# Pathological Characteristics of Both Tumors in Bifocal and Bicentric Breast Cancer

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**Abstract.** *Aim: The objective of the present study was to describe the biological characteristics of each lesion in patients with bifocal/bicentric (BF/BC) breast cancer. Patients and Methods: We retrospectively reviewed the charts of 205 patients diagnosed with BF/BC cancer. The degree of concordance between the two lesions was assessed using Pearson product-moment correlation coefficients. Results: A total of 205 patients were included. Both tumors displayed the same histological type in 182 patients (89%). The same grade was found for both tumors in 178 of the cases (96.7% and 100% for grade 3 lesions). Immunohistochemical concordance between the two tumors was excellent, with correlation coefficients of 0.98, 0.96 and 0.99 for estrogen receptors (ER), progesterone receptors (PR) and Ki67, respectively. Human Epidermal growth factor Receptor 2 (HER2) status was available for both tumors in 177 cases (86%), with a perfect concordance. We did not find any differences in molecular sub-type between tumor foci. Conclusion: Immunohistochemistry should be performed only on the main tumor in cases of BF/BC cancer.*

The incidence of multifocal/multicentric (MF/MC) breast cancer ranges from 6% to 60% (1, 2). This significant variation in incidence rates reported in the literature can be explained by the diversity of multifocality definitions: inclusion or exclusion of *in situ* disease, MF or MC, distance between tumors and method of pathological examination (3). Increased access to magnetic resonance imaging (MRI) has resulted in increased rates of MF breast cancer diagnosis (4, 5). In addition, poorer outcomes are observed in multifocal breast cancer because of larger tumor size, greater lymph node involvement, grade 3 disease and more frequent lymphovascular invasion (1, 6-10). Adjuvant therapy is, therefore, a challenge to improving survival in MF/MC breast cancer. Classification of breast cancer sub-types [luminal A, luminal B, human epidermal growth factor receptor 2(HER2), basal-like] has rapidly become the new standard for adjuvant treatment decisions (11, 12). Immunohisto-chemical assessment of protein expression profiling is now widely used to define molecular sub-types (13). In cases of MF/MC breast cancer, most guidelines recommend assessment of biological markers only on the largest tumor focus (13, 18). This approach can lead to an underestimation of the molecular sub-type and under-treatment of patients, as heterogeneity of individual foci in MF/MC breast carcinoma has not been widely studied and remains a subject of debate (19-27).

The objective of the present study was to describe the biological characteristics of each lesion in bifocal (BF)/bicentric (BC) breast cancer and to assess the differences in molecular subtype classification between disease foci.

## Patients and Methods

*Studied population*. We retrospectively reviewed the charts of patients diagnosed with multifocal breast cancer who were consecutively managed at our Institution from March 2003 to June 2005. We focused exclusively on BF and BC breast cancer, defined respectively as the presence of two malignant lesions in the same quadrant separated by normal breast tissue (>5 mm), and two different malignant lesions also separated by normal breast tissue and located in different quadrants. The preoperative diagnosis of BF/BC was performed either clinically by palpation or radiographically by ultrasound, mammography or magnetic resonance imaging (MRI).

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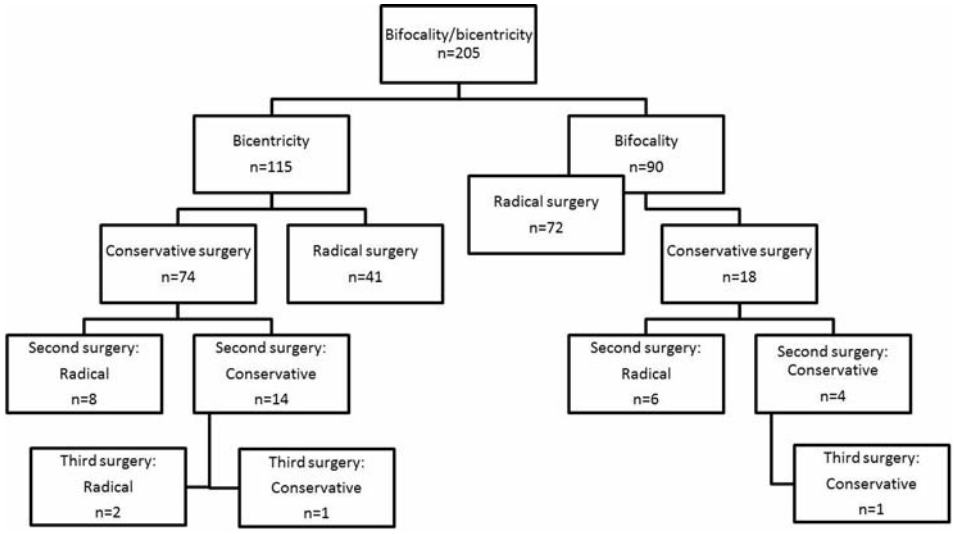


Figure 1. *Surgical management of the studied population.*

All BF/BC breast cancer was confirmed after pathological examination of both lesions. The patients with history of ipsilateral breast cancer, concomitant contralateral breast cancer, more than two lesions in the same breast, distant metastasis or those who received primary medical treatment were excluded from the study. The Ethical Committee of our Institution approved this study.

*Management of the patients*. All patients in this study were first treated by surgery. Local surgical treatment of the patients is described in Figure 1. The sentinel lymph node was examined in 57 patients, and axillary lymph node resection was performed in 167 patients. Axillary lymph node involvement was observed in 39% (n=80) of patients. Adjuvant therapy was determined for each patient during a multidisciplinary meeting based on the pathological analysis and immunohistochemical results of both foci. Chemotherapy was administered in 51.7% (n=106), hormone therapy in 80% (n=164), breast or chest radiotherapy in 79.5%, lymph node radiotherapy in 48.8% and Herceptin in 10% (n=21). Patients had long-term follow-up in our Institution for a median period of 113 months (range: 52-130).

*Pathological examination*. We reviewed the pathological reports of all included patients. At our Institution, histological type, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status and Ki67 rate were prospectively and systematically determined in every tumor focus in patients with MF/MC breast cancer. The antibody used for HER2 immunohistochemistry during the investigation period was A0485 (1/800; Dako, Glostrup, Denmark). When HER2 testing was equivocal by immunohistochemistry, fluorescence *in situ* hybridization was performed. The main tumor, or tumor 1 (T1), was the largest focus of breast cancer and the minor focus was identified as tumor 2 (T2). Breast cancer sub-types were defined as described in the St. Gallen International Expert Consensus, with a 20% cut-off for PR and a 14% cut-off for Ki76 (28).

*Statistical analysis*. Comparisons of pathological characteristics between the two tumors were performed with a Pearson's Chi-square test, a Fisher's exact test or Student's *t*-test. Concordance was assessed using the Pearson product-moment correlation coefficient. Differences were considered significant at $p<0.05$. All data analyses were performed using R software (http://lib.stat.cmu.edu/r/CRAN) (29).

## Results

Between March 2003 and June 2005, 205 patients with BF/BC were managed at our Institution and included in this study. Bi-focality and bi-centricity were histologically proven for 115 and 90 patients, respectively. The mean distance between tumors was 16 (range=6-60) mm in the pathological examination (12.4 mm for BF and 25.3 mm for BC).

The pathological characteristics of each tumor are presented in Table I. Invasive carcinoma was found in 196 cases (96%) for T1 and in 194 cases (95%) for T2. Both foci displayed the same histological type in 182 patients (89%). Tumor grade information for both lesions was available in 184 cases (90%). The same grade was found in both foci in 178 cases (96.7% and 100% for grade 3 lesions). For the 6 patients with discordant grades, 3 had a grade 2 T1 and grade 1 T2, while 3 exhibited a grade 1 T1 and grade 2 T2. We did not find any differences between BC and BF breast cancer in terms of discordance of tumor grades. The grade was the same for the two lesions in 97.1% of the BF cases and in 96.2% of the BC Cases ($p=0.32$).

Immunohistochemical concordance between the two tumor foci was excellent, with correlation coefficients of

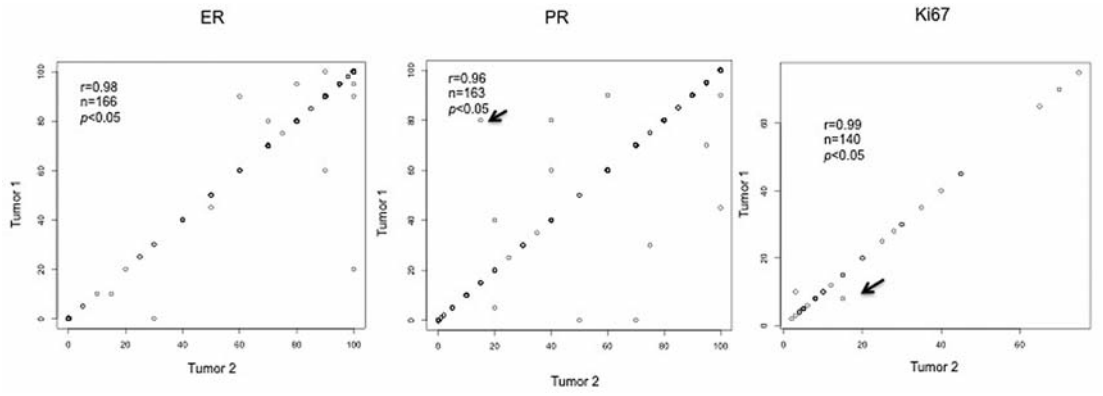


Figure 2. *Degree of concordance between Tumor 1 and Tumor 2 for percentage of Estrogen receptors (ER), Progesterone receptors (PR) and Ki-67.*

Table I. *Pathological characteristics of both tumors in bifocal and bicentric breast cancer.*

| | Tumor 1 | | Tumor 2 | | *p*-Value |
|---|---|---|---|---|---|
| Clinical diagnosis, n, % | 130 | 63.4% | 41 | 20.0% | <0.05 |
| Histology, n, % | | | | | 0.23 |
| Invasive ductal carcinoma | 128 | 62.5% | 124 | 60.5% | |
| Invasive lobular carcinoma | 28 | 13.7% | 28 | 13.7% | |
| Invasive ductal+lobular | 35 | 17.1% | 32 | 15.6% | |
| *In situ* ductal carcinoma | 9 | 4.4% | 13 | 6.3% | |
| Other* | 5 | 2.4% | 8 | 3.9% | |
| Histological size in mm, median (interval) | 17 | (3-80) | 9.6 | (1-40) | <0.05 |
| Tumor grade, n, % (missing n=13 and n=20) | | | | | 0.4 |
| I | 40 | 20.8% | 40 | 21.6% | |
| II | 84 | 43.8% | 79 | 42.7% | |
| III | 68 | 35.4% | 66 | 35.7% | |
| Lymphovascular embolism, n, % (missing n=10 and n=13) | 57 | 29.2% | 57 | 29.7% | 0.16 |

*Mucinous, micropapillary, NS: non-significant.

0.98, 0.96 and 0.99 for ER, PR and Ki67, respectively. HER2 status was available for both tumors in 177 cases (86%), with perfect concordance (151 negative-negative and 26 positive-positive). Figure 2 presents the degree of concordance for ER, PR and Ki67. We then focused on the immunohistochemical results of the six patients with different tumor grades. The same ER, PR, HER status and Ki67 rates were found for both lesions. We did not find any differences in terms of discordance of immunohistochemistry between tumors with the same histotype and tumors with different histotypes ($p$=0.58). Table II illustrates the mismatches in biological markers between T1 and T2.

Only one patient exhibited PR and Ki67 differences between foci using the St. Gallen cut-off. T1 had a 15% PR positivity rate and an 8% Ki 67 rate, while T2 had an 80% PR positivity rate and a 15% Ki67 rate (identified by an arrow in Figure 2). However, this T1 was classified as luminal B because of its low PR rate (ER-positive and HER2-negative); T2 was also classified luminal B because of its high Ki67 (ER-positive and HER2-negative). For all other patients in the study, even when PR or Ki67 differed in T1 and T2, the rates remained on the same side of the cut-off.

Table II. *Mismatches in biological features between T1 and T2 tumors in bifocal/bicentric breast cancer.*

| | Mismatches, n (%) |
|---|---|
| Histological type, N=203 | 21 (10.3) |
| Histological grade (1 *versus* 2), N=184 | 6 (3.3) |
| Estrogen receptors, N=168 | 9 (5.4) |
| Progesterone receptors, N=165 | 12 (7.3) |
| Ki67, N=42 | 2 (4.8) |
| HER2, N=177 | 0 0 |

N: Number of patients with data available for both lesions.

Table III. *Discordance between foci in multifocal and multicentric breast cancers in the literature.*

| Reference | Year | Number of patients | Histotype | Discordance between foci (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Grade | ER status | PR status | HER2 status | Ki67 | Molecular subtype* |
| Middleton *et al.* (19) | 2002 | 32 | 38% | 0% | 0% | 0% | 0% | 6% | NA |
| Garimella *et al.* (20) | 2007 | 18 | 0% | 17% | 12% | 12% | NA | NA | NA |
| Boros *et al.* (21) | 2012 | 91 | 12% | 10% | NA | NA | NA | NA | NA |
| Choi *et al.* (22) | 2012 | 65 | 37% | 12% | 3% | 11% | 6% | NA | 8% (a) |
| Buggi *et al.* (23) | 2012 | 113 | NA | 18.6% | 4.4% | 15.9% | 9.7% | 15% | NA |
| Pekmezci *et al.* (24) | 2013 | 51 | 12% | 13.7% | 7.8% | 7.8% | 2% | NA | NA |
| Bethune *et al.* (25) | 2013 | 246 | 11.8% | NA | 2.8% | 2.8% | 6.5% | NA | NA |
| Pekar *et al.* (26) | 2014 | 110 | 14.6% | 5.5% | NA | NA | NA | NA | 10% (b) |
| Boros *et al.* (27) | 2014 | 155 | 14.8% | 15.5% | 11.6% | 18.7% | 16.1% | 29% | NA |
| Our results | 2014 | 205 | 11% | 3.3% | 5.6% | 5.5% | 0% | 4.8% | 0% |

*As defined by the St. Gallen International Expert Consensus (28). (a) 3.2% of luminal A/luminal B discordance, 4.8% of HER2+/luminal A or HER2+/ triple-negative discordance. (b) 6.4% of luminal A/luminal B discordance, 1.8% of luminal A/triple-negative discordance, 1.8% of HER2+/luminal A or HER2+/ triple-negative discordance.

## Discussion

This retrospective study including 205 BF/BC breast cancer cases revealed very similar histological characteristics between the two lesions. Only few patients had different tumor grades, and even in these cases, the ER, PR, HER2 status and Ki67 rates were similar. These results suggest that pathological examination is necessary to determine the tumor histological type, size and grade. However, immunohistochemistry performed solely on the main tumor seems to be sufficient to characterize BF/BC breast cancer.

Few articles have been published regarding the pathological characteristics of both lesions in MF breast cancer (19-27). The strength of the present study lies in the detailed prospectively assessed description of the two lesions by both pathological examination and immunohistochemistry. All charts were reviewed and all pathological reports checked. Because the analyses were conducted prospectively, the pathologist might have been influenced by the results of T1 in determining the rates of T2; we know there is a degree of subjectivity in interpretation of immunohistochemistry. The retrospective nature and the limited sample size are the main limitations of our study. However, previously published literature reports are almost entirely from smaller retrospective series, especially when pathological and immunohistochemical data are available.

One of the first studies comparing the biological characteristics of the different lesions in MF/MC breast cancer included 32 patients (19). They observed discordant histotypes in 38% of the cases, which is much higher than in our study; however, they did not find any discordance in terms of HER2, PR or ER status. The largest series to our knowledge was published in 2013 and included 246 patients (25). Their results were similar to ours in terms of discordance of histological type, ER and PR status. However, they observed a 6.5% discordance for HER2 status, as did Choi *et al.* in 2012 (22). and Buggi *et al.* in 2012 (23). The major studies examining the variability of histotype, tumor grade, ER status, PR status, HER2 status and Ki67 between lesions in cases of MF breast cancer are summarized in Table III.

Pekar *et al.* analyzed the classification of foci in MF/MC breast cancer into molecular sub-types in 2014 (26). The molecular sub-type classification discordance between foci in MF/MC breast cancer ranged in this study from 10% to 12.7%, depending on the classification system used [Nielsen system (30), St. Gallen 2011 system (13), Sotiriou system (31, 32)]. In brief, the luminal A sub-type is defined in all systems as ER-positive, PR-positive or -negative, HER2-negative cancer, with low Ki67 (<14%) in the St. Gallen system and grade 1 or 2 in the Sotiriou system. The Luminal B subtype is defined as ER-positive, PR-positive or -negative, HER2-positive cancers in the Nielsen system, ER-positive, PR-positive or -negative and HER2-negative grade 3 cancer in the Sotiriou system and ER-positive, PR-positive or -negative, HER2-positive or -negative cancer with high Ki67 (>14%) in the St. Gallen system. The HER2-positive subtype corresponds to HER2-overexpressing cancer in all classification systems associated with ER-negative and PR-negative for both the Nielsen and St. Gallen systems, and regardless of ER and PR status in the Sotiriou system. Finally, the triple-negative or basal-like sub-type is defined as ER-negative, PR-negative, HER2-negative cancer in all systems. In Pekar *et al.*'s study, when heterogeneity in sub-type classification was found, patients had a statistically significantly shorter survival with a

greater risk of death in the Nielsen (HR=2.879, 95% CI=1.084-7.649; $p$=0.034) and Sotiriou systems, but not for the St. Gallen system (HR=0.898, 95% CI=0.270-2.992; $p$=0.861) (26). In our study, we did not find similar heterogeneity. This can, perhaps, be partially explained by the fact that we only included patients with two lesions, whereas other series studied patients with larger and multifocal tumors, with up to six lesions in the same breast in the Pekar *et al*. series. Moreover, determining the additional tumor foci would have changed therapy decisions in fewer than 4% of the cases (4/110) in this series.

## Conclusion

We have presented one of the largest series comparing pathological and immunohistochemical characteristics between the two tumors in cases of BF and BC breast cancer. Our results suggest that ER, PR and HER2 status or Ki67 rates are equivalent in both foci of BC/BF breast cancer. In addition, the molecular sub-type classification determined by immunohistochemistry was similar in both tumors. Moreover, the literature demonstrates that even if discordance is found between tumor foci, the differences would ultimately have little influence on treatment decisions. Therefore, based on these results and the existing literature, immunohistochemistry need only be performed on the main tumor focus, even if the lesions demonstrate different tumor grades. Our results showed homogeneity of the immunohistochemical characteristics of MF breast cancer in cases of bifocality or bicentricity.

## Conflicts of Interest

The Authors indicated no potential conflicts of interest with regard to this study.

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