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ORIGINAL ARTICLE

Characteristics and outcomes of patients with multifocal/multicentric and unifocal breast cancer

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Summary

Purpose: *The clinical behavior and outcome of multifocal (MF) and multicentric (MC) breast tumors are not well characterized. The purpose of this study was to compare the prognosis of MF/MC tumors with unifocal (UF) tumors and its correlation with other pathological characteristics and patient outcomes.*

Methods: *Eighty-three patients with MC/MF breast cancer and 501 with UF breast cancer treated at the Surgical Clinic Nis were studied. We compared MC/MF and UF breast cancer patients with respect to demographics, tumor characteristics, adjuvant systemic therapy, local recurrence-free survival (LRFS) and overall survival (OS).*

Results: *There was no significant statistical difference between the two groups with respect to mean age at diagnosis, tumor grade, nodal status, estrogen receptor status, lymphovascular invasion (LVI) and adjuvant systemic therapy. The MC/MF group had more patients with modified radical mastectomy and the UF group had more patients with breast-conserving surgery. Cox multivariate regression analysis showed that the regional lymph node metastases and LVI were the most important predictors of 5-year OS rate. During this period, locoregional recurrence was registered in 29 (5.78%) patients in the UF group and in 5 (6.02%) patients in the MF/MC group (p=0.48). No statistically significant differences in the 5-year LRFS and OS between the two groups were noticed.*

Conclusion: *The prognostic value of MF/MC disease is still not well known, although some studies have suggested that it is associated with a worse prognosis. This study showed no statistically significant difference in the 5-year LRFS and OS between UF and MF/MC groups.*

Key words: *breast cancer, multicentric, multifocal, outcome, unifocal*

Introduction

No precise characterization of the clinical behavior and outcome of MF and MC breast tumors exists. MF breast cancer can be defined as two or more separate tumors in the same quadrant of the breast while MC can be defined as two or more separate invasive tumors found in more than one quadrant of the same breast. There has been a lot of research on UF breast cancer. However, MF and MC breast tumors were not explored enough. It is reported that the incidence is between 6 and 77% [1,2]. Multifocality can be associated with several more aggressive characteristics such as increased rate of axillary lymph node metastases, larger tumors and possible adverse patient outcome [3]. The tumor size can be determined by observing the largest diameter of the largest focus.

The purpose of this study was to compare the prognosis of MF/MC breast tumors with UF tumors and its correlation with other pathological characteristics and patient outcomes.

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Methods

Female patients aged 18 and older, diagnosed with unilateral stage I to III breast cancer and treated with breast surgery at the Surgical Clinic Nis between January 2005 and December 2007 were identified from our database.

Patients were excluded if they had neo-adjuvant treatment, or were known to have had a previous breast cancer or bilateral cancer. If a patient had both MF and MC disease, was classified as MC. The tumor stage at primary diagnosis was determined according to the UICC/TNM classification [4]. Patient and clinical characteristics including age, pathologic stage**,** tumor size, nodal status, histology, nuclear grade, presence of LVI and therapy received (surgery, adjuvant chemotherapy, radiation therapy and endocrine therapy) were compared between groups. Mammography, breast ultrasonography and breast magnetic resonance imaging (MRI) were used to diagnose breast cancer multifocality.

The primary surgical treatment consisted of either breast conservation or modified radical mastectomy. Routine axillary dissections were performed on lymph nodes of levels I and II, while level III nodal excision was carried out only in cases with macroscopic metastatic disease of I and II level. Post-mastectomy radiation therapy was delivered to patients treated with breast-conserving surgery, in those with axillary nodal involvement of 4 or more nodes and in those with tumor diameter 5 cm or more. Patients were administered adjuvant chemotherapy in case of lymph node

Table 1. Characteristics and outcomes of patients with multifocal/multicentric and unifocal breast cancer (p=0.72)

Characteristics	*Multifocal/ multicentric (n=83)*	*Unifocal (n =501)*	*p value*
Age, years, mean ± SD	54.7 ±11.9	53.9 ± 13.1	1.00*
Median follow up, mo (range)	54 (11-143)	47 (12-141)	0.20
Pathologic stage, n (%)			<0.0001†
I	29 (34.90)	251 (50.10)	
II	42 (50.60)	165 (32.93)	
III	12 (14.50)	85 (16.97)	
Tumor size, n (%)			0.005†
T1	40 (48.20)	292 (58.30)	
T2	31 (37.35)	175 (34.93)	
T3	12 (14.45)	34 (6.77)	
Nodal status, n (%)			0.071
N0	50 (60.25)	334 (66.67)	
N+	33 (39.75)	167 (33.33)	
Histology, n (%)			<0.0001†
Ductal	40 (48.20)	371 (74.05)	
Ductal +lobular	17 (20.48)	66 (13.17)	
Lobular	22 (26.50)	101 (9.43)	
Other	4 (4.82)	17 (3.35)	
Grade, n (%)			0.57
G1	27 (32.53)	191 (38.13)	
G2	36 (43.37)	206 (41.12)	
G3	20 (24.10)	104 (20.75)	
ER status, n (%)			0.41
Positive	70 (84.33)	421 (84.03)	
Negative	13 (15.67)	80 (15.97)	
LVSI, n (%)			0.33
Present	28 (33.74)	122 (24.35)	
Absent	55 (66.26)	379 (75.65)	
Primary operation, n (%)			0.005†
Breast-conserving	11 (13.25)	179 (35.72)	
Mastectomy	72 (86.75)	322 (64.28)	
Adjuvant therapy, n (%)			0.46
Chemotherapy	37 (44.57)	191 (38.12)	
Hormonal therapy	70 (84.33)	421 (84.03)	
Radiotherapy	29 (34.94)	153 (30.54)	
Local recurrence, n (%)	4 (4.81)	19 (3.79)	NA
5-y overall survival, %	93	92	NA

LVSI: Lymphovascular invasion, NA: not applicable *Student's *t*-test †Analysis by Cochran Armitage test

involvement, in premenopausal women and for some women diagnosed with early-stage breast cancer if cancer was hormone-receptor-negative. Depending on the hormone receptor status they received adjuvant endocrine therapy.

Statistics

Chi-square test was used to compare the MF/MC with the UF group. Continuous variables were analyzed using the Student's *t*-test and Cochran Armitage test.

Five-year LRFS and OS were calculated. A patient was censored for OS if she was alive at the time of last follow-up. A patient was censored for LRFS if she did not have a local or regional recurrence at the time of last follow-up. The survival outcomes were generated by the Kaplan-Meier product limit method and compared by the log-rank test. Multivariate analysis was performed by the Cox proportional hazards regression analysis. A p value <0.05 was considered statistically significant.

Results

We identified 83 patients with MC/MF breast cancer and 501with Unifocal breast cancer.

The mean patient age with MC/MF breast cancer at diagnosis was 54.7 ±11.9 years and for the UF breast cancer it was 53.9 ± 13.1 years. Comparison between the 2 groups of patients with respect to tumor characteristics is shown in Table 1. The UF group had a higher proportion of patients with stage I tumors compared with the MC/MF group (50.10 vs 34.90%, p <0.0001).

There was a significant difference between the two groups concerning T status (p=0.005). The MC/MF group had more T3 tumors compared with the UF group but the UF group had more T1 tumors. When it comes to histology, a significant difference between the two groups (p<0.0001) was noticed; the MC/MF group had more lobular tumors and the UF group had more ductal tumors. There was no statistically significant difference between the two groups with respect to age at diagnosis, tumor grade, nodal status, estrogen receptor status, and LVI. In addition, no significant statistical difference was found between the two groups in terms of adjuvant systemic therapy (chemotherapy and hormone therapy). According to primary operation there was a significant difference between the two groups (p=0.005); the MC/MF group had more patients with modified radical mastectomy and the UF group had more patients with breast-conserving surgery.

Clinical and biological characteristics of the tumor for the occurrence of locoregional recurrences are shown in Table 2. On multivariate analysis, histological grade (G), relative hazard ratio (RH) 4.76 (1.48-14.41); p=0.001) and LVI RH 3.88 (0.66-12.741); p=0.001) were found as the most important parameters for the occurrence of locoregional recurrence in our series of patients.

Table 3 shows the patient clinical and biological prognostic factors for OS. Cox multivariate regression analysis showed that the regional lymph node metastases (hazard ratio/HR=0.43; 95% CI 0.31-0.69, p<0.0001), and LVI (HR=0.41; 95% CI 0.27-0.78, p<0.0001) were the most important predictors of 5-year OS.

There was no statistically significant difference in the 5-year LRFS between the UF and MF/MC groups (p=0.72; Figure 1).

Also, no significant difference in the 5-year OS between the UF and MF/MC groups was noticed (p=0.92; Figure 2).

Table 2. Multivariate analysis of a 5-year follow-up using Cox proportional hazard models for local recurrence-free survival

Characteristics	*Odds ratio*	*95% confidence interval*	*p value*
Age (years)			
>50	0.56	0.25-1.48	0.441
≤50	1		
Group			
Unifocal	1		
MF/MC	0.93	0.56–1.55	0.42
Tumor size (mm)			
≤20	1		
>20	3.15	0.88-11.16	0.005
Nodal status			
N0	1		
N+	0.39	0.15-1.41	0.243
Histology			
Ductal	1		
Other	0.77	0.51-1.23	0.766
Grade			
G1	1		
G2-3	4.76	1.48-14.41	<0.0001
LVSI			
Present	3.88	0.66-12.741	<0.0001
Absent	1		
Adjuvant chemotherapy			
Yes	1		
No	0.55	0.22–0.97	0.005
Radiotherapy			
Yes	1		
No	0.42	0.31–0.69	0.005
Adjuvant hormonal therapy	1		
Yes			
No	1.92	0.64-5.83	0.209

MF: multifocal, MC: multicentric, LVSI: Lymphovascular invasion

Table 3. Multivariate analysis a 5-year follow-up using Cox proportional hazard model for overall survival

Characteristics	*Odds ratio*	*95% confidence interval*	*p value*
Age (years)			
>50	1		
≤50	0.78	0.44-1.32	0.32
Group			
Unifocal	1		
MF/MC	0.91	0.65–1.21	0.51
Tumor size (mm)			
≤20	1		
>20	0.46	0.23-0.81	0.006
Nodal status			
N0	1		
N+	0.43	0.31-0.69	<0.0001
Histology			
Ductal	0.85	0.51-1.61	0.55
Other	1		
Grade			
G1	1		
G2-3	1.34	0.94-1.88	0.07
LVSI			
Present	0.41	0.27-0.78	<0.0001
Absent	1		
Adjuvant chemotherapy			
Yes	1		
No	0.46	0.34-0.77	0.001
Adjuvant hormonal therapy			
Yes	0.73	0.43-1.15	0.17
No	1		
Radiotherapy			
Yes	0.55	0.22-1.27	0.16
No	1		

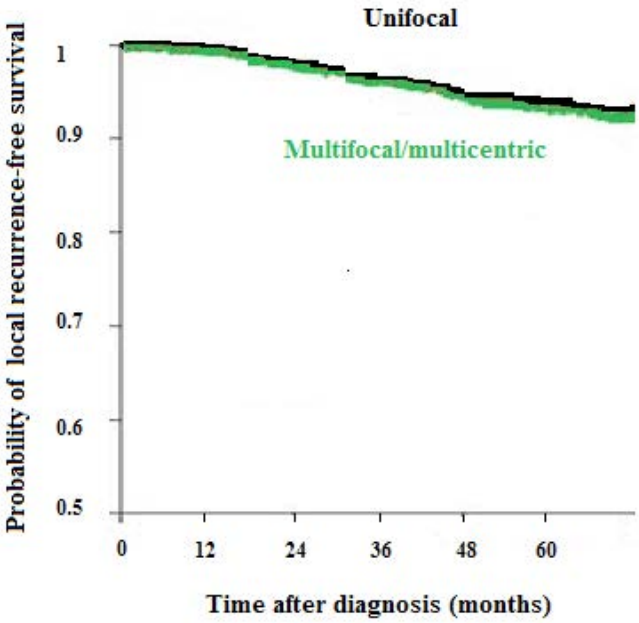

Figure 1. Local recurrence-free survival estimates comparing MF/MC and UF disease (p=0.72).

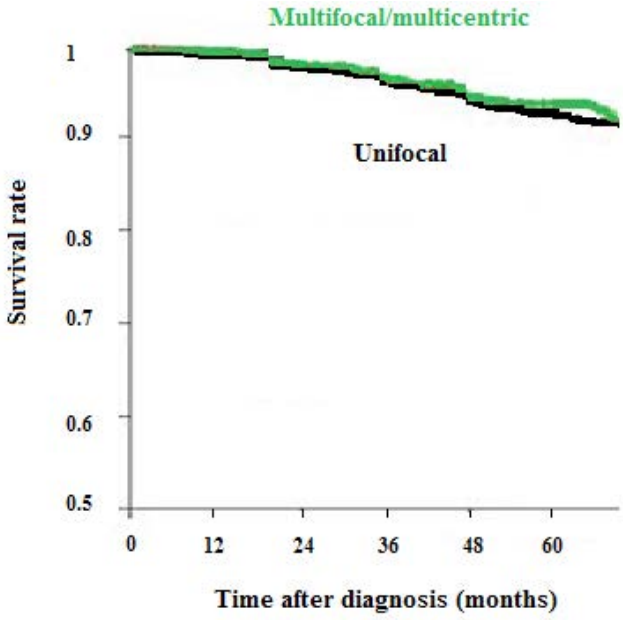

Figure 2. Overall survival estimates comparing MF/MC with UF disease (p=0.92).

Discussion

MF/MC breast cancer is an enigmatic disease comprising many important paradigms in current breast cancer practice. Despite that multifocality/multicentricity may affect prognosis in breast cancer, it has not been well assessed and studied [6].

In the last years the definition of multifocal breast cancer has been changed. The previous definition of multiple synchronous breast cancer lesions was that they can be MF or MC depending on the lesion location (in the same or different quadrants). Now it is considered inappropriate to use the breast cancer quadrants to make a classification because it is an inconsistent definition which does not match the anatomy of the breast [3].

In the present study, preoperative imaging has detected in about 48% of the patients in the MF/MC group. Pathological review of lumpectomy and mastectomy specimens was used to characterize these tumors as MF/MC. Some other MF/MC tumors could have been found by using preoperative MRI but, however, this detection didn't have a great influence on the outcomes [6].

In our study, using the pathological examination of lumpectomy and mastectomy specimens, 60% of the patients were identified as having multiple disease foci. MF/MC breast cancer is more successfully detected by using ultrasound and MRI. Nevertheless, it is possible that all MF/ MC cases may not be found using these imaging techniques [1].

This study examined two groups of patients with MF/MC and UF breast cancer. Both groups were well balanced for established prognostic indicators: tumor size, nodal status, histology, nuclear grade, presence of LVI and therapy received (surgery, adjuvant chemotherapy, radiation therapy and endocrine therapy).

With regard to tumor diameter, a statistically significant difference between the MC/MF and UF groups was noticed (p=0.005). In both patient groups (MC/MF and UF groups) T1 tumors predominated.

There was no significant difference between the two groups with respect to age at diagnosis, tumor grade, nodal status, estrogen receptor status, and LVI. Furthermore, no significant difference was found between the two groups in terms of adjuvant systemic therapy.

Our study and many others [10-13] have shown an association between MF and MC breast cancer and the increased incidence of regional lymph node metastases. This association poses the question of whether the overall tumor burden of MF and MC tumors is simply underestimated with the current staging system, or whether MF and MC tumors have an inherently more aggressive behavior that causes them to grow and metastasize at a faster rate. Both Andea et al. [14] and Coombs et al. [15] found that when T stage was assigned by the diameter of the largest lesion, multifocality and multicentricity were independent predictors of axillary lymph node involvement. However, reassigning the T stage based on the combined diameter of all of the foci corrected this disparity and the rate of lymph node metastases between MC/MF and UF tumors became even. These findings suggest that the increase in lymph node involvement is not due to the inherent nature of MF and MC tumors but to the underestimation of the disease burden by the current staging system. There was no significant statistical difference between the two groups with respect to regional lymph node metastases, but MF/MC had more patients with regional lymph node metastases than the UF group (39.75 vs 33.33%).

According to primary breast operation there was a difference between the two groups (p=0.005); the MC/MF group had more patients with mastectomy and the UF group had more patients with breast-conserving surgery.

Diagnosis and treatment have also changed over the years for MC/MF breast tumors, although at a much slower pace. Breast-conserving treatment is now an established alternative to radical mastectomy. As for tumors with more than one lesion, treatment suggestions are currently changing. Many authors support the extension of conservative surgery for MC/MF tumors [16,17]. Nevertheless, the indications should be accurately applied as some authors report a higher rate of recurrence after conservative treatment [18].

A number of studies have examined the prognostic significance of MF/MC tumors with UF tumors on the occurrence LRFS and OS.

In their study of 3,924 patients, Lynch et al. [2] found that patients who had MF/MC disease, also had higher T stages, grade III disease, LVI and lymph node metastases. A worse 5-year LRFS was more connected to MF than MC breast cancers (90 vs 95%, p=0.02). In the Lych et al. study analysis showed that MF or MC shouldn't be considered to have an independent impact on LRFS or OS. Patients who have MF/MC breast cancers have poor prognostic factors, but this doesn't mean that these cancers are independent predictors of worse survival outcomes.

A retrospective analysis by Weissenbacher et al. [19] was performed on survival-related events in a series of 5,691 breast cancer patients. Patients entered into two groups of 288 patients after categorizing them as having MF/MC or UF cancers. Matching criteria were tumor size, grade and hormone receptor status, which were equally distributed between both groups. In the UF group, the mean breast cancer specific survival time was 221.6 months as opposed to 203.3 months in the MC/MF group (p<0.001). Cox proportional hazards model demonstrated focality and centricity to be highly significant predictors for reduced OS (p=0.016), local relapse (p=0.001) and distant metastasis (p=0.038).

Chung et al. [20] reviewed a prospective database of 1,169 women with invasive breast cancer who were treated with segmentectomy and whole breast irradiation from 1991 through 2009.

They compared two groups, MF and UF breast cancer patients, with respect to demographics, tumor characteristics, adjuvant systemic therapy, local recurrence, disease-free survival (DFS), and OS. One hundred sixty-four patients with MF and 999 with UF invasive breast cancer were treated with breast conserving surgery. Median follow-up was 112 months. Compared with the UF group, patients in the MF group had higher 10-year local recurrence rate (0.6 vs 6.1%, p<0.001), and lower 10-year DFS (97.7 vs 89.3%, p<0.001) and OS (98.4 vs 85.8%, p<0.001). On multivariate analysis, multifocality was independently significantly associated with LRFS, DFS, and OS.

There are some limitations in our study and

practical issues that require discussion. An important limitation is the median follow-up of only 60 months. The MF and MC patients were more likely to undergo modified radical mastectomy as opposed to breast-conserving therapy with adjuvant radiation. They were also more likely to receive adjuvant chemotherapy. In the present study, patients with MF and MC tumors received more aggressive postoperative therapy and this may explain why MF and MC tumors had similar survival outcomes despite being associated with a number of more aggressive features. On multivariate analysis, adjuvant chemotherapy correlated with LRFS and OS.

We conclude that MF and MC breast cancers are associated with more aggressive features, including an increased rate of regional lymph node metastases. But our data could not show any difference in LRFS and OS between patients with MF/MC breast cancer and patients with UF breast cancer.

Conflict of interests

The authors declare no confict of interests.

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