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Multicentric/multifocal breast cancer with a single histotype: is the biological characterization of all individual foci justified?

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Background: Invasive multiple breast cancers with a single histological feature (MBCSH) are routinely assessed for biological parameters to indicate adjuvant treatments only in the largest invasive carcinomas. However, the heterogeneity of individual foci in multiple carcinomas has not been widely studied. We analyzed whether such biological features are differently expressed in different MBCSH foci.
Patient and methods: One hundred and thirteen invasive MBCSH were tested over a 5-year period. The expression of estrogen (ER) and progesterone (PgR) receptors, Ki-67 proliferative index, expression of HER2 and tumor grading were prospectively determined in each tumor focus, and mismatches among foci were recorded.
Results: Mismatches in ER status were present in 5 (4.4%) cases and PgR in 18 (15.9%) cases. Mismatches in tumor grading were present in 21 cases (18.6%), proliferative index (Ki-67) in 17 (15%) cases and HER2 status in 11 (9.7%) cases.
Conclusions: In our experience, invasive MBCSH showed heterogeneity among foci. In our clinical practice, such assessment led to 14 (12.4%) patients receiving different adjuvant treatments compared with what would have been indicated if we had only taken into account the biologic status of the primary tumor.
Key words: adjuvant therapy, breast cancer, invasive, multicentric disease, multifocal disease, prognostic factors

introduction

Multiple breast cancers may present with different clinical and biologic characteristics that have implications for the therapy of multifocal/multicentric disease compared with unicentric disease [1]. Multiple tumors have increased lymph node (LN) involvement compared with unifocal tumors, and available data suggest that multifocal/multicentric breast cancer is actually more aggressive and carries worse overall outcomes than unifocal disease [2]. In other studies, multifocality itself does not appear to a contributing factor for worse outcome; more aggressive systemic disease or decreased response to systemic therapies also plays a role [3]. It has been suggested that multifocal and unifocal tumors do not share the same biology since factors other than tumor volume/surface area, histology, tumor grade and vascular invasion have been shown

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to affect behavior [4]. In fact, the prognostic impact of multiple breast cancer has been poorly studied and the necessity for specific adjuvant treatment to counteract the potentially unfavorable effect of multifocality is unknown [5].

Clinical decisions in systemic adjuvant therapy for breast cancer are presently based on quite separate criteria justifying the use of a particular therapeutic agent [6]. In particular, international guidelines recommend adjuvant endocrine treatment in patients whose tumors show estrogen receptor (ER) positivity and anti-HER2 therapy in HER2-positive diseases; lower ER and progesterone receptor (PgR) positivity, high histological grade and elevated Ki-67 proliferative index are characteristics that favor the use of chemotherapy [6]. The aforementioned parameters are also associated with poor prognosis [3]. However, in cases of multiple breast cancer with a single histology (MBCSH), it is accepted that such parameters are assessed only in the largest invasive carcinomas [College of American Pathologist (CAP) guidelines 2009, p. 26] [7]. The smaller cancers tend to be ignored even though the heterogeneity of individual foci in multiple carcinomas has not been widely studied [8].

The aim of this study was to analyze whether biological features that play a role in the choice of adjuvant treatment of breast cancer are differently expressed in different MBCSH foci.

patients and methods

Multiple cancer was defined as 'more than one focus of invasive carcinoma separated by benign tissue' whether in the same or a different quadrant, and therefore, all multifocal and multicentric lesions were included in the study. Multiple lesions with different histological features in different foci were excluded. At our institution, all breast cancer specimens are routinely analyzed by pathologists according to CAP guidelines [7] and, since June 2004, expression of ER, PgR, HER2, Ki-67 proliferative index and tumor grading have been prospectively determined in every tumor focus of multiple lesions with a single histological feature, the results being included in the standard pathologic report.

Immunohistochemical methods were used to assess ER, PgR status and Ki-67 and FISH to determine HER2 status. In addition, for the present study, the actual percentage of ER/PgR staining was further classified for each focus as 'positive' (staining of at least 10% of cells) or 'negative'. Ki-67 staining in any focus was labeled 'high' (in at least 20% of cells) or 'low'. Grading was reported according to the Nottingham combined histological grading system [9, 10] and classified as 'G3' or 'G1 or G2'. HER2 amplification was defined according to CAP guidelines [7] or the presence of a focal HER2-amplified clone in at least 30% of tumor cells and reported as 'amplified' or 'nonamplified'. A 'mismatch' was considered to be present within a tumor when at least one smaller focus showed a difference in at least one biological parameter compared with the larger focus.

results

From 1 June 2004 to 31 December 2009, 1499 infiltrative breast cancers, 139 (9.27%) cases of which were multiple, were treated at our institution. Among the latter, 113 displayed the same histological type in the foci and were eligible for study inclusion. None of the patients received prior neoadjuvant treatment. Patients were treated with mastectomy in 89 cases (78.8%) [with Sentinel Lymph Node Biopsy (SLNB) in 40 cases and with Axillary Lymph Node Dissection (ALND) in 49] and quadrantectomy in 24 cases (21.2%) (with SLNB in 14 cases and with ALND in 10).

Infiltrating ductal carcinoma was present in 95 (84%) cases, infiltrating lobular carcinoma in 14 (12.4%), and other rarer histotypes accounted for the remaining 4 (3.6%) cases. According to AJCC/TNM (American Joint Committee on Cancer/tumour–node–metastasis) classification, pT1 tumors accounted for 72 cases (63.7%), pT2 for 37 cases (32.7%) and pT3 tumors for 4 cases (3.6%); 54 cases (47.8%) were pN0, while 59 (52.2%) had metastatic LNs. In particular, up to 3 LNs were metastatic in 47 cases (41.6%), 4–9 LNs in 7 cases (6.2%) and >10 LNs in 5 cases (4.4%) (Table 1).

Regarding ER status, five (4.4%) mismatches were present: in two cases, a smaller focus was positive and the main focus was negative, while in the remaining three cases, a smaller focus was negative and the main focus was positive. For PgR status, 18 (15.9%) mismatches were present: in 10 cases, a smaller focus was positive and the main focus was negative, while in the remaining 8 cases, only the larger focus was positive. For tumor grading, 21 (18.6%) mismatches were present: in 3 cases, a higher grade (G3) was detected in a small focus and the main focus had a medium/low grading score, while the situation was reversed in the remaining 18 cases. Proliferative index (Ki-67) differed in 17 (15%) cases: in eight cases, a 'high' index was reported in the smallest foci. An HER2 amplification mismatch was present in 11 (9.7%) cases and HER2 was amplified exclusively in one of the smallest foci in 4 cases (Table 2).

Table 1. Patients characteristics

	N (%)
Age (mean: 57; range 27–92), years	
All	113
<55	57 (50 4)
≥55	56 (49 6)
Number of foci	
2	88 (77 9)
3	19 (16 8)
4	4 (3 5)
5	2 (1 8)
Histotype	
Ductal infiltrating	95 (84)
Lobular infiltrating	14 (12 4)
Other	4 (3.6)
T stage	
pT1	72 (63.7)
pT2	37 (32.7)
pT3	4 (3.6)
N stage	
N0	54 (47.8)
N+	59 (52.2)
1–3 LN	47 (41.6)
4–9 LN	7 (6.2)
>10 LN	5 (4.4)

LN, lymph node.

Table 2. Mismatches in biological features among foci of MBCSH

	Minor focus: ER positive, Main focus: ER negative	Minor focus: ER negative, Main focus: ER positive	Total *N* (%)
Mismatches in ER	2 (1.7%)	3 (2.5%)	5 (4.4)
	Minor focus: PgR positive, Main focus: PgR negative	Minor focus: PgR negative, Main focus: PgR positive	Total *N* (%)
Mismatches in PgR	10 (8.8%)	8 (7.7%)	18 (15.9)
	Minor focus: G3, Main focus: G1/G2	Minor focus: G1/G2, Main focus: G3	Total *N* (%)
Mismatches in grading	3 (2.6%)	18 (15.9%)	21 (18.6)
	Minor focus: high, Main focus: low	Minor focus: low, Main focus: high	Total *N* (%)
Mismatches in Ki-67	8 (7%)	9 (7.9%)	17 (15)
	Minor focus: amplified, Main focus: not amplified	Minor focus: not amplified, Main focus: amplified	Total *N* (%)
Mismatches in HER2	4 (3.5%)	7 (6.2%)	11 (9.7)

ER, estrogen receptor; PgR, progesterone receptor.

discussion

There has been considerable debate on the understaging of multiple breast cancer and its contribution to a more aggressive nature [3]. Recently, Weissenbacher et al. [11] compared two equivalent groups of early breast cancer patients with multiple versus unifocal tumors, apparently identical in tumor size according to the TNM staging system, using a matched-pair analysis: at the mean follow-up of 5.8 years, the cancer-specific survival time was significantly higher in patients with unifocal disease compared with patients with multiple tumors (221.6 versus 203.3 months, $P< 0.0001$), and this was also true for the relapse-free survival (205.9 months in patients with unifocal disease as opposed to 169.6 months in patients with multiple disease, $P< 0.0001$). A local relapse occurred in 7.3% of patient with unifocal disease compared with 17.4% of patients with multiple tumors ($P< 0.0001$). The multivariate analysis showed that multicentricity/multifocality was a significant independent predictor of reduced breast cancer-specific and relapse-free survival [11]. These findings led the authors to highlight how the current treatment algorithms, which employ the diameter of the largest nodule, result in the downplaying of multifocal breast carcinomas due to underestimation of actual tumor size. In fact, because the tendency of breast tumors to metastasize is reflected on the total tumor load [12], failure to measure additional tumor burden has been claimed to possibly deny patients the opportunity of adjuvant treatment [11].

The biological features of the tumor play an important part in deciding the best adjuvant treatment, namely ER, PgR and HER2 positivity, balanced with the likely prognosis and foreseeable risk of relapse based on TNM stage, histological grade and Ki-67 proliferative index [6]. According to the AJCC/International Union Against Cancer (Union Internationale Contre le Cancer) TNM system (7th edition), protocols for the examination of MBCSH specimens recommend that the highest T category tumor should be the one selected for classification and staging; the reported grade corresponds to the largest area of invasion, and ER, PR and HER2 status are determined only on the largest invasive carcinoma. Biological tests on smaller invasive carcinomas are recommended only if these cancers are of different histological type or of higher grade [7].

In our study, we focused on different features expressed by multiple nodules; we analyzed 113 MBCSH and evaluated whether multiple foci are as biologically homogeneous as assumed in current practice. Biological data were prospectively collected and subsequent analysis showed that mismatches among foci were present in 4.4%–18.6% of cases according to the parameter considered (Table 2). ER positivity was reported in a minor focus in only two cases: since any ER staining is considered an indication for endocrine therapy [6], the standard approach to the analysis of multiple tumors would have prevented two (4.4%) patients from receiving this treatment. Similarly, four (3.5%) patients had HER2 amplification in a smaller focus, the main one being negative, and thus, anti-HER2 therapy would not have been considered as a viable adjuvant treatment if the smaller foci had not been examined. High tumor grading and elevated Ki-67 proliferative index showed high mismatch rates (18.6% and 15%, respectively) between foci and would not have played a proper role in the treatment selection algorithm if only the main tumor focus had been characterized. The indications for adjuvant treatment were prospectively issued by the multidisciplinary clinical team and recorded: the presence of mismatches in ER status among foci led to a change in adjuvant treatment in all patients because the two (1.8%) patients whose smaller foci had ER positivity were given hormonal therapy even though the main focus did not express any ER. Conversely, the three (2.6%) patients with an ER-positive main focus also had at least one ER-negative focus and therefore received adjuvant chemotherapy. Those four (3.5%) patients whose smaller foci only showed HER2 amplification received targeted therapy (and chemotherapy) even if the biology of the main focus would not have justified treatment. Among the patients with mismatches in elevated proliferative index, in five (4.4%) cases, the finding led to the chemotherapy of hormone-responsive tumors even though the main focus did not show any elevated Ki-67 staining (Table 3).

Former studies based on histological and immunocytochemical evaluation of markers such as B72.3, DF3, c-erb-B2, SP1, carcinoembryonic antigen and p53 claimed that the development of multifocal breast cancer may be based on either intramammary spread of tumor cells from a single primary focus or simultaneous development of

Table 3. Therapy according to biological features in MBCSH

Patient number	Status of main focus			Therapy according to main focus only	Mismatch in minor focus	Therapy according to all foci
	ER	Mib-1	HER2			
1	ER+	Low	Not amplified	HT	High Mib-1	HT + CHT
2	ER+	High	Not amplified	HT + CHT	HER2 amplified	HT + CHT + TT
3	ER−	Low	Not amplified	CHT	ER+	CHT + HT
4	ER−	Low	Not amplified	CHT	ER+	CHT + HT
5	ER+	Low	Not amplified	HT	High Mib-1	HT + CHT
6	ER+	High	Not amplified	HT + CHT	HER2 amplified	HT + CHT + TT
7	ER+	High	Not amplified	HT + CHT	HER2 amplified	HT + CHT + TT
8	ER+	High	Not amplified	HT + CHT	HER2 amplified	HT + CHT + TT
9	ER+	Low	Not amplified	HT	High Mib-1	HT + CHT
10	ER+	Low	Not amplified	HT	High Mib-1	HT + CHT
11	ER+	Low	Not amplified	HT	High Mib-1	HT + CHT
12	ER+	Low	Not amplified	HT	ER−	HT + CHT
13	ER+	Low	Not amplified	HT	ER−	HT + CHT
14	ER+	Low	Not amplified	HT	ER−	HT + CHT

ER, estrogen receptor; HT, hormonal therapy; CHT, chemotherapy; TT, Anti-HER2-targeted therapy.

independent foci of carcinoma [12]. On these grounds, other authors more recently found nearly identical results performing immunohistochemistry with ER, PgR, Ki-67 and HER2 in cases of early multicentric breast carcinoma, thus supporting the mechanism of clonal growth and/or intramammary spread of a single carcinoma [13]; their results led the authors to conclude by supporting the performance of immunohistochemical analysis of prognostic markers on only one invasive tumor in each case of low-stage multicentric breast cancer. Nevertheless, in the work of Middleton [14], only 14 cases were amenable to comparison between the index tumor and a secondary lesion and, actually, heterogeneity in at least one biological characteristic was reported in 3 cases of the 14. Such experiences were conducted in retrospective fashion and were based on small series of patient but led to results that we could substantially confirm by our observations even though our larger ground of data depicted a more complex scenario that does not challenge the pathogenetic hypothesis but led us to different conclusion that all foci in MBCSH should possibly be analyzed; our work is, to our knowledge, the first to address biological heterogeneity of multiple breast cancers in a prospective fashion and studies on a larger set of specimens are nevertheless necessary to confirm our findings.

In our daily clinical practice, the biological classification of each tumor focus in MBCSH has led to 14 (12.4%) patients of 113 being issued different indications to adjuvant treatment compared with what would have been prescribed if we had only taken into account the status of the main focus.

In conclusion, in our experience, MBCSH shows important heterogeneity among foci in terms of the biological parameters, and this plays a crucial role in the adjuvant treatment decision-making process. As previously claimed, the design of a rational therapeutic strategy for breast cancer should begin with a clear understanding of the biologic basis of multicentricity and multifocality; once this information is known, the correct therapeutic strategy can be followed [1]. Our findings, if confirmed, may provide a more comprehensive biological evaluation of the overall tumor burden of multiple breast cancers.

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disclosure

The authors declare no conflict of interest.

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Breast Cancer Index predicts pathological complete response and eligibility for breast conserving surgery in breast cancer patients treated with neoadjuvant chemotherapy

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Background: The aim of neoadjuvant chemotherapy is to increase the likelihood of successful breast conservation surgery (BCS). Accurate identification of BCS candidates is a diagnostic challenge. Breast Cancer Index (BCI) predicts recurrence risk in estrogen receptor + lymph node – breast cancer. Performance of BCI to predict chemosensitivity based on pathological complete response (pCR) and BCS was assessed.
Methods: Real-time RT-PCR BCI assay was conducted using tumor samples from 150 breast cancer patients treated with neoadjuvant chemotherapy. Logistical regression and c-index were used to assess predictive strength and additive accuracy of BCI beyond clinicopathologic factors.
Results: BCI classified 42 % of patients as low, 35 % as intermediate and 23 % as high risk. Low BCI risk group had 98.4 % negative predictive value (NPV) for pCR and 86 % NPV for BCS. High versus low BCI group had a 34 and 5.8 greater likelihood of achieving pCR and BCS, respectively ($P = 0.0055$; $P = 0.0022$). BCI increased c-index for pCR (0.875–0.924; $P = 0.017$) and BCS prediction (0.788–0.843; $P = 0.027$) beyond clinicopathologic factors.
Conclusions: BCI significantly predicted pCR and BCS beyond clinicopathologic factors. High NPVs indicate that BCI could be a useful tool to identify breast cancer patients who are not eligible for neoadjuvant chemotherapy. These results suggest that BCI could be used to assess both chemosensitivity and eligibility for BCS.
Key words: Breast Cancer Index, breast conserving surgery, gene expression signature, neoadjuvant chemotherapy, pathological complete response

introduction

Neoadjuvant chemotherapy, as opposed to adjuvant chemotherapy, is used to enable breast conserving surgery (BCS) in patients with large tumor size [1]. Long-term follow-up from six randomized trials indicates no survival benefit for neoadjuvant over adjuvant chemotherapy and because of this, in many countries (e.g. USA) the standard of care remains conventional adjuvant chemotherapy [2–5]. However, neoadjuvant chemotherapy can cause tumor shrinkage, which enables a proportion of patients to be eligible for BCS, thus avoiding mastectomy. Moreover, patients who achieve a complete pathological response (pCR) have a better long-term survival [3, 6, 7]. This clinical utility of neoadjuvant chemotherapy is becoming increasingly more common for operable breast cancer [1, 3, 8–10]. In addition, clinical studies demonstrate that neoadjuvant chemotherapy increases BCS rate in comparison to adjuvant only chemotherapy [3, 4].

Overall, this background emphasizes that the primary aim of preoperative chemotherapy, in the context of daily practice, is to increase the likelihood of breast conservation in patients with large tumors. Nevertheless, most trials suggest that a significant subset of patients will not be eligible for BCS after

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