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ORIGINAL ARTICLE

Multifocal and multicentric breast cancer: is breast conserving surgery acceptable?

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Summary

Purpose: *The purpose of our study was to evaluate the significance of multifocal (MF) and multicentric (MC) breast cancer in the diagnosis and treatment of this condition.*

Methods: *This retrospective study was a combination of clinical and laboratory data. The patient population consisted of 274 women operated on with Madden mastectomy for breast cancer. Assessed were the following parameters: age, menstrual status, histopathological parameters, HER-2 status, estrogen receptor (ER) and progesterone receptor (PR) status, disease stage, quadrant(s) in which breast cancer was detected and axillary lymph nodes status.*

Results: *Of 274 patients 206 (85%) has unifocal disease, 41 (15%) suffered of MF (n=27; 9.9%)/MC (n=14; 5.1%) disease. MC disease was associated with metastatic axillary lymph nodes in 92.9% of the cases. MF/MC cases were primarily dependent on histology. MF/MC cancer was best related to the lobular type (85.7% of the cases), while ductal histological type was characteristic of unifocal tumors.*

Conclusion: *Quadrantectomy as a form of conservative breast surgery is acceptable in cases of MF tumors, because all tumor foci can be removed. We suggest radical surgical treatment in all cases of suspected MC tumors because they are most often associated with metastasis to the axillary lymph nodes. Lobular histology characterizes MC breast cancer.*

Key words: breast cancer, conservative surgery, multicentricity, multifocality

Introduction

Breast cancer is the most common malignancy and the leading cause of death in females in the Western world. In highly developed Western countries, breast cancer makes 15-20% of all cancer deaths in females [1]. The risk of developing invasive breast cancer can be calculated using the so-called Gail model which has been confirmed in several studies [2-4]. The Gail model takes into account 5 factors including age, menarche, previous breast biopsy (taking into account the tissue atypia in these biopsies), age at first childbirth, and family history of breast cancer in the next of kin. A revised Gail model is used at the University of Texas Southwestern Medical Center in Dallas and called the NSABP model 2 [5]. The calculation is a bit different from the Gail model, as well as programming techniques and differences in the use of data and results of genetic testing (BRCA 1 and BRCA 2). The terms MF and MC are often used to describe the characteristics of certain types of breast cancer. The presence of 2 or more foci of breast cancer in the same quadrant is defined as MF, while the presence of 2 or more foci of cancer in different quadrants of the breast is defined as a MC [6]. The nomenclature is widely used to describe multiple tumors diagnosed on clinical examination, mammography, ultrasound (US) and magnetic resonance imaging (MRI) or histological analysis [7]. All foci of MF breast cancer are located in the same quadrant of the breast and all depart from a primary focus. MF breast cancer is a less invasive cancer, as distinct foci are not independent units, and invasive growth and metastasis depend on the primary focus. MC

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breast cancer has more than one tumor in the breast that do not depart from a primary focus. MC breast tumors are located in different parts of the breast. This is an invasive cancer, because each focus is a special unit that has a special propensity for invasive growth and metastasis. Although there is evidence that MF/MC breast cancers have a higher incidence of spread to the regional axillary lymph nodes, this has not been clearly demonstrated [8]. It is recommended that the treatment of diagnosed MF/MC breast cancer should start with neoadjuvant chemotherapy regardless of the size of a particular focus. After neoadjuvant chemotherapy, treatment should be followed by locoregional therapy. There are no data so far for the use of conservative therapies for clinically proven MC tumors [9]. The most important diagnostic method involves taking a detailed family history and palpation of both breasts and the axilla in different positions by an experienced specialist [10]. When the US examination can not characterize the nature of the changes, US-guided biopsy should be performed. Standard diagnostic procedures include US and mammography. Dynamic contrast enhanced MRI mammography is a technique that has been widely introduced into practice in the past 10 years, especially as a modality for young women at high risk for breast cancer and women with dense breasts. [11,12]. It was concluded that the diagnosis of breast cancer in these groups is improved by using MRI, with a sensitivity of 79-92%. The American Cancer Society guidelines recommend mammography and MRI to be used for annual testing of all women with BRCA mutations or a lifetime risk of 20-25% or more [13]. PET scan is costly, available in very few centers and used in special conditions only [14-17]. No single screening imaging method is specific for MF/MC breast cancer. Early diagnosis of breast cancer, neoadjuvant chemotherapy and postoperative radiotherapy have enabled conservative surgery for breast cancer during the last decades. Conservative surgery should not be done with tumors larger than T2, irrespective of the preoperative status of axillary lymph nodes. Mutilating surgery has an important impact on the psychological status of the patient [18,19]. The benefit of sentinel lymph node (SLN) biopsy is that with negative SLN biopsy one can avoid axillary lymph node dissection with its undesirable sequelae.

The purpose of the present study was to evaluate the therapeutic results of breast conserving surgery in patients with MF/MC cancer.

Methods

Our study was a combination of clinical and laboratory data. We have operated on 470 women with breast cancer. Out of that number, we performed 274 Madden operations, and only these patients were subjected to histological studies, because in these cases the entire breast can be examined and it is possible to compare preoperative with postoperative results. For the assessment of aggressiveness of MF/MC tumors, the following parameters were examined and compared: age, menstrual status, histological type, histological grade, nuclear grade, mitotic index, vascular invasion, perineural invasion, lymphatic invasion, HER-2 status, ER and PR status, stage, quadrant and axillary lymph node status.

Statistical analysis

Standard statistical methods were used to analyse data. We used the ANOVA test to compare data with normal distribution and x^2 test for non-parametric data. Fisher's exact test was performed in cases where sample sizes were small and binary logistic regression analysis was used to analyse tumor aggressiveness. A p-value of less than 0.05 was regarded as statistically significant. SPSS Statistics, version 19, was used for statistical analysis.

Results

Most of the patients had already begun treatment for stage II (157 patients; 57.5%) and III (87 patients; 31.9%). Post-menopausal women prevailed (n=191; 69.7%). More than half of the patients (173; 63.1%) had T2 tumors (2-5 cm). In 122 patients (44.5%) no clinical or histological metastatic disease in the regional lymph nodes was registered. The most common histological type of breast cancer was ductal carcinoma (172 patients; 62.8%), while almost one third of cases (90 patients; 32.8%) had lobular breast cancer. Ten cases had papillary histological type and 2 some of the other types of breast cancer. According to the localization of the primary tumor in breast quadrants, the most common site was the upper outer quadrant (129 patients; 47.1%). Two hundred and thirty-three (85%) patients had unifocal tumors, 14 (5.1%) had MC and 27 (9.9%) MF tumors (Table 1). Pathological analysis of postoperative breast cancer preparations of all patients showed that more than half of the patients had a relatively advanced stage of disease when the tumor had significant invasive and metastatic potential, and when its growth was mainly dependent on ER/PR status, and only in one quarter of the cases there was a significant HER-2 expression. Age differences between unifocal and MF and/or MC breast cancer were not statistically significant ($p = 0.825$). Analysing the impact of prognostic parameters we found that MF and MC tumors were related to stage II disease ($p=0.020$) and the lobular histological type of breast cancer ($p <0.0005$). MF/MC tumors most often occurred in the central and upper quadrants of the breast ($p <0.0005$). MC or MF correlated with the metastatic status of regional lymph nodes ($p = 0.001$). MC tumors in a large percentage correlated with metastatic deposits in the regional lymph nodes (4-

Table 1. Epidemiological characteristics of breast cancer in the studied group

Characteristics	*Patients, N*	*%*
Age (years)		
20 - 30	3	1.1
30 - 40	7	2.6
40 - 50	77	28.1
50 - 60	84	30.7
60 - 70	69	25.2
70 - 80	34	12.4
Menstrual status		
Premenopausal	83	30.3
Postmenopausal	191	69.7
T stage		
T1	9	3.3
T2	70	25.5
T3	173	63.1
T4	22	8.0
N stage		
N0	122	44.5
N1 (< 4)	82	29.9
N2 (4 - 8)	40	14.6
N3 (> 8)	30	10.9
TNM stage		
I	28	10.3
II	157	57.5
III	87	31.9
IV	1	0.4
Histological type		
Ductal	172	62.8
Lobular	90	32.8
Papillary	10	3.6
Others	2	0.7
Quadrant		
Upper outer	129	47.1
Lower outer	28	10.2
Upper inner	48	17.5
Lower inner	19	6.9
Central	36	13.1
More than one quadrant	14	5.1
Focality		
Unifocal	233	85.0
Multifocal	27	9.9
Multicentric	14	5.1
Total	274	100.0

8 positive nodes), while MF tumors were mostly without metastases. MF and MC showed no correlation with tumor size, histological and nuclear grade, invasion of lymph and blood vessels and nerves. The same was true for ER, PR and HER-2 receptor. MF was significantly related to the lobular type of breast cancer, and ductal histological type was characteristic of unifocal tumors (Table 2). Most cases (85.7%) of MC tumors had lobular histology (p <0.0005), while 68.7% of unifocal cases had ductal histological type. MC was correlated with advanced disease stages because 57% of unifocal cancer occurred in stage II disease while 71.4% of patients with MC tumors had stage III disease with a positive correlation between MC and stage (p=0.001). This relationship was confirmed by the fact that in most cases MC tumors were positively correlated with the nodal status. MC tumors in 92.9% of the cases were associated with the presence of metastatic deposits in the regional lymph nodes, unlike unifocal tumors where such an association was seen in 54.9% of the cases (p <0.0005). Stage II MF disease was found in 76.9% of the cases, while stage III MC disease was confirmed in 71.4% of the cases (p=0.005). According to these results, it is not surprising that MF tumors, in most cases, were not associated with metastasis in the regional lymph nodes (63%), unlike the MC tumors which were almost always associated with metastatic deposits in the regional lymph nodes (p <0.0005) (Table 3). Advanced stage was 3-fold higher in premenopausal compared with postmenopausal patients (OR 0.347, 95% CI 0.126-0.955). Greater tumor size was related with more advanced disease stage (p <0.0005) and increase in tumor diameter of 1 cm increased the risk of higher disease stage even 5.5 times (OR 5.506, 95% CI 2.587-11.720). MC tumors had 12-fold higher risk compared to unifocal tumors that the disease is in advanced stage, and thus 12-fold more worse prognosis (OR 12.126, 95% CI 1.842-79.933). Vascular invasion increased the probability of higher disease stage (p <0.0005) and this risk was increased 4 times compared to tumors without invasion (OR 4.095, 95% CI 1.921-8.727). Tumor localization was significant for disease staging (p=0.006). Specifically, our results showed that tumors localized in the upper inner quadrant had the lowest risk to be associated with advanced disease and this risk was 10-fold lower than the worst localization of tumors in the central quadrant (OR 0.097, 95% CI 0.022-0.424). Expression of PR was a good prognostic factor because any increase in PR expression by 10% decreased the probability of the risk of advanced disease stage by 15% (OR 0.851, 95% CI 0.730-0.993) (Table 4). Analyzing factors contributing to the capacity of the tumor to metastasize to the regional lymph nodes, our results showed that this phenomenon depended on the size of primary tumor (p=0.015), presence of invasion of blood vessels (p=0.001) and tumor localization (p <0.0005) (Table 5).

Discussion

Our results showed that more than half of the patients had undergone surgical treatment in a relatively advanced disease stage, when the tumor had a significant invasive and metastatic potential. Its growth was

Table 2. Relationship between unifocal and multifocal breast cancers by epidemiological and histopathological prognostic factors

	Menstrual status				
	Premenopausal		*Postmenopausal*		
	Patients, N	*%*	*Patients, N*	*%*	
Unifocal	74	31.8	159	68.2	
Multifocal	7	25.9	20	74.1	p=0.352
	TNM stage				
	Patients, N (%)				
	I	*II*	*III*	*IV*	
Unifocal	27 (11.6)	133 (57.1)	72 (30.9)	1 (0.4)	
Multifocal	1 (3.8)	20 (76.9)	5 (19.2)		p=0. 257
	T stage				
	Patients, N (%)				
	T1	*T2*	*T3*	*T4*	
Unifocal	8 (3.4)	59 (25.3)	147 (63.1)	19 (8.2)	
Multifocal	1 (3.7)	7 (25.9)	18 (66.7)	1 (3.7)	p=0. 878
	N stage				
	Patients, N (%)				
	0	*<4*	*4-8*	*>8*	
Unifocal	105 (4.5)	71 (30.5)	31 (13.3)	26 (11.2)	
Multifocal	17 (63.0)	5 (18.5)	2 (7.4)	3 (11.1)	p=0. 321
	Histological type				
	Patients, N (%)				
	Ductal	*Lobular*	*Papillary*	*Others*	
Unifocal	160 (68.7)	61 (26.2)	10 (4.3)	2 (0.9)	
Multifocal	10 (37.0)	17 (63.0)			p=0. 001
	Quadrant localization (%)				
	UOQ	*LOQ*	*UIQ*	*LIQ*	*CQ*
Unifocal	51.1	11.2	16.7	8.2	12.9
Multifocal	37.0	7.4	33.3		22.2 p=0. 071
	Histological grade				
	Patients, N (%)				
	G1	*G2*	*G3*	*G4*	
Unifocal	32 (13.7)	58 (24.9)	77 (33.0)	66 (28.3)	
Multifocal	2 (7.4)	12 (44.4)	9 (33.3)	4 (14.8)	p=0. 121
	Nuclear grade (Ng)				
	Patients, N (%)				
	Ng 1	*Ng 2*	*Ng 3*		
Unifocal	74 (31.8)	102 (43.8)	57 (24.4)		
Multifocal	11 (40.7)	14 (51.9)	2 (7.4)		p=0. 254
	Lymphatic invasion				
	Patients, N (%)				
	Invasion negative		*Invasion positive*		
Unifocal	50 (21.5)		183 (78.5)		
Multifocal	7 (25.9)		20 (74.1)		p=0.595
	Perineural invasion				
	Patients, N (%)				
	Invasion negative		*Invasion positive*		
Unifocal	77 (33.0)		156 (67.0)		
Multifocal	11 (40.7)		16 (59.3)		p=0. 424
	Vascular invasion				
	Patients, N (%)				
	Invasion negative		*Invasion positive*		
Unifocal	152 (65.5)		80 (34.5)		
Multifocal	14 (51.9)		13 (48.1)		p=0.161
	HER-2 expression				
	Patients, N (%)				
	Expression negative		*Expression positive*		
Unifocal	178 (76.4)		55 (23.6)		
Multifocal	23 (85.2)		4 (14.8)		P=0. 302

UOQ: upper outer quadrant, LOQ: lower outer quadrant, UIQ: upper inner quadrant, LIQ: lower inner quadrant, CQ: central quadrant

Table 3. Distribution of epidemiological and histopathological prognostic factors in multifocal and multicentric breast carcinoma

Menstrual status, N (%)	*Premenopausal*		*Postmenopausal*		
Multifocal	7	(25.9)	20	(74.1)	
Multicentric	2	(14.3)	12	(85.7)	p=0.393

Disease stage, N (%)	*Stage*				
	I	*II*	*III*	*IV*	
Multifocal	1 (3.8)	20 (76.9)	5 (19.2)		
Multicentric		4 (28.6)	10 (71.4)		p=0.005

T stage, N (%)	*T1*	*T2*	*T3*	*T4*	
Multifocal	1 (3.7)	7 (25.9)	18 (66.7)	1 (3.7)	
Multicentric		4 (28.6)	8 (57.1)	2 (14.3)	p=0.555

N stage, N (%)	*0*	*< 4*	*4 - 8*	*> 8*	
Multifocal	17 (63.0)	5 (18.5)	2 (7.4)	3 (11.1)	
Multicentric		6 (42.9)	7 (50.0)	1 (7.1)	p < 0.0005

Histological type, N (%)	*Ductal*	*Lobular*	*Papillary*	*Others*	
Multifocal	10 (37.0)	17 (63.0)			
Multicentric	2 (14.3)	12 (85.7)			p=0.129

Quadrant (%)	*UOQ*	*LOQ*	*UIQ*	*LIQ*	*CQ*		
Multifocal	37.0	7.4	33.3		222		
Multicentric						100.0	p< 0.0005

Histological grade, N (%)	*G1*	*G2*	*G3*	*G4*	
Multifocal	2 (7.4)	12 (44.4)	9 (33.3)	4 (14.8)	
Multicentric	2 (14.3)	2 (14.3)	8 (57.1)	2 (14.3)	p=0.244

Nuclear grade (Ng), N (%)	*Ng 1*	*Ng 2*	*Ng 3*	
Multifocal	11 (40.7)	14 (51.9)	2 (7.4)	
Multicentric	3 (21.4)	10 (71.4)	1 (7.2)	p=0.471

Invasion of lymphatic vessels, N (%)	*Invasion negative*	*Invasion positive*	
Multifocal	7 (25.9)	20 (74.1)	
Multicentric	2 (15.4)	12 (84.6)	p=0.455

Perineural invasion, N (%)	*Invasion negative*	*Invasion positive*	
Multifocal	11 (40.7)	16 (59.3)	
Multicentric	3 (21.4)	11 (78.6)	p=0.216

Vascular invasion, N (%)	*Invasion negative*	*Invasion positive*	
Multifocal	14 (51.9)	13 (48.1)	
Multicentric	9 (64.3)	5 (35.7)	p=0.447

Expression of HER-2, N (%)	*Expression negative*	*Expression positive*	
Multifocal	23 (85.2)	4 (14.8)	
Multicentric	12 (85.7)	2 (14.3)	p=0.964

mainly dependent on ER / PR, and only in one quarter of the cases there was a significant HER-2 expression. The most common histological type of breast cancer in this study was ductal carcinoma, while the lobular type was registered in only one third of the cases, which is consistent with the literature data [20]. According to the localization of the primary tumor in breast quadrants, the most common site was the upper outer quadrant. Multifocality and multicentricity of breast cancer, tumor size, histological and nuclear grade, invasion of lymph and blood vessels and nerves in the tumor showed no interdependence. The same was true for the expression of ER, PR and HER-2 receptors. Multicentricity, as an important feature, is related to the lobular type of breast cancer, while ductal histological type is characteristic of unifocal tumors. MC disease was an extremely unfavorable

Table 4. Epidemiological and pathological factors of breast cancer affecting the stage of disease and prognosis

Variables	*B*	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*	*95,0% C.I. for EXP(B)*	
							Lower	*Upper*
Age	0.039	0.022	3.091	1	0.079	1.040	0.996	1.086
Menstrual status	–1.058	0.516	4.203	1	0.040	0.347	0.126	0.955
Tumor size	1.706	0.385	19.590	1	0.000	5.506	2.587	11.720
Histological type			3.702	3	0.295			
Ductal	2.024	15.740	0.017	1	0.898	7.568	0.000	18905501
Lobular	1.114	15.741	0.005	1	0.944	3.045	0.000	76330746
Others	2.256	15.767	0.020	1	0.886	9.548	0.000	25161254
Multifocality or multicentricity		8.390	2	0.015				
Multifocal	–0.503	0.668	0.567	1	0.451	0.604	0.163	2.241
Multicentric	2.495	0.962	6.735	1	0.009	12.126	1.842	79.833
Histological grade	0.032	0.425	0.006	1	0.939	1.033	0.449	2.376
Nuclear grade	–0.486	0.481	1.023	1	0.312	0.615	0.240	1.578
Perineural invasion	0.793	0.610	1.689	1	0.194	2.209	0.668	7.301
Invasion of lymphatic vessels	0.660	0.530	1.552	1	0.213	1.935	0.685	5.467
Vascular invasion	1.410	0.386	13.332	1	0.000	4.095	1.921	8.727
HER-2 status	–0.042	0.424	0.010	1	0.921	0.959	0.418	2.200
Localization (quadrant)			14.370	4	0.006			
Upper outer	–0.038	0.520	0.005	1	0.942	0.963	0.347	2.669
Lower outer	0.431	0.650	0.439	1	0.507	1.539	0.430	5.504
Upper inner	–2.332	0.752	9.618	1	0.002	0.097	0.022	0.424
Central	–0.294	0.772	0.145	1	0.704	0.745	0.164	3.387
ER status	0.032	0.070	0.207	1	0.649	1.032	0.900	1.183
PR status	–0.161	0.079	4.198	1	0.040	0.851	0.730	0.993
Constant	–8.423	15.773	0.285	1	0.593	0.000		

Table 5. Epidemiological and pathological factors of breast cancer affecting the appearance of metastases in regional lymph nodes

Variables	*B*	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*	*95,0% C.I. for EXP(B)*	
							Lower	*Upper*
Multifocality or multicentricity			2.325	2	0.313			
Multifocal	–0.810	0.582	1.937	1	0.164	0.445	0.142	1.392
Multicentric	8.910	14.621	0.371	1	0.542	7402.496	0.000	20630495
Age	–0.012	0.021	0.301	1	0.583	0.988	0.948	1.030
Menstrual status	0.051	0.500	0.010	1	0.919	1.052	0.395	2.802
Tumor size	0.718	0.295	5.946	1	0.015	2.051	1.151	3.654
Histological type			3.393	3	0.335			
Ductal	–0.997	1.598	0.389	1	0.533	0.369	0.016	8.457
Lobular	–1.726	1.583	1.189	1	0.276	0.178	0.008	3.963
Others	–1.456	1.651	0.778	1	0.378	0.233	0.009	5.927
Histological grade	–0.412	0.408	1.020	1	0.313	0.662	0.297	1.474
Nuclear grade	–0.179	0.445	0.162	1	0.687	0.836	0.349	2.001
Perineural invasion	0.321	0.476	0.454	1	0.500	1.379	0.542	3.507
Invasion of lymphatic vessels	1.204	0.422	8.154	1	0.004	3.333	1.459	7.617
Vascular invasion	1.308	0.391	11.168	1	0.001	3.699	1.718	7.965
HER-2 status	0.595	0.440	1.825	1	0.177	1.812	0.765	4.294
ER status	0.007	0.067	0.012	1	0.915	1.007	0.883	1.149
PR status	–0.048	0.069	0.491	1	0.484	0.953	0.833	1.091
Localization			24.915	4	0.000			
Upper outer quadrant	–0.002	0.489	0.000	1	0.997	0.998	0.383	2.604
Lower outer quadrant	1.604	0.725	4.893	1	0.027	4.973	1.201	20.601
Upper inner quadrant	–1.873	0.595	9.894	1	0.002	0.154	0.048	0.494
Central quadrant	–0.375	0.692	0.295	1	0.587	0.687	0.177	2.666
Constant	–0.111	1.870	0.004	1	0.953	0.895		

prognostic sign in our results, since it was frequently associated with axillary lymph nodes metastasis and with advanced disease stage. Fifty-five percent of the cases of unifocal cancer had stage II disease while MC tumors in 71.4% of the cases had stage III disease at the time of initiation of therapy, with a positive correlation between multicentricity and stage. Certainly, this relationship is confirmed by the fact that in most cases, MC tumors were positively correlated to the nodal status. MC tumors in 92.9% of the cases were associated with the presence of metastatic deposits in the regional lymph nodes, while unifocal tumors were associated with nodal metastasis in only 54.9% ($p<0.0005$). Comparing the two characteristics (multicentricity and multifocality), we found that MF cancers are usually diagnosed in stage II of the disease (76.9%), while MC tumors are diagnosed in the unfavorable stage III (71.4%). This difference was of great importance. According to this result, it is not surprising that MF tumors, in most cases, are not associated with metastasis to the regional lymph nodes, unlike the MC tumors which are almost always associated with nodal metastasis with highly significant difference. According to the literature, if aggregate diameters are used, unifocal and MF breast carcinomas are similar with respect to the frequency of regional lymph node metastasis [21]. Using binary logistic regression analysis to examine the material, the obtained results indicated that the initial diagnosis of a tumor in stage III was primarily dependent on the menstrual status ($p = 0.040$). Treatment initiation at an advanced stage of disease is 3-fold more common in premenopausal than in postmenopausal women. This fact is not unexpected because in premenopausal women, estrogen deprivation (by surgical or pharmaceutical castration) is very effective and has become the adjuvant treatment of choice [22]. MC tumors are discovered in advanced stage 12-fold more common compared to unifocal tumors. The existence of vascular invasion increases the probability of higher disease stage and this risk is increased 4 times compared to tumors without invasion. Our results showed that tumor localization in the breast as well as expression of PR is associated with disease stage, which is consistent with literature data [23]. Tumor size directly affects the occurrence of metastasis to the regional lymph nodes [24]. However, in the presence of vascular invasion, regardless of tumor size, the risk of nodal metastasis is increased about 4 times.

Based on these data we believe that all lobular breast cancers should be treated with radical surgery, because they are often associated with MC disease and metastases to the axillary lymph nodes. Yet, some authors reported that in selected patients with MF/MC breast cancer, wide conservative surgery was proven to be safe [25].

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