ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211168

Does focal heterogeneity affect survival in postoperative ipsilateral multifocal and multicentric breast cancers?

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SUMMARY

OBJECTIVE: In multicentric/multifocal breast tumors, there may be immunological and histological differences between foci that may affect survival and treatment choice. We aimed to evaluate the effect of focal heterogeneity seen in multicentric/multifocal breast tumors on survival.

METHODS: We retrospectively collected and analyzed the clinicopathological data of 89 female patients with multifocal/multicentric breast cancer, whose surgical and medical treatment was completed and who were followed up for 5 years.

RESULTS: Of all patients, 29.2% (26/89) were heterogeneous. Heterogeneity of these foci was as follows: histologic heterogeneity of index foci (mix type): 15.7% (14/89), histologic heterogeneity of inter-foci: 7.9% (7/89), and immunohistochemical heterogeneity of inter-foci: 10.1% (9/89). When additional foci were evaluated, oncological therapy was changed for 3 (3.3%) of 89 patients. Heterogeneity does not have a significant (p>0.05) effect on recurrence and survival in multicentric/multifocal breast cancers. Pathological N stage is an independent risk factor for disease-free survival (hazard ratio=2.29, 95% confidence interval=1.39–3.76, p=0.001).

CONCLUSIONS: In multifocal/multicentric breast cancers, less than 4% of patients may experience heterogeneity requiring change in the therapeutic decision. However, heterogeneity does not have a significant effect on recurrence and survival in multifocal/multicentric breast cancers. The pathological N stage is an independent risk factor for disease-free survival.

KEYWORDS: Breas cancer. Multifocal. Multicentric. Tumor heterogeneity. Survival.

INTRODUCTION

Invasive ductal carcinoma (IDC) is the most frequently diagnosed and the most common type of breast cancer among women. In the latest classification of the World Health Organization, at least 17 different special histological types have been described, which constitute 25% of all breast cancers. Histological types are associated with the morphological and cytological features of the cell, derived from the growth pattern of breast cancer[1]. Depending on different histological methods employed and the cases selected, 6–75% of these tumors are multicentric (MC) or multifocal (MF) breast tumors[2].

The presence of multiple foci on the same quadrant or different quadrants of breast is defined as MC/MF[3]. The development of MF/MC breast cancers may be explained through two mechanisms in the literature. The first mechanism (polyclonal) may occur as multiple independent tumor foci. In these foci, different phenotypes may occur due to underlying molecular changes. The second mechanism (monoclonal) may be the genetic or phenotypic change in the foci during the intramammary spread of the tumor or the progression of the tumor[4]. In case of multiple breast cancers, there may be different histological types and/or histological grades between tumors in 3–37.5% of cases[5]. This situation may affect survival and treatment choice[6].

We aimed to investigate the effect of focal heterogeneity on 5-year disease-free survival (DFS) in MC/MF breast cancers because there is limited number of publications in the literature regarding intra- and inter-focal heterogeneity in MC/MF breast tumors.

METHODS

Ethical approval

Local ethics committee approval (dated November 13, 2020, Decision no.: 2588) was obtained.

Patient selection

Inclusion criteria: The patient files of Health Sciences University, Istanbul Training and Research Hospital, were retrospectively scanned and 89 female patients who underwent operation

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on December 15, 2021. Accepted on January 04, 2022.

between January 1, 2010 and January 1, 2015, had surgical, immunohistochemical, and histopathological results [i.e., estrogen receptor (ER), progesterone receptor (PR), human epithelial growth factor receptor-2 (HER-2), proliferation index (KI-67)] for MC/MF breast cancer and who were given postoperative complementary medical treatments and followed up were identified and included in the study.

Exclusion criteria: Male patients; patients with preoperative stage 4 metastatic breast cancer, unifocal breast cancer, or bilateral breast cancer; and patients who received neoadjuvant chemotherapy, who did not undergo surgery and who did not have immunohistochemical and histopathological results, and follow-up records were excluded from the study.

Immunohistochemical subtypes classification

ER, PR (if ER or PR ≥1%, positive; if ER or PR <1%, negative), and HER-2 [HER-2 score=1–0, negative; HER-2 score=3, positive; and HER-2 score =2, positive which was tested using the Silver-enhanced in situ hybridization (SISH)] were accepted. The recommendations in the St. Gallen International Consensus Guidelines were taken into consideration in the immunohistochemical classification of subtypes.

Luminal A: ER+, PR+, HER-2-, Ki67<20% and/or PR≥20%, and/or low grade (G1/2).

Luminal B: ER+, PR+/-, HER-2-, Ki67≥20% and/or PR<20%, and/or high grade (G3) or ER+, PR +/-, HER-2+, any Ki67, any PR.

HER-2-positive: ER-, PR-, and HER-2+.

Triple-negative: ER-, PR-, and HER-2-[7].

Focal heterogeneity

Histologic heterogeneity of index intra-foci (HhİİF) (mix type=intra-focal): Heterogeneity of index focus observed in histological type, which is the large tumor size.

Histologic heterogeneity of inter-foci (HhİF): Heterogeneity observed in histological type between foci.

Immunohistochemical heterogeneity of inter-foci (İhİF): Heterogeneity observed in immunohistochemical (phenotypic) subtype between foci.

Statistical analysis

The analyses were carried out using SPSS version 26.0.

RESULTS

The median age of 89 patients included in the study was 48 years. The most dominant findings in the study were as follows: ER+=78.7% (70/89), PR+=73% (65/89), HER-2-=75.3% (67/89), Ki67≥20%=51.7% (46/89), LVI+=61.8% (55/89), G2=65.2% (58/89), two foci=74.2% (66/89), IDC=70.8% (63/89), and homogeneity with the rates of 70.7% (63/89). In total, 29.2% (26/89) of MF/MC breast carcinomas were heterogeneous. Heterogeneity distribution of the relative foci was HhİİF (15.7%, 14/89), HhİF (7.9%, 7/89), and İhİF (10.1%, 9/89). Evaluation of additional foci resulted in alteration of postoperative oncology treatment of three patients according to the histopathology of index focus. In those three (3.3%, 3/89) patients, there was heterogeneity in immunohistochemical subtypes, and the tumor grade was G3 in two patients and G2 in one patient (Tables 1 and 2).

The median duration of clinical follow-up was 83 months (min–max: 5–120 months, mean: 81.3±24 months). Recurrence was recorded in 23.6% (21/89) of the patients during follow-up. The most common postoperative recurrence types were local recurrence (4.5%, 4/89), visceral organ (5.6%, 5/89), bone (12.4%, 11/89), and bone plus visceral organ (1.1%, 1/89). The pathological N (pN) stage and mortality rate were significantly higher (38.1%, 8/21) in the recurrence group as compared to the group without recurrence ($p<0.05$) (Table 1).

The univariate analysis assessing DFS showed that pathological T (pT) stage, pN stage, and histological grade of index focus were significantly effective ($p<0.05$). Similarly, the multivariate analysis indicated that pN stage had a significantly independent (HR=2.29, 95%CI 1.39–3.76, p=0.001) effect on DFS. In the univariate analysis evaluating overall survival (OS), however, pN stage had significant effect only on OS (HR=5.82, 95%CI 1.580–21.43, p=0.008) (Table 3).

DISCUSSION

TNM classification is accepted as the gold standard in breast cancer staging. In its latest version, the largest diameter in MF/MC breast cancers is taken into account, and other foci are not[8]. As a result, cumulative tumor burden does not affect the choice of treatment. In many studies in the literature, it is known that MF/MC breast cancers have higher metastases, recurrence, and decreased survival when compared with similar stage unifocal (UF) breast cancers[6,9-11]. The state of the axillary lymph node (ALN) (or pN stage) is one of the most important prognostic factors. An increase in the number of the state of ALN metastases proportionally decreases DFS and OS. In the literature, the factors indicative of the presence of the state of ALN metastases are large tumor size, presence of lymphovascular invasion, high grade (G3), molecular status, and tumors with lateral or central localization[5,8,12]. This situation has brought along discussions on subjects such as survival, mortality, cost, staging, biological, and

Table 1. Comparison of clinicopathological, recurrent and non-recurrent patients after postoperative oncological treatment.

		Clinicopathological data			Recurrence (-)			Recurrence (+)			p
		Min.–Max.	Median	Mean±SD/n-%	Mean±SD/n-%		Median	Mean±SD/n-%		Median	
		28.0–79.0	48.0	50.4±12.5	50.0±12.5		48.0	53.8±12.9		55.5	0.498 [m]
Age	≤50			50 56.2%	39	57.4%		11	52.4%		0.688 [m]
	>50			39 43.8%	29	42.6%		10	47.6%		
İndex focus T size (cm)		0.3–9.0	2.5	2.9±1.8	2.8±1.8		2.5	3.8±2.2		3.3	0.186[m]
Surgery type	Breast conserving			17 19.1%	16	23.5%		1	4.8%		0.056[x2]
	Mastectomy			72 80.9%	52	76.5%		20	95.2%		
Histologic types of index foci	Ductal carcinoma			63 70.8%	51	75.0%		12	57.1%		0.194[x2]
	Lobular carcinoma			3 3.4%	2	2.9%		1	4.8%		0.558[x2]
	Mix types			14 15.7%	8	11.8%		6	28.6%		0.132[x2]
	Special types			9 10.1%	7	10.3%		2	9.5%		0.755[x2]
Pathological T category	pT1≤2 cm			29 32.6%	24	35.3%		5	23.8%		0.148[x2]
	2 cm<pT2≤5 cm			35 39.3%	28	41.2%		7	33.3%		
	pT3			5 5.6%	4	5.9%		1	4.8%		
	pT4			20 22.5%	12	17.6%		8	38.1%		
Pathological N category	pN0			20 22.5%	20	29.4%		0	0.0%		**0.003[x2]**
	pN1			25 28.1%	19	27.9%		6	28.6%		
	pN2			23 25.8%	18	26.5%		5	23.8%		
	pN3			20 22.5%	10	14.7%		10	47.6%		
	Missing			1 1.1%							
Grade of index foci	I			5 5.6%	5	7.5%		0	0.0%		0.258[x2]
	II			58 65.2%	46	68.7%		12	60.0%		
	III			24 27.0%	16	23.9%		8	40.0%		
	Missing			2 2.2%							
Number of foci	II			66 74.2%	52	76.5%		14	66.7%		0.540[x2]
	III			18 20.2%	12	17.6%		6	28.6%		
	IV			4 4.5%	4	5.9%		0	0.0%		
	V			1 1.1%	0	0.0%		1	4.8%		
İndex focus ER status	≥1%			70 78.7%	55	80.9%		15	71.4%		0.355[x2]
	<1%			19 21.3%	13	19.1%		6	28.6%		
İndex focus PR status	≥1%			65 73.0%	53	77.9%		12	57.1%		0.060[x2]
	<1%			24 27.0%	15	22.1%		9	42.9%		
İndex focus HER2 (SİSH) status	Positive			22 24.7%	18	26.5%		4	19.0%		0.491[x2]
	Negative			67 75.3%	50	73.5%		17	81,0%		
Index focus Ki67 status	≥ 20%			46 51.7%	33	48.5%		13	61.9%		0.284[x2]
	< 20%			43 48.3%	35	51.5%		8	38.1%		
Lymphovascular invasion	Yes			55 61.8%	39	58.2%		16	76.2%		0.137[x2]
	No			33 37.1%	28	41.8%		5	23.8%		
	Missing			1 1.1%							
Perineural invasion	Yes			18 20.2%	14	21.9%		4	20.0%		0.252[x2]
	No			66 74.2%	50	78.1%		16	80.0%		
	Missing			5 5.6%							

Continue...

Table 1. Continuation.

		Clinicopathological data				Recurrence (-)			Recurrence (+)			p
		Min.–Max.	Median	Mean±SD/n-%		Mean±SD/n-%		Median	Mean±SD/n-%		Median	
Perinodal invasion	Yes			39	43.8%	27	40.3%		12	57.1%		0.1752
	No			49	55.1%	40	%59.7%		9	42.9%		
	Missing			1	1.1%							
Histologic heterogeneity of index foci	Homogeneity			75	84.4%	59	86.8%		15	71.4%		0.101 x2
	Heterogeneity			14	15.7%	8	11.8%		6	28.6%		
Histologic heterogeneity inter-foci	Homogeneity			82	92.1%	63	92.6%		19	90.5%		0.888 x2
	Heterogeneity			7	7.9%	5	7.4%		2	9.5%		
Immunohistochemical heterogeneity inter-foci	Homogeneity			80	89.9%	60	88.2%		20	95.2%		0.352 x2
	Heterogeneity			9	10.1%	8	11.8%		1	4.8%		
Follow-up time						84.9±20.6		89.0	45.0±27.7		38.0	0.106 m
Disease-related mortality	No					68	100%		13	61.9%		**0.000 x2**
	Yes					0	0.0%		8	38.1%		
Recurrence	No			68	76.6%							
	Yes			21	23.6%							
Recurrence location	Local			4	4.5%							
	Visceral			5	5.6%							
	Bone			11	12.4%							
	Bone+visceral			1	1.1%							

m Mann–Whitney U test/x2 Chi-square test (Fischer's exact); T: tumor size, N: lymph node; ER: estrogen receptor; PR: progesterone receptor; HER-2: human epithelial growth factor receptor-2; SİSH: Silver-enhanced in situ hybridization; Ki67: proliferation index. Bold indicates statistically significant values.

morphological behaviors in MF/MC breast tumors at a time when personalized surgical and oncological treatments gain momentum.

Breast cancer is a heterogeneous group of neoplasms with clinical, morphological, and immunohistochemical differences within a single tumor or between tumors. Depending on different histological methods employed and the cases selected, 6–75% of these tumors are MC/MF breast tumors. Inter-focal heterogeneity is one of the major discussion topics in MF/MC breast tumors. In the literature, the rates of HhİİF, HhİF, and İhİF in MF/MC breast cancers are reported as 0–17.1, 0–37, 0–12.7%, respectively[2,6,13,14]. Similar to the literature, we found the rates of 15.7, 7.9, and 10.1%, respectively.

In their series dated 2012 of 65 cases with MF/MC IDC, Choi et al. found additional heterogeneous tumor foci that would change the treatment decision in 8% (5/65) of the patients. Choi et al. suggested that immunohistochemical analysis of the index tumor may be sufficient in routine practice, but if there is high-grade, different histological features or heterogeneous ductal carcinoma in situ component in the index tumor, additional foci should be examined[2]. In 2014, Parker et al. evaluated HhİİF (heterogeneity in histological type and grade) and HhİF using three classification systems (i.e., modified Nielsen[15], St. Gallen 2011[16], and Sotiriou[17]] in their study of 100 cases. In the evaluation of additional heterogeneous tumor foci using the modified Nielsen, St. Gallen 2011, and Sotiriou systems, the rate of changes in treatment decision were as follows: 3.63% (4/110), 7.27% (8/118), and 7.27% (8/110), respectively. In MF/MC breast cancers that were classified according to the modified Nielsen system, the risk of death was significantly higher ($p<0.05$) and survival was shorter in the İhİF group. However, there was no significant difference ($p>0.05$) between the groups according to the classifications by the St. Gallen 2011 and Sotiriou classification systems. There was no significant difference ($p>0.05$) between HhİİF MF/MC breast cancers and the other homogeneous group of the series. The authors reported that in patients with inter-focal histological type and/or degree of heterogeneity, up to five foci of inter-focal immunohistochemical evaluation may reduce the risk of death from the disease[6]. Mosbah et al. did not detect any heterogeneity that could change the treatment decision in the study they conducted in 2015 on

Table 2. Heterogeneity distribution of MF/MC breast cancers.

Patient	Number of foci	Size (cm)	Grade of index foci	Histology of intra- index and inter-foci	Histology of inter foci	Immunohistology of inter-foci (St. Galen)	Those whose medical treatment changed
1	2	1.2/0.3	2	D-MP/D-MP	D-MP/D-MP	LuA/LuA	–
2	2	1.9/1.6	3	L-T/L-T	L-T/L-T	LuA/LuA	–
3	2	2.3/2	3	D-MP/D-MP	D-MP/D-MP	LuB/LuB	–
4	2	2.5/1.5	2	M-D/M-D	M-D/M-D	LuB/LuB	–
5	2	3.5/0.2	2	D-M/D-M	D-M/D-M	LuB/LuB	–
6	2	4/2.5	2	D-MP/D-MP	D-MP/D-MP	LuB/LuB	–
7	2	5/0.2	2	N-D/N-D	N-D/N-D	LuB/LuB	–
8	2	2.5/0.3	2	D-MP/D-MP	D-MP/D-MP	HER/HER	–
9	2	5.5/1	2	D-MP/D-MP	D-MP/D-MP	HER/HER	–
10	2	6/0.9	3	M-MP/M-MP	M-MP/M-MP	HER/HER	–
11	3	6/4/1	2	D-L/D-L/D	D-L/D-L/D	LuA/LuA/LuA	–
12	3	3.5/1.9/1.4	3	D-MP/D-MP/D-MP	D-MP/D-MP/D-MP	LuB/LuB/LuB	–
13	2	0.9/0.6	1	C/T	C/T	LuA/LuA	–
14	2	1/0.6	2	D/T	D/T	LuA/LuA	–
15	2	2/0.2	2	C/L	C/L	LuA/LuA	–
16	2	2/1.8	3	D/D-L	D/D-L	Tn/Tn	–
17	3	2.8/2/0.2	2	D/L/L	D/L/L	LuA/LuA/LuA	–
18	2	1.5/1.2	2	D/D	D/D	LuB/LuA	–
19	2	1.8/1.5	2	D-P/D-P	D-P/D-P	LuB/LuA	–
20	2	2.5/2.5	2	D-L/D-L	D-L/D-L	LuB/LuA	–
21	2	4/3	2	D/D	D/D	LuB/LuA	–
22	3	2.4/1.8/1.5	2	D/D/D	D/D/D	LuB/LuB/LuA	–
23	3	2.6/1.1/0.3	2	D/D/D	D/D/D	LuB/LuA/LuA	–
24	2	2.5/2.1	3	D/D	D/D	LuA/LuB	+
25	2	3/1.6	2	D/D	D/D	LuA/LuB	+
26	2	1/1	3	D/D	D/D	Tn/LuB	+

D: invasive ductal carcinoma; L: invasive lobular carcinoma; MP: invasive micropapillary carcinoma; M: mucinous carcinoma; N: neuroendocrine carcinoma; T: invasive tubular carcinoma; C: invasive cribriform carcinoma; LuA: Luminal A; LuB: Luminal B; HER: human epidermal growth factor receptor; Tn: triple negative.

205 cases, in which they performed histopathological evaluations of up to two foci. Mosbah et al. reported that even if there is a discrepancy between tumor foci, it had little effect on the treatment decision, and that even if the focus showed different tumor grades, performing immunohistochemical evaluation on the index tumor focus only may be sufficient[14]. In our study, evaluation of additional foci changed postoperative oncological treatment for three patients. In those three (3.3%, 3/89) patients, the number of foci was two and there was heterogeneity in immunohistochemical subtypes. The histological grade of index tumor foci was G3 in three patients and G2 in one patient (Tables 1 and 2). When compared with the literature considering the cost and individualized oncological treatments, it seems sufficient to evaluate grades 2–3 tumors in the index focus up to two foci. Nevertheless, it should also be noted that heterogeneity (i.e., HhİİF, HhİF, and İhİF) does not have a statistically significant effect on recurrence and survival (DFS and OS) in MF/MC breast cancer (Tables 1 and 3).

Boros et al. evaluated the risk of ALN metastasis in their study of 155 cases with MF/MC breast cancer in 2015 and found that there was not a statistically significant difference between homogeneous patients (73.91%, 85/115) and those (80%, 32/40) with

Table 3. Univariate and multivariate analyses for disease-free survival and overall survival.

Survival	Disease-free survival						Overall survival					
	Univariate model			Multivariate model			Univariate model			Multivariate model		
Disease-free survival	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Age (≤50/>50)	0.99	0.96–1.03	0.628				1.02	0.969–1.08	0.411			
Index focus size (cm)	1.13	0.93–1.37	0.230				1.22	0.912–1.64	0.178			
Surgery type (breast conserving/mastectomy)	4.38	0.59–32.70	0.149				28.28	0.016–>100	0.383			
Histological types of index foci	1.24	0.87–1.79	0.239				1.52	0.891–2.59	0.125			
Pathological T stage	1.58	1.07–2.33	**0.021**				1.82	0.987–3.34	0.055			
Pathological N stage	2.29	1.39–3.76	**0.001**	2.29	1.39–3.76	**0.001**	5.82	1.580–21.43	**0.008**			
Grade of index foci	2.32	1.01–5.32	**0.048**				1.85	0.500–6.85	0.356			
Number of foci	1.52	0.76–3.02	0.236				11.19	0.408–3.47	0.750			
Index focus ER status (ER≥1%/ER<1%)	1.64	0.64–4.23	0.306				2.41	0.575–10.09	0.229			
Index focus PR status (PR≥1%/PR<1%)	2.71	1.14–6.45	**0.024**				2.81	0.701–11.24	0.145			
Index focus HER-2 (SİSH) status (+/–)	1.15	0.39–3.41	0.805				2.21	0.272–17.98	0.458			
Index focus Ki67 status (≥20%/<20%)	0.52	0.21–1.15	0.145				0.61	0.146–2.55	0.499			
Lymphovascular invasion (yes/no)	0.46	0.17–1.27	0.133				0.21	0.025–1.70	0.143			
Perineural invasion (yes/no)	1.36	0.45–4.07	0.586				1.85	2.223–15.46	0.568			
Perinodal invasion (yes/no)	0.67	0.28–1.58	0.356				0.24	0.049–1.21	0.084			
Histologic heterogeneity of index foci (homogeneity/heterogeneity)	1.90	0.73–4.89	0.186				3.47	0.823–14.60	0.090			
Histologic heterogeneity of inter-foci (homogeneity/heterogeneity)	1.10	0.26–4.74	0.895				1.71	0.210–13.93	0.616			
Immunohistochemical heterogeneity of inter-foci (homogeneity/heterogeneity)	0.32	0.04–2.39	0.267				0.04	0.000–984.83	0.537			

Cox regression (forward LR); T: tumor size; N: lymph node; ER: estrogen receptor; PR: progesterone receptor; HER-2: human epithelial growth factor receptor-2; SİSH: Silver-enhanced in situ hybridization; Ki67: proliferation index. Bold indicates statistically significant values.

mismatches between histological type, grade, or both regarding the rate of ALN metastases (p>0.05). The rate of heterogeneous MF/MC breast cancer determined ALN metastases as follows: 72.73% (8/11) with histological type heterogeneity, 87.5% (14/16) with inter-focal grade heterogeneity, and 76.92% (10/13) with histological type and grade heterogeneity. Most (33.33%, 8/24) of the heterogeneous MF/MC tumors with differences in inter-focal grade (87.5%, 21/24) had a high histological grade. In that study, the authors stated that the histological features (e.g., type and grade) of ALN metastases in MF/MC breast cancers correspond to the histological type with unfavorable prognosis or the highest histological grade, which is not necessarily of the index focus, and emphasized that it is necessary to conduct an individual histopathological evaluation for each tumor focus with high grade[5]. It is known that before the inclusion of prognostic biomarkers (e.g., grade, hormone receptor, oncogene expression,

and multigene panel recurrence score) in the current TNM classification, hormonotherapy increased the long-term survival by decreasing the recurrence rate of ER+/PR+ breast tumors, yet had no effect on long-term survival in ER+/PR- breast tumors[8,18]. In our study, a significant ($p<0.05$) effect of pT stage, pN stage, and index focus histological grade was observed in univariate analysis in which DFS was evaluated. In multivariate analysis, pN stage had a significantly independent (HR=2.29, 95%CI 1.39–3.76, p=0.001) effect on DFS. In the univariate analysis evaluating OS, however, pN stage had a significant effect only on OS (HR=5.82, 95%CI 1.580–21.43, p=0.008) (Table 3). This result supports the literature.

The limitations of the study are as follows: it evaluated the long-term effects, it had a retrospective design, and it could not evaluate the histological/immunohistochemical footprints of the foci in metastatic ALN.

CONCLUSION

At present, when oncological treatments are personalized with a multidisciplinary approach, less than 4% of patients have heterogeneity in MF/MC breast cancers, which necessitate an alteration in therapeutic decisions. As evaluating multiple foci would increase the cost and labor, it may be enough to evaluate grade 2–3 tumors in the index focus up to two foci. However, heterogeneity does not have a significant effect on recurrence and survival in MF/MC breast cancers. The pN is an independent risk factor for DFS.

ETHICAL APPROVAL

All procedures performed in this study, involving human participants, were in accordance with the ethical standards of the İnstitutional Research Committee and 1964 Helsinki Declaration. Local ethics committee approval was obtained from Health Sciences University, Istanbul Training and Research Hospital (dated November 13, 2020, Decision no.: 2588).

AVAILABILITY OF DATA

All data generated or analyzed during this study are included in this published article (and its supplementary information files). But restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of Health Sciences University Turkish Ministry of Health İstanbul Research and Training Hospital.

ACKNOWLEDGMENTS

As authors, we thank the Health Sciences University Turkish Ministry of Health İstanbul Research and Training Hospital Research Projects Unit.

AUTHORS' CONTRIBUTIONS

FD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, and Writing – review & editing. **HÖ:** Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Software, Supervision, Validation, and Visualization. **KU:** Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Software, Supervision, Validation, and Visualization. **ŞÇ:** Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, and Visualization. **SBH:** Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, and Visualization. **FDCT:** Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, and Visualization. **EF:** Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, and Visualization. **SS:** Methodology, Resources, Supervision, Validation, Visualization, and Writing – review & editing.

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