	1.498-35.624	**0.014**
Histological grade	**I-II**	71/121(59)	Referent		
	III	24/35(69)	0.651	0.292-1.449	0.293
LVI	**(-)**	36/88 (41)	Referent		
	(+)	59/68 (87)	0.106	0.047-0.240	**0.001**
PNI	**(-)**	52/99 (53)	Referent		
	(+)	37/46 (80)	0.269	0.118-0.616	**0.002**
Ki-67	**Low (<14)**	28/49 (57)	Referent		
	High (≥14)	67/107 (63)	1.256	0.631-2.500	0.516
ER status	**Negative**	17/31 (55)	Referent		
	Positive	78/125 (62)	0.732	0.331-1.620	0.441
PR status	**Negative**	25/41 (61)	Referent		
	Positive	70/115 (61)	1.004	0.484-2.086	0.990
HER2 status	**Negative**	69/114 (61)	Referent		
	Positive	26/42 (62)	0.944	0.456-1.953	0.876
Molecular subtypes	**Luminal A**	22/39 (57)	Referent		
	Luminal B	56/86 (65)	0.693	0.320-1.502	0.353
	HER-2	3/8 (38)	2.157	0.451-10.316	0.336
	TNBC	14/23 (61)	0.832	0.291-2.377	0.731
DCIS	**(-)**	28/50 (56)	Referent		
	(+)	67/106 (63)	0.741	0.374-1.468	0.39
Pathological type	**IDC**	83/126 (66)	Referent		
	ILC	3/3 (100)	3.860	1.600-9.315	**0.003**
	Others	9/27 (33)	0.010	0.001-0.014	0.999

LVI: lymphovascular invasion, PNI: perineural invasion, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, TNBC: triple-negative breast cancer, DCIS: ductal carcinoma in situ, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

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Table 4. Multivariate analysis of lymph node positivity

	Multivariable analysis					
	Using the largest tumor diameter (T_{max})			Using the aggregate tumor diameter (T_{sum})		
	Odds ratio	95% CI for odds ratio	p value	Odds ratio	95% CI for odds ratio	p value
Multiplicity						
MF/MC vs unifocal	0.327	0.087-1.227	0.098	0.505	0.136-1.878	0.308
T stage						
T2 vs T1	0.691	0.283-1.686	0.417	0.875	0.347-2.206	0.777
T3 vs T1	0.219	0.039-1.236	0.085	0.159	0.028-0.916	**0.040**
LVI						
(+) vs (-)	0.203	0.083-0.494	**0.001**	0.196	0.08-0.481	**0.001**
PNI						
(+) vs (-)	0.555	0.214-1.439	0.226	0.579	0.223-1.505	0.262
Pathological type						
Others vs IDC	0.004	0.002-0.007	0.999	0.009	0.002-0.012	0.999
ILC vs IDC	2.864	1.016-8.07	**0.047**	3.259	1.122-9.469	**0.030**

MF: multifocal, MC: multicentric, LVI: lymphovascular invasion, PNI: perineural invasion, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

Discussion

Ipsilateral multiple breast cancers are traditionally considered more aggressive than UF cancers. It has been shown that MF/MC tumors are seen at a younger age than UF, have more frequent LVI and ALNM, and have a higher T stage and grade [8,15-19]. In our study, a relationship was found with age, ALNM and LVI (Table 1). These features in themselves can be seen as indicators of aggressive biological behavior and poor prognosis. However, in past studies, there is no consensus on the effect of MF/MC on survival or recurrence [4,16,18-22].

Another important issue in multiple breast cancers is the definition of MF and MC tumors. MF is considered as the cells that separate from a single cancer focus, move through the ducts, implant in different locations, and form new tumor formations. In MF, the process starts with a single tumor cell clone. In MC, there is independent malignant transformation of two different cell groups [2,10]. It is easy to define lesions with a >90° angle between them and the nipple or with a distance of more than 5 cm between them as MC. However, it is difficult to define all tumors that do not meet these criteria as MF. Considering the development mechanism of MF tumors, they can be expected to be located close to each other. On the other hand, two cell groups that independently undergo malignant transformation can be at any distance from each other. Therefore, some of the tumors considered MF may be MC tumors originating from different clones. In addition, it has been shown that there may be mismatches in tumors defined as MF in terms of histopathological type, histological grade, receptor status and molecular subtypes, as in MC tumors [5,13]. The occurrence of mismatches in MF tumors reduces the reliability of these definitions based on tumor location. Therefore, the definition of MC and MF tumors is not clear. It is thought that there may be differences in the biological behavior of MC and MF tumors due to the difference in developmental mechanisms. Kanumuri et al reported that MC tumors are more aggressive than MF and that MC is an independent predictor of ALNM [13]. In our study, we made MF/MC definitions according to the 5 cm distance criterion and there was a difference between MF and MC tumors only in terms of PR positivity (Table 2).

The diameter and histopathological features of the largest tumor are considered for staging according to the tumor-node-metastasis (TNM) system and treatment plans [23]. However, the importance of total tumor burden in multiple tumors is controversial. There is no consensus on whether to use aggregate tumor diameter or largest diameter [15,17,24-26]. It has been shown that tumor diameter is an effective factor on lymph node metastasis [27,28]. Additionally, it has been reported that the frequency of ALNM increases in MF/MC tumors [8,15,17,18]. Some studies argue that the total tumor burden, not multiplicity, is effective on ALNM. Coombs and Boyages investigated the factors affecting ALNM. They applied multivariate analysis through two different models in which they determined T stage separately as T_{sum} and T_{max}. While MF/MC had a significant effect on ALNM in the model using T_{max}, it was observed that this effect disappeared when T_{sum} was used [17]. In Tong et al's study, it was observed that MF/MC lost its significant effect on ALNM when T stage was calculated based on T_{sum} [5]. In our study, MF/MC, T_{sum}, T_{max}, LVI, PNI and invasive lobular histology had a significant effect on ALNM in univariate analysis (Table 3). Previous studies also show that multiplicity, T_{sum}, T_{max}, LVI and histological grade are associated with lymph node metastasis [5,17,29]. In our multivariate analyses, MF/MC had no significant effect on ALNM in either model using T_{sum} or T_{max}. While T stage had no effect on ALNM in the model using T_{max}, a significant

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effect was seen when T_{sum} was used (Table 4). These results show the effect of total tumor burden on lymph node metastasis.

Conclusion

There is still no consensus regarding the definitions and behavior of MF and MC breast cancers. In our study, it was observed that MC/MF tumors showed aggressive features such as LVI, ALNM and being diagnosed at a young age more frequently than UFs. Our retrospective data supports that MF/MC is not a direct risk factor for ALNM and that the main factor affecting ALNM is the total tumor burden. Therefore, high-volume prospective studies on the use of aggregate tumor diameter in the staging of MF/MC tumors are required.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This study was approved by the Institutional Review Board (Approval Number: 2022-10/07, Date: 19.10.2023).

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