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ORIGINAL ARTICLE

Prognostic impact of multifocal and multicentric breast cancer versus unifocal breast cancer

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Abstract

Purposes The clinical behavior of multifocal and multicentric breast cancers (MMBCs) is not well characterized. We conducted this study to ascertain whether patients with MMBCs have a worse prognosis than patients with unifocal breast cancers (UBC).

Methods The subjects of this retrospective study were 734 consecutive patients who underwent definitive surgery for invasive breast carcinoma at our hospital between January 2004 and December 2006. MMBC was defined as ≥ 2 separate invasive unilateral breast tumors and pathological T stage was redefined based on the sum of the maximum diameter of each tumor. We evaluated disease-free survival (DFS) using the Kaplan–Meier method and Cox proportional hazards models.

Results Of the 734 patients, 136 (18.5%) had MMBC. The pathological T stage of 36 of the patients with MMBC was upstaged by adopting the sum of each focus. MMBC did not have any survival impact, but MMBC upstaged by the modified pathological T stage was associated with worse DFS than non-upstaging MMBC ($P=0.004$). Multivariate analysis revealed that upstaging MMBC was an independent factor for poor prognosis and worse DFS (HR 2.757, $P=0.043$).

Conclusions MMBC itself may not be predictive of a worse prognosis; however, the sum of the invasive diameters of MMBC might be an important prognostic factor. Further studies are needed to confirm the prognosis associated with MMBC, taking into consideration the biological characteristics of each invasive focus.

Keywords Breast cancer · Multifocal · Multicentric · Prognosis

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Introduction

Multifocal and multicentric breast cancer (MMBC) is generally defined as two or more tumors in the same breast. With improvements in the sensitivity of imaging modalities, MMBC is likely to be detected with increasing frequency [1–3]. The incidence of MMBCs ranges from 6 to 60% and varies according to the inclusion or exclusion of in situ disease and sampling methods. This wide range in the reported incidence also reflects the lack of a standard definition for MMBC [4, 5].

The accepted terminology is that multifocality refers to a single tumor with two or more foci through the ductal system, whereas multicentricity indicates multiple primary tumors within the same breast [6]. A standardized definition has not been established and multifocal and multicentric breast cancers are often grouped together as "MMBC" [7]. The behavior of MMBCs has been well characterized by several studies. Some reports have associated age, larger tumor size, invasive lobular carcinoma, higher nuclear grade, lymphovascular invasion, estrogen receptor (ER) positivity, and lymph node metastases with MMBC [8–14]. However, to the best of our knowledge, no large reviews have been published on the clinicopathological characteristics of MMBC in Japanese women.

Conventionally, patients with MMBCs are staged and treated according to the diameter of their largest lesion, as per the current TNM-staging guidelines, without taking other disease foci into consideration. This implies that the outcome depends on the largest lesion and whether the other lesions affect prognosis is unclear. This study compares the survival outcomes between patients with MMBCs and those with unifocal breast cancers (UBCs) and examines the effects of daughter lesions on prognosis.

Materials and methods

We reviewed, retrospectively, consecutive patients who underwent definitive surgery for diagnosed breast cancer at our hospital between January 2004 and December 2006. In patients who underwent partial mastectomy, it was confirmed that there were no other lesions in the affected side on image inspections, with thorough preoperative assessment using diagnostic breast imaging studies, including mammography, ultrasound, and MRI. MMBC was defined pathologically as two or more separate invasive tumors in the ipsilateral breast, irrespective of any ductal carcinoma in situ (DCIS) between lesions. Separate invasive tumors were defined as invasive tumors with a distance of 10 mm or more between them, because the surgical specimen was cut into 5 mm slices. UBC was defined as breast cancer with only one invasive lesion in the surgical specimen. An invasive tumor was defined as a tumor with invasion measuring ≥ 0.1 cm. Radiographic data were not considered.

The following patients were excluded from the final analysis: male patients, patients receiving neoadjuvant chemotherapy, those with bilateral breast cancer, those with DCIS without invasive lesions, those with pT4 breast cancer, and those with unknown information. We also excluded patients who had contralateral breast cancer recurrence, which was regarded as bilateral breast cancer.

In reviewing the surgical specimens from patients with MMBC, we counted the number of invasive foci and measured the maximum diameter of each lesion. In patients with five or more invasive foci, the size was measured up to five foci, and the number of tumors was set at five because we assumed that there would be many invasive lesions of 1 mm or smaller, which could not be counted accurately. We added up the diameters of all the invasive foci in each patient with MMBC and redefined the modified pT stage by adopting the sum of invasive foci as follows: modified pT1, the sum of the invasive areas in the breast is 20 mm or smaller; modified pT2, the sum of the invasive areas in the breast is larger than 20 mm but not larger than 50 mm or smaller; and modified pT3, the sum of the invasive areas in the breast is larger than 50 mm. We did not consider modified pT4 because patients with pT4 breast cancer had already been excluded from this research. We did not examine the tumor characteristics of the second largest lesion because immunostaining for each focus is not done routinely in our institute.

The primary endpoint was disease-free survival (DFS), and the secondary endpoints were overall survival (OS) and distant disease-free survival (DDFS). DFS was defined as the period from the date of surgery for primary breast cancer to the date of first recurrence or relapse, second cancer, or death. DDFS was defined as the period from the date of surgery for primary breast cancer to the date of appearance of distant metastases. OS was defined as the period from the date of surgery for primary breast cancer to death from any cause or to the date of last communication. Simultaneous local and distant recurrence in a patient was considered distant recurrence in the analysis. The institutional review board approved this retrospective study (approval number, 12-J021), and waived the requirement to obtain written informed consent.

We compared the patient and clinical characteristics between the MMBC and UBC groups using the χ^2 test. The parameters and characteristics of MMBC were compared between non-upstaging MMBC and upstaging MMBC using the *t* test and χ^2 test, respectively. DFS, DDFS, and OS were evaluated using the Kaplan–Meier method and univariate analysis was done using the log-rank test. Prognostic independent clinicopathological features associated with DFS were assessed using Cox proportional hazards models. The variables were based on independent variables, which may affect the DFS of patients with MMBC, as previously reported. Adjuvant chemotherapy and endocrine therapy were decided based on clinicopathological factors, and thus because they are not independent factors they were not included as variables of multivariate analysis. $P < 0.05$ was considered to indicate significance. All statistical tests were two-tailed. Data were analyzed using IBM SPSS statistics software version 20.0J (IBM, Tokyo, Japan) and Stata/IC version 15.0 for Windows (StataCorp LLC, College Station, TX, USA).

Results

Between 2004 and 2006, 1605 consecutive patients underwent breast cancer surgery at our institution. We excluded 42 patients with bilateral breast cancer, 465 who had received neoadjuvant chemotherapy, 304 who had DCIS without invasive lesions, 19 with pT4 breast cancer, 34 with missing information, and 7 male patients. The remaining 734 patients with breast cancer were included in our analysis (Table 1), 136 (18.5%) of whom had MMBC and 598 (81.5%) of whom had UBC, according to their pathological specimens. More of the MMBC patients than the UBS patients were premenopausal (62.5% versus 53.7%, respectively; $P=0.062$). Patients with MMBC had lower T stages (T1: 80.1% versus 67.4%; T2: 17.6% versus 31.6%; T3 2.2% versus 1.0%, $P=0.003$). The MMBC and UBC groups did not differ significantly in age, histological type, hormone receptor status, nuclear grade, or lymphovascular invasion or in whether they received adjuvant chemotherapy and endocrine therapy. Patients with MMBC were more likely to undergo mastectomy (48.5% versus 17.7%, $P<0.001$) and less likely to receive postoperative radiation (47.1% versus 76.8%, $P<0.001$).

The median follow-up duration was 82 months (range 3–106 months).

Twenty-seven patients (3.0%) had loco-regional recurrence: 5 (3.7%) in the MMBC group and 22 (3.7%) in the UBC group. Thirty patients (4.1%) had distant metastases: 3 (2.2%) in the MMBC group and 27 (4.5%) in the UBC group. Seventeen patients died from any cause: 1 (0.7%) in the MMBC group and 16 (2.7%) in the UBC group. There were no significant differences in the DFS, DDFS, and OS between the MMBC and UBC groups (Log-rank $P=0.260$, 0.143, and 0.204, respectively; Fig. 1).

Table 1 Patient characteristics

		UBC		MMBC		P
		N = 598	%	N = 136	%	
Age at surgery	≤49/>50 years	275/323	46/54	69/67	50.7/49.3	0.316
Menopause status	Pre/post	321/277	53.7/46.3	85/51	62.5/37.5	0.062
Tumor size	pT1/T2/T3	403/189/6	67.4/31.6/1	109/24/3	80.1/17.6/2.2	0.003
Node status	pN0/pN1–3	497/101	83.1/16.9	111/25	81.6/18.4	0.667
Histology	IDC/ILC/others	526/26/46	88/4.3/7.7	121/6/9	89/4.4/6.6	0.912
ER	+/−	514/84	86/14	121/15	89/11	0.352
PR	+/−	463/135	77.4/22.6	107/29	78.7/21.3	0.752
HER2	+/−	60/538	10/90	16/120	11.8/88.2	0.55
Subtype	L/H/L-H/TN	482/22/38/56	81/4/6/9	115/8/8/5	85/6/6/4	0.117
Nuclear grade	1–2/3	436/162	72.9/27.9	106/30	77.9/22.1	0.228
LVI	+/−	313/285	52.3/4.7	73/63	53.7/46.3	0.778
Mastectomy	Partial/total	492/106	82.3/17.7	70/66	51.5/48.5	< 0.001
RT	Yes/no	459/139	76.8/23.2	64/72	47.1/52.9	< 0.001
Omitting RT after partial	Yes/no	42/556	7.0/93.0	7/129	5.1/94.9	0.429
ACT	Yes/no	164/434	27.4/72.6	33/103	24.3/75.7	0.453
Endocrine therapy	Yes/no	492/106	82.3/17.7	116/20	85.3/14.7	0.399

ACT adjuvant chemotherapy, *ER* estrogen receptor, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *LVI* lymphovascular invasion, *MMBC* multifocal and multicentric breast cancer, *PR* progesterone receptor, *L* Luminal type, *H* pure HER2 type, *L-H* Luminal-HER2 type, *TN* triple negative type, *RT* radiation therapy, *UBC* unifocal breast cancer

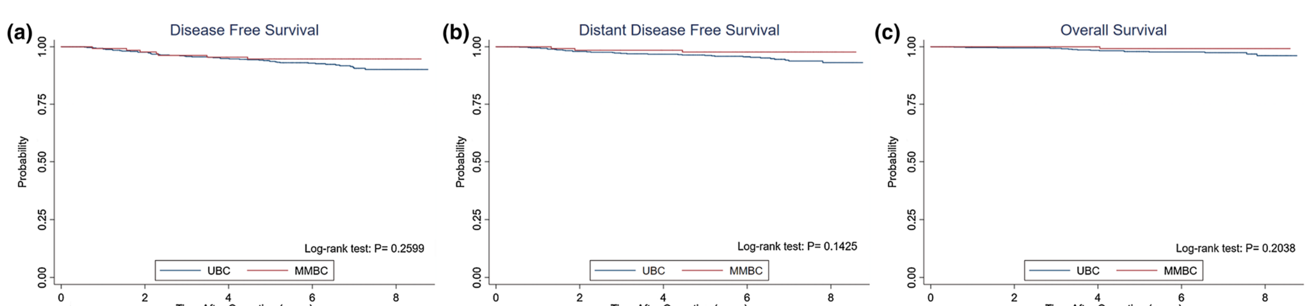

Fig. 1 Disease-free survival (**a**), distant disease-free survival (**b**) and overall survival (**c**) in women with multifocal and multicentric breast cancer (MMBC) and unifocal breast cancer

Table 2 Frequencies of transition from the conventional pathological T stage to the modified pathological T stage based on the sum of each lesion in multifocal and multicentric breast cancers

	Conventional pathological T stage by the maximum tumor size		
	pT1	pT2	pT3
	$N=109$	$N=24$	$N=3$
Modified pathological T Stage according to the sum of each lesion			
Modified pT1	74	–	–
Modified pT2	35 (upstage)	23	–
Modified pT3	0	1 (upstage)	3

By redefining the modified pT stage by adopting the sum of invasive focus, the T stage of 36 patients raised by one step (T1–T2: 35 patients, T2–T3: 1 patient, Table 2). Upstaging MMBC resulted in a significantly larger number of invasive foci and a larger sum of invasive foci than that of non-upstaging MMBC (3.0 versus 2.5, $P=0.015$, 29.1 mm versus 20.8 mm, $P=0.0001$, respectively), although the maximum tumor size of upstaging MMBC was also significantly larger than that of non-upstaging MMBC (16.7 mm versus 12.4 mm, $P=0.041$, Table 3).

There were no significant differences in patient characteristics between upstaging MMBCs and non-upstaging MMBCs, except for conventional pT stage (Table 4). While a higher conventional pT stage had no impact on the DFS of patients with MMBC, a higher modified pT stage tended to affect DFS (Log-rank: $P=0.683$, $P=0.053$, respectively, Fig. 2). Moreover, upstaging MMBC had a significant effect on DFS compared with non-upstaging MMBC ($P=0.0043$).

Table 3 Number, size, and sum of invasive lesions in multifocal and multicentric breast cancers

		All MMBC	Non-upstaging MMBC	Upstaging MMBC	*P*
		$N=136$	$N=100$	$N=36$	
Number of lesions	Mean ± SD	2.6 ± 1.0	2.5 ± 0.9	3.0 ± 1.2	0.0149
Max tumor size (mm)	Mean ± SD	13.6 ± 10.8	12.4 ± 12.0	16.7 ± 5.4	0.0406
Second tumor size (mm)	Mean ± SD	5.7 ± 5.0	4.5 ± 4.6	9.0 ± 4.8	< 0.0001
Sum of tumor size (mm)	Mean ± SD	20.8 ± 14.9	17.8 ± 15.6	29.1 ± 8.7	0.0001

Table 4 Characteristics of the patients with multifocal and multicentric breast cancer

		Non-upstaging MMBC		Upstaging MMBC		*P*
		$N=100$	%	$N=36$	%	
Age at surgery	≤ 49/> 50 years	50/50	50.0/50.0	19/17	52.8/47.2	0.775
Menopause status	Pre/post	61/39	61.0/39.0	24/12	66.6/33.3	0.547
Tumor size	pT1/T2/T3	74/23/3	74.0/23.0/3.0	35/1/0	97.2/2.8/0	0.011
Node status	pN0/pN1–3	82/18	82.0/18.0	29/7	80.6/19.4	0.848
Histology	IDC/ILC/others	90/2/8	90.0/2.0/8.0	31/2/3	86.1/5.6/8.3	0.553
ER	+/–	88/12	88.0/12.0	33/3	92/8	0.547
PR	+/–	79/21	79.0/21.0	28/8	78/22	0.878
HER2	+/–	14/86	14.0/86.0	2/34	6/94	0.178
Subtype	L/H/L-H/TN	82/7/7/4	82.0/7.0/7.0/4.0	33/1/1/1	91.7/2.8/2.8/2.8	0.571
Nuclear grade	1–2/3	82/18	82.0/18.0	24/12	66.6/33.3	0.057
LVI	+/–	49/51	49.0/51.0	24/12	66.6/33.3	0.068
Mastectomy	Partial/total	51/49	51.0/49.0	19/17	52.8/47.2	0.855
RT	Yes/no	54/46	54.0/46.0	18/18	50.0/50.0	0.680
Omitting RT after partial	Yes/no	5/95	5.0/95.0	2/34	5.6/94.4	0.897
ACT	Yes/no	77/23	77/23	26/10	72.2/28.8	0.566
Endocrine therapy	Yes/no	83/17	83.0/17.0	33/3	91.7/8.3	0.208

ACT adjuvant chemotherapy, *ER* estrogen receptor, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *LVI* lymphovascular invasion, *MMBC* multifocal and multicentric breast cancer, *PR* progesterone receptor, *L* Luminal type, *H* pure HER2 type, *L-H* Luminal-HER2 type, *TN* Triple negative type, *RT* radiation therapy

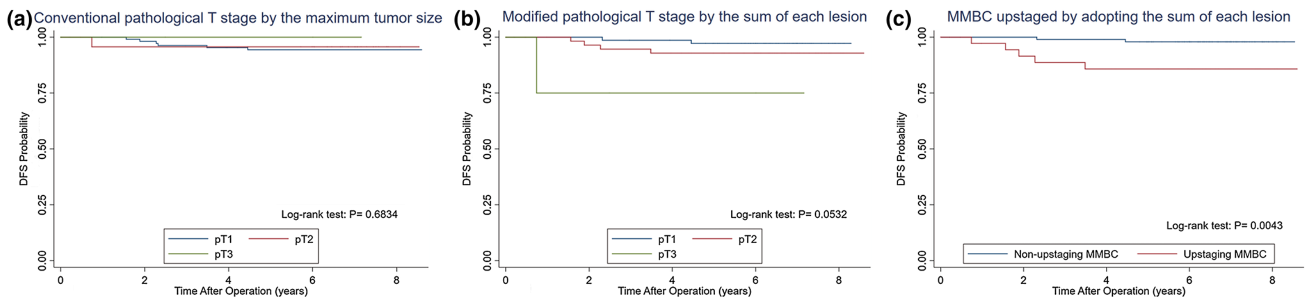

Fig. 2 Disease-free survival in women with multifocal and multicentric breast cancer (MMBC) on conventional pathological T stage by the maximum tumor size (**a**) and on modified pathological T stage by the sum of each lesion (**b**). Disease-free survival in women with non-upstaging and upstaging MMBC (**c**)

Table 5 Univariate and multivariate analyses for disease-free survival

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
pT stage (2–3/1)	2.775	1.641–4.693	< 0.001	2.189	1.212–3.954	0.009
pN stage (1–3/0)	3.149	1.841–5.385	< 0.001	2.050	1.127–3.727	0.019
Subtype (Luminal/others)	1.073	0.542–2.127	0.839	–	–	–
HER2 (+/−)	0.994	0.426–2.319	0.989	–	–	–
NG (3/1–2)	2.524	1.493–4.268	0.001	1.915	1.120–3.274	0.018
LVI (+/−)	3.011	1.618–5.602	0.001	1.625	0.801–3.298	0.179
Partial or Total mastectomy	0.451	0.264–0.771	0.004	–	–	–
Partial without RT or not	2.393	1.084–5.284	0.031	2.613	1.174–5.813	0.019
ACT	4.792	2.789–8.232	< 0.001	–	–	–
Endocrine therapy	0.886	0.447–1.756	0.729	–	–	–
MMBC or UBC	0.637	0.288–1.406	0.264	–	–	–
Modified pT(2–3/1)	3.035	1.775–5.189	< 0.001	–	–	–
Upstaging or not	2.142	0.855–5.371	0.104	2.710	1.011–7.264	0.048

ACT adjuvant chemotherapy, *CI* confidence interval, *HR* hazard ratio, *NG* nuclear grade, *LVI* lymphovascular invasion, *RT* radiation therapy, *MMBC* multifocal and multicentric breast cancer, *UBC* unifocal breast cancer, *DFS* disease-free survival, *DDFS* distant disease-free survival, *OS* overall survival

We used univariate Cox regression analysis to evaluate the effect of MMBC and upstaging MMBC on DFS (Table 5). Axillary lymph node involvement, higher nuclear grade and lymphovascular invasion were associated with poor DFS (HR 3.149, 2.524 and 3.011, respectively). Conventional pT stage and modified pT stage also affected DFS (HR 2.775 and 3.035, respectively). Omitting radiation therapy after partial mastectomy was a significantly poor factor for DFS (HR 2.393, $P = 0.031$), while partial mastectomy was a significantly better factor for DFS than total mastectomy (HR 0.451, $P = 0.004$). Although MMBCs were not a worse factor for DFS (HR 0.637, $P = 0.264$), upstaging MMBCs tended to be a poor factor for DFS (HR 2.142, $P = 0.104$).

We used multivariate Cox regression analysis to evaluate the effect of upstaging MMBC on DFS, using risk factors that were significant in the univariate analysis (Table 5). Upstaging MMBCs independently affected DFS in the multivariate analysis (HR 2.710, P = 0.048), after adjusting for conventional pT, pN, nuclear grade, lymphovascular invasion, and omitting radiation therapy after partial mastectomy.

Discussion

To our knowledge, this is the first study to examine the effect of MMBC on DFS, DDFS, and OS in Japanese women. Our results indicate that MMBC itself may not be a worse prognostic factor of breast cancer, but the sum of the invasive diameters of MMBC may be an important prognostic factor. In considering MMBC as a risk factor for poor prognosis, the following confounding factors should also be examined: lymph node metastasis, biological factors other than the main lesion, and actual tumor burden.

First, several studies argue that MMBC has been consistently associated with a higher risk of nodal involvement than UBC [5, 8, 10, 15–18]. Rezo et al. analyzed

812 patients (141 with MMBC and 671 with UBC) and observed that the MMBC group was more likely to exhibit nodal involvement than the UBC group (49.6% versus 33.7%, $P = 0.001$) [10]. Both Coombs et al. and Rezo, et al. reported that although MMBC predicted worse prognosis in univariate analyses, it was not an independent predictor, after adjusting for nodal involvement and another factor in multivariate analyses [10–14]. On the other hand, a study by Weissenbacher et al. claimed that MMBC is an independent prognostic factor by multivariate analysis of lymph node metastasis. They compared 288 patients with MMBC with a cohort of UBC controls matched by tumor size, grading, and hormone receptor status and found that the MMBC group was more likely than the UBC group to have nodal involvement (51.7% versus 41.7%, $P = 0.0001$) [11]. In multivariate analysis, MMBC exhibited significantly poorer relapse-free survival (HR 1.74) and breast cancer-specific survival (HR 1.57) than UBC. The increased risk of nodal involvement, despite a similar largest tumor diameter to that of UBC, may reflect that the invasive lesions other than the largest tumor affect node metastasis or that MMBC is a more aggressive cancer type.

In our study, only 18.4% of the MMBC group and 16.9% of the UBC group had nodal involvement ($P = 0.667$), these values in both groups being lower than those in previous studies. We excluded patients with potentially unfavorable prognoses who underwent neoadjuvant chemotherapy (465/1605 = 29%) because this treatment is generally selected for more aggressive cancers. Therefore, the patients in this study had better prognoses and underwent surgery at earlier stages than patients in previous studies. Moreover, as pT1 tumors were frequent in the MMBC group, this group had a relatively good prognosis.

Second, the feature of lesions other than the main lesion may affect prognosis because of missed opportunities to receive treatment that may be appropriate. For example, if the second lesion was hormone-positive or HER2-positive and the main lesion was triple-negative, the opportunity to undergo endocrine therapy or molecular targeted therapy may be missed. We did not examine the tumor characteristics of the second largest lesion because immunostaining for each focus is not routine in our institute. However, our finding that the second tumor of upstaging MMBC was larger than that of non-upstaging MMBC suggests that the biology of the second tumor may influence prognosis. Desmedt et al. assessed the exonic lesions of 360 cancer-related genes among ipsilateral invasive tumors from 36 patients with MMBC [19]. In 12 patients, the lesions did not share any mutations despite similar histopathological features. Immunostaining of the second largest tumor may reveal inter-lesion tumor heterogeneity, which may change the decision about whether to give adjuvant chemotherapy or molecular targeted therapy, which may subsequently affect the prognosis.

Finally, a study by Hilton et al. showed that a larger summation of the largest tumor dimensions was associated with a worse breast-cancer-free-interval on multivariate analysis (HR 1.09, $P = 0.003$) [20]. Coombs et al. reported that the larger the total tumor load was, the greater the tendency for axillary lymph node metastasis [14]. These studies support our finding that the sum of the diameters of tumor invasion affects DFS, and it might be appropriate to reconsider the TNM classification.

In this study, selection bias could not be excluded because of the retrospective nature of the analysis and also the exclusion criteria, which may have affected survival outcomes. Moreover, the median follow-up duration was only 6.8 years, and approximately 86.5% of the patients had ER-positive disease; hence, it is likely that there would be many cases of recurrence after ≥ 5 years. However, this is the first large single-institute retrospective study of MMBC in Japan and our data will contribute to a better understanding of the prognosis of MMBC.

Conclusion

The findings of our study showed that MMBC may not be a worse prognostic factor of breast cancer; however, the sum of the invasive diameters of MMBC could be an important prognostic factor. To verify our results, studies considering receptor status and genomic data for each focus in MMBC are needed.

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Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

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