

Chapter 2

Multicentric/Multifocal Breast Cancer: Overview, Biology, and Therapy

Federico Buggi, Annalisa Curcio, Fabio Falcini, and Secondo Folli

Abstract Multiple breast cancers may present with different clinical and biological characteristics as compared with unicentric disease, and in certain instances this may have implications as far as treatment is concerned. Multiple tumors may have increased lymph node involvement compared with unifocal tumors, and some available data suggest that multifocal/multicentric breast cancer is actually more aggressive and carries worse overall outcomes than unifocal disease. In other studies, multifocality itself does not appear to be a contributing factor for worse outcome; more aggressive systemic disease or decreased response to systemic therapies, instead, seem to play a role. It has been suggested that multi- and unifocal tumors do not share the same biology since factors other than those currently employed for staging and prognostic purposes have been shown to affect behavior. In fact, the prognostic impact of multiple breast cancer has been poorly studied, and the necessity for specific adjuvant treatment in order to counteract the potentially unfavorable effect of multifocality is still subject to investigation.

2.1 Introduction

The presence of multiple foci of disease in the cancer-containing breast has been reported during most of the twentieth century [1]. Its significance has been lively discussed over the last 30 years [2], and sequential revisions of the biological and clinical implications of multiple breast cancer foci have followed one another over time; at least in part, the interpretation of multicentric tumors has been paralleled by the contemporary shift in paradigms for the treatment of breast cancer, with mutual influence.

F. Buggi • A. Curcio • S. Folli (✉)
Breast Unit, Morgagni-Pierantoni Hospital, Forlì, Italy
e-mail: federicobuggi@hotmail.com; s.folli@ausl.fo.it

F. Falcini
Romagna Cancer Institute (IRST), Meldola, Italy

2.2 Multifocality: What Definition?

In our opinion, the peculiarity of multifocal/multicentric breast cancer resides in the question whether the intrinsic profile of a certain multiple breast cancer can be extrapolated from the characterization of a single lesion (namely, the major, as is currently assumed) or, otherwise, whether each focus carries its own independent contribution to the overall behavior of the disease. An additional issue is whether multifocality itself may represent an independent biological feature to take into account when outlining a tumor profile.

The early findings by Holland et al. [3] (see below) in terms of high prevalence of multiple cancer foci as well as his depiction of the distribution of multiple lesions over a sort of topographic gradient around the biggest focus were fully confirmed in more recent studies: for example, Vaidya et al. reported [4] that 63 % of patients in their series harbored multiple foci in addition to the primary tumor and, in particular, only 53 % of patients had all foci contained within 2 cm, while 80 % of lesions could be found within 4 cm and 90 % within 5 cm of the main tumor edge. The importance of such a distribution of cancer within the breast has come to be well valorized after breast-conserving surgery became a standard procedure in order to optimize breast conservation [5], and, possibly, it has even been enhanced by the most extreme conservative efforts adopted in most recent times, such as oncoplastic surgery.

However, results in the literature regarding the significance of multiple breast cancer foci are still conflicting, and the impact of multifocality on overall survival is still controversial, mainly due to the use of various definitions lacking a wide international consensus and to methodological limitations [6].

Several definitions have in fact been used in the literature addressing multifocal breast cancer. Some studies required that tumors should be separated from each other by some arbitrarily selected distance or be located in different quadrants of the breast to be considered multifocal. Others included carcinoma in situ in the definition of multifocality [7] or used the term multicentricity as well: e.g., Katz et al. [8] defined “multicentricity” as more than two areas of carcinoma in more than one quadrant of the breast and separated by at least 4 cm, while “multifocality” was defined as two or more separate areas of carcinoma within the same quadrant and/or separated by less than 4 cm. Often multicentricity implies more than one primary tumor, whereas multifocality indicates multiple foci of the same tumor; some researchers operate with a minimum distance between the foci of 2 cm, and others require normal breast tissue between tumors but no minimal distance between the tumor foci [9].

Some authors, on the other hand, stated that the dichotomous classification of multifocal and multicentric disease is arbitrary and could simply represent different degrees of spatial separation rather than any biological difference between categories; breast quadrants are indeed typically defined by tracing lines which radiate perpendicularly from the nipple, but the lack of anatomical boundaries within the breast can result in variability of these “quadrants” with respect to patient position and the modality of assessment (clinical or radiological); therefore, lesions in

different quadrants can in fact have closer proximity than lesions occupying remote locations within the same quadrant [10].

It could thus be argued that despite being quite common in practice, categorizing multifocality solely on metric parameters may not be the most effective approach, and, actually, for some authors the definition of multifocality based on the distance between the individual foci appears to impede the ability to obtain comparable and significant results, first, because the biological importance of a distance is hard to test but also because it is impossible to achieve consensus regarding the required amount of millimeters [6].

In one study of cytogenetic changes, macroscopically distinct tumors in 9 of 12 mastectomy specimens were monoclonal, suggesting a common origin [11], and in these monoclonal cases, multiple foci were in closer proximity. Similar findings resulted from a study where a panel of immunohistochemical markers was utilized [12]. These data would need confirmation with contemporary profiling techniques but would suggest that when multiple lesions are in close proximity (multifocal), they are biologically similar, but not so when they are far apart (multicentric) [2]. However, on the practical side, even with molecular studies it can be difficult to differentiate between multifocal tumors, defined as the presence of multiple foci of the same tumor, and multicentric carcinomas, defined as multiple primary carcinomas in the same breast [13], hence many recent studies did not attempt to separate them.

In this vein, it has also been suggested that a classification based on quadrant location and distance from the nipple and rooted in the notion that the “quadrants” of the breast have some anatomic and biological meaning needs to be reconsidered [2]. A trend in this direction has been included among the changes from the sixth to the seventh edition of the AJCC Cancer Staging Manual, where it has been acknowledged that it is not necessary for tumors to be in separate quadrants to be classified as multiple simultaneous ipsilateral carcinomas, providing that they can be unambiguously demonstrated to be macroscopically distinct and measurable using available clinical and pathological techniques [14].

2.3 Multifocality and Breast Conservative Treatment

From approximately 1890 to 1970, radical mastectomy as introduced by William Halsted was generally accepted as the standard treatment for breast cancer [1], and the many studies that were carried out over such period in order to investigate multicentricity in breast cancer were conducted mainly with the purpose of understanding the process of *origin* of multiple cancers: due to the lack of therapeutic alternatives to destructive surgery, the relevance of multifocality in terms of treatment is yet to come. In the mid-1970s, Fisher et al. effectively summarized the findings yielded so far by the studies in the domain of breast cancer multicentricity when they stated that “the detection of multicentric cancers in mammary quadrants

other than that harboring the primary cancer in mastectomy specimens represents a conservative estimate since the probability of identifying such a lesion appears to increase as the number of [tissue] samples [examined] per patient increases” [15].

Actually, the incidence of multicentric foci in the breast has been reported to vary from 18 %, when 1–2 random samples from each quadrant were examined [16], to 69 % when 5 mm sections of whole breast were examined [17].

Some studies that addressed the topic of multiple breast cancer [18] used radiography, but it was Egan [17] who standardized the “correlated pathological-radiological” method of whole-organ analysis, which provides optimum sampling of breast tissue. Many studies conducted with Egan’s technique on this matter over the years reported rates of multiple lesions ranging from 56 % [19] to 69 % [17].

In the 1970s, the major debate in the local therapy of breast cancer was the safety of the switch from radical mastectomy to modified radical mastectomy. In that environment, the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B04 trial [15] studied the contribution to survival deriving from the removal of the axillary nodes in clinically node-negative women: its results eventually led to the direct repudiation of the Halstedian concept of breast cancer biology and opened the door to studies that tested the effectiveness of breast conservation treatment.

Over the course of the studies on breast conservation, the new option of partial removal of the breast coupled with the long-standing awareness of high frequency of additional cancer foci beyond an index lesion focused concerns upon the eventuality of local recurrences and brought into focus the importance of assessing the extent and the topographical distribution of tumor foci in the surroundings of an overt cancer.

In a landmark paper on multifocality, Holland et al. [3] examined with Egan’s method a consecution series of breast cancers that appeared clinically and radiologically unifocal and that constituted virtual candidates to conservative treatments; the actual presence of additional undetected cancer foci beyond the index lesion was studied in mastectomy specimens of these cases with the purpose to estimate the frequency with which tumor would remain in the breast after a breast-conserving surgical intervention.

Their results showed that only a minority of tumors had their clinical unifocality confirmed in the surgical specimen, and actually a 63 % rate of multicentricity was reported; moreover, the authors addressed the additional issue of the spatial distribution of clinically undetected foci in terms of their distances from the primary tumor, and the results showed that the likelihood of finding additional tumor foci in breast tissue decreased as the distance from the index lesion increased, despite the size of the index tumor.

In other words, assuming the distance of additional tumor foci from the index lesion as a surrogate for the surgical margin during breast-conserving surgery for infiltrating carcinoma, the percentage of patients still harboring tumor foci following excision would be higher with a margin of 2 cm rather than 4 cm (42 % and 10 %, respectively, according to Holland). Therefore, the emerging scenario was

that an average quadrantectomy on an average-sized breast was unlikely to remove all cancer foci: earlier concerns “that local excision may ignore residual tumors, particularly those which may occur as clinically and pathologically undetected *de novo* cancers at sites within the breast quite remote from the dominant mass” [15] still represented a deterrent to the acceptability of breast-conserving surgery.

At this stage it was difficult to scientifically accept the possibility that a cancer might not be a cancer of clinical significance and there was a need for information regarding the kinetics of the multicentric foci. In 1969 a randomized study to compare radical mastectomy with breast-conserving surgery, which was termed “quadrantectomy,” was approved by the World Health Organization Committee of Investigators for Evaluation of Methods of Diagnosis and Treatment of Breast Cancer; after the new procedure was standardized, the recruitment of patients began at the Milan Cancer Institute in 1973, and preliminary data showed that survival rates were equal after radical and breast-conserving surgery [20]. A few years later, another randomized controlled clinical trial—NSABP-06 [21]—was conducted in order to evaluate the efficacy of breast-conserving surgery and the biological importance of tumor multicentricity: after 20 years of follow-up, the absence of a significant difference in overall survival among women who underwent mastectomy and those who underwent conservation treatment was confirmed. Besides, the rate of ipsilateral breast tumor recurrence, as well, did not differ significantly among the two groups [22]. Over time, the association of breast-conserving surgery with radiotherapy has proved to grant patients equivalent survival with respect to mastectomy, as pointed out by six prospective randomized trials with long-term follow-up, some more than 20 years [22].

Moreover, adjuvant treatments have been extensively employed and refined with increasing success: in a report of 3,799 node-negative women participating in five NSABP trials of adjuvant systemic therapy, the cumulative incidence of in-breast recurrence at 12 years for those receiving adjuvant therapy was only 6.6 % [23].

In summary, the persistence of tumor foci after breast conservation treatment was known for a fact, but, nevertheless, the observation of increasing survival rates and a parallel decrease in local recurrence due to improvements in adjuvant treatments and refinements of diagnostic tools led to the replacement of concerns about the mere presence of remnant cancer cells by issues concerning the specific biological feature of the (remaining) disease.

The importance of biology and targeted therapy has been supported by the emerging literature on the impact of tumor subtypes on local recurrence after BCT or mastectomy. Both Millar et al. [24] and Nguyen et al. [25] demonstrated that the rate of local recurrence after BCT varies among the intrinsic subtypes of breast cancer as approximated by the ER, progesterone receptor (PgR), and human epidermal growth factor receptor (HER)-2 status.

2.4 Multifocality and Outcome

When it comes to considering outcomes of multiple tumors, overall survival and other prognostic factors (that may in turn indirectly affect overall survival) should deserve distinct consideration.

An insight of the appropriateness in this separation comes from a study published by Pedersen et al. [9], which also offers an effective example of mismatches in results due to differences in definitions and methodologies. Pedersen et al. reported that in a study from 1982 [17], Egan found that the presence of multifocality signaled a worse prognosis, while in their own investigation, it was not found to have an independent effect on overall survival, when controlling for known prognostic factors. The findings Pedersen reported were in accordance with the data published by Rakowsky et al. [26], who also found that multifocality had no influence on disease-free survival, and those of Vlastos et al. [27], who found in a set of patients with early-stage cancer that patients with unicentric tumors had a 10-year disease-free survival of 84 % and the patients with multicentric tumors had a 10-year disease-free survival of 83 %. The differences in the conclusions reported by Egan and Pedersen could be explained by differences in the criteria adopted for defining multifocality (Egan had a broader definition of multifocality including lobular carcinoma in situ) and by the fact that the former did not use a multivariate analysis to find the prognostic influence of multifocality; in fact, when comparing the prognostic influence of multifocality against other prognostic factors in a Cox multivariate analysis, multifocality lost its independent prognostic influence. Patients with multifocal disease often had more positive lymph nodes and larger tumors than patients with unifocal cancers: these two factors are known to be strong prognostic factors, and this can explain why multifocality appeared as a prognostic factor in the univariate analysis and why it had no significant effect on overall survival in the Cox multivariate analysis.

Actually, on a more general level, multiple carcinomas have been repeatedly reported to carry a higher frequency of lymph node metastases and a less favorable patient outcome when compared with unifocal lesions; unfortunately, it is still unclear whether this difference reflects a different biological behavior (which could be responsible for the multifocality as well) or merely larger tumor burden [13].

Other studies led to depict a multifaceted scenario as far as outcome of multiple breast cancer is concerned. Litton [28] studied a subset of young women with breast cancer (<35 years old), and multifocality by itself did not prove to worsen the initially poor prognosis of young breast cancer patients. Multifocal disease was associated with an increase in the risk of death (hazard ratio, 1.57) and decrease in the risk of recurrence (hazard ratio, 0.87), but did not reach statistical significance. Multifocality was instead statistically associated with an increase in the risk of death after recurrence (HR, 3.71). There were, however, statistically significant differences when looking at specific biological features, including pathological tumor grade, hormone receptor status, DCIS, and oral contraceptive use. For those women who did recur a more aggressive systemic disease, a decreased response to systemic

therapies was hypothesized, and other biological factors or genetic profiling that might help explain these differences beyond multifocality itself were claimed to play a role.

Similarly, Cabioglu [29] reported that no difference could be found between patients with unifocal or multiple breast cancer in terms of rates of systemic metastases, local recurrences, and disease-free or overall survival when patients were tabulated according to the stage, but their findings led the authors to conclude that breast tumors with multiple foci have a different biology, with an increased metastatic potential to axillary lymph nodes, regardless of tumor size (that reflects an advanced stage).

Theoretically, the difference in behavior may be a reflection of either the increased intrinsic aggressiveness of multiple tumors or their larger tumor size, in keeping with a consistent biological relation between tumor burden and angiolymphatic dissemination. In fact, the prognostic relevance of the T category has been extensively established, but survival of patients with breast cancer depends on two different types of prognostic factors: tumor size as a marker of tumor biology (as a time-dependent phenomenon) and biological factors (i.e., histological grade, the estrogen and progesterone receptor status, as well as the number of mitotic figures per ten high-power fields), which represent tumor aggressiveness [30].

2.5 Assessing Tumor Burden in Multiple Foci

Unfortunately, evaluating the burden of breast carcinomas is subject to several problems; routinely, the diameter of tumor nodules is used, primarily for practical reasons, but tumors are in fact variably and irregularly shaped tridimensional objects, and therefore diameters inaccurately reflect their real size. Nevertheless, the largest tumor diameter is currently used as an approximation (or surrogate) of the tumor volume for staging purposes in cases of unifocal breast carcinoma, and, in the same line, the American Joint Committee on Cancer and the International Union Against Cancer (AJCC/UICC) recommend the usage of the diameter of the largest tumor (only) also for the staging of multifocal/multicentric breast carcinomas [31]. Therefore, in practice, for the purpose of obtaining a simple and consistent measurement, the actual tumor burden is underestimated because secondary tumor foci, which are often sizable, are not included [32].

Andea et al. [32] hypothesized that the propensity of multifocal/multicentric tumors for metastasis is best described as a function of aggregate tumor size. This prompted the authors to explore the relation between tumor size and lymph node involvement in multifocal/multicentric tumors by using aggregate tumor size estimates, and the findings were used to investigate whether the current staging criteria optimally reflect the metastatic behavior of multifocal breast carcinomas.

Two different methods for estimating tumor size in multifocal/multicentric carcinomas (i.e., diameter of the largest nodule and combined diameters) were used, and the two methods resulted in statistically significant differences in both size and

T classification distribution when compared with unifocal cases. Using the diameter of the largest nodule as a size estimate produced a lower mean tumor size for multifocal than for unifocal cases (2.53 vs. 3.47 cm, respectively; $P=0.026$), and, conversely, combining the diameters of multifocal/multicentric tumors resulted in a larger mean tumor size compared with unifocal lesions (4.2 vs. 3.47 cm, respectively; $P=0.003$). Consequently, the multifocal tumors had a different distribution within T classifications depending on the method of tumor size estimation.

However, as far as the relation between T-stage and lymph node involvement is concerned, when utilizing the standard tumor size estimate, multifocal/multicentric tumors were demonstrated to have a significantly higher incidence of axillary lymph node metastases than unifocal tumors of similar size (odds ratio, 2.8; $P=0.0001$), but if combined diameters of all tumor nodules were utilized for the T-stage assessment, the metastatic behavior of multifocal carcinomas was not significantly different from that of unifocal tumors (odds ratio, 1.4; $P=0.13$). A multivariate logistic regression model was analyzed assessing the impact of multifocality versus unifocality on lymph node status when controlling for tumor size, and results showed that multifocality did not significantly influence lymph node status for the same tumor size when a combined diameter is used as a tumor size estimate.

In other words, results by Andea et al. [32] confirmed that, within similar T classification groups, the currently used measurement methods for staging multifocal carcinomas (diameter of the largest nodule) resulted in a significantly higher incidence of positive lymph node status in multiple tumors as compared to unifocal tumors; on the other hand, using the combined diameters as a size estimate resulted in frequencies of positive lymph nodes that did not significantly differ from the unifocal control series. In particular, the most prominent change was observed in T1 classification, where the incidence of lymph node positivity for multifocal and unifocal series became equal.

2.6 Tumor Burden Versus Lymphatic Metastases

As the authors acknowledge, one potential criticism in this study is that it uses tumor diameters when, more likely, the propensity for metastases is a function of tumor volume or surface area. In multiple tumors, adding diameters of nodules in an attempt to estimate total tumor bulk would result in a consistent error because volumes and areas are proportional to the third and second power of the diameter, respectively, and therefore summing diameter of tumor nodules would overestimate total tumor volume and, to a lesser extent, area. Thus, the same author pushed further his research [13] and quantified the relationship between tumor volume and area in multifocal tumors as compared to single cancers. The results confirmed former findings and showed that multifocal tumors have a significantly larger aggregate diameter, but they have a lower median volume and a similar distribution of tumor surface area than unifocal tumors of similar stage. So it was concluded that aggregate diameter measurements would actually overestimate the total volume of multiple tumors, but such an approach was sustained because, even though

summing diameters of multifocal tumors “overcorrects” for volume, this inadvertently accounts for their increased biological aggressiveness.

Based on these data, the authors suggested that alternative T classification algorithms for multiple breast carcinomas should be investigated; in their opinion the utilization of aggregate diameter measurements would allow multifocal/multicentric and unifocal tumors to be staged uniformly, although this may not reflect accurately the total tumor burden. Alternatively, multiple tumors could be designated in a separate T classification to convey the increased risk for metastatic dissemination.

This sort of concern was addressed by the College of American Pathologists and in the protocol for the examination of specimens from patients with invasive carcinoma of the breast, based on the 7th edition of the AJCC cancer staging manual [33], where the size of the largest invasive carcinoma is still used for T classification but, if multiple carcinomas are present, the modifier “m” is used in the assessment of the “T” stage to indicate that multiple foci are present.

Others have addressed the issue that, currently, in multicentric/multifocal disease the size of the tumor is assessed by measuring the largest tumor focus only. The aim of a study of Weissenbacher et al. [30] was to compare the prognosis of multicentric/multifocal tumors with unifocal tumors with apparently identical tumor size according to TNM staging. A total of 288 pairs, each consisting of one patient with unifocal disease and one patient with multifocal or multicentric breast cancer, were created by matched-pair analysis to achieve statistical balance of the major prognostic factors between both groups. All match criteria (tumor size, grading, and hormone receptor status) were equally distributed in both sets, and, furthermore, no significant difference was found between the two groups in terms of systemic therapy and primary operation. The Cox multivariate regression analysis regarding breast cancer-specific survival and local or systemic relapse showed that multicentricity/multifocality is a significant independent predictor of reduced breast cancer-specific survival as well as of reduced relapse-free survival. Tumor size, grading, and lymph node status were also significant independent predictors. As far as overall survival is concerned, hormonal therapy resulted in significance ($P=0.002$), while both chemotherapy and radiation showed no statistical significance by multivariate analysis. Concerning disease recurrence, neither chemotherapy, hormonal therapy, nor radiation showed any significance.

In order to explain their findings, the authors stated that the currently used algorithms, which employs the diameter of the largest nodule, result in the downplaying of multifocal breast carcinomas due to the underestimation of actual tumor size. They concluded that failure to measure the additional tumor burden provided by multiple small foci may underestimate the disease, and, besides, ignoring the contribution of the smaller foci to the incidence of node positivity and survival may deny patients the opportunity of adjuvant therapies.

In summary it appears that, even when biases due to obsolete topographic definitions are left aside, foreseeing multiple breast cancer prognosis still poses peculiar difficulties that may reside in the incomplete adequacy of the presently used staging systems when applied to multiple disease and in the practice of neglecting smaller tumor foci, each one carrying its own biological features.

2.7 Future Perspectives: Biological Determinants of Aggressiveness

The sensitivity of some breast cancers to hormones and the possibility of reducing the growth of these tumors by removal of circulating estrogens have been known for over 100 years; quantitatively, it is reported that 50–80 % of breast cancers are ER positive, thus hormone therapy has possibly prognostic relevance for a significant proportion of patients [34]. However, as mentioned above, in cases of multiple breast cancer current guidelines 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, PgR, and HER2 status are determined solely 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 [33]. Smaller cancers thus tend to be ignored, and homogeneity among different cancer foci is assumed.

Among papers that created grounds for such an attitude, a pilot study [34] involving 18 patients showed that ER status was the same in all foci of multiple breast cancers and therefore concluded that the current practice of establishing ER status in the primary focus is adequate in relation to hormone therapy. Yet, as acknowledged by the authors themselves, the variability of ER and PgR status between individual foci in multiple breast cancer has not been widely studied, and, besides, it has been previously demonstrated by allelotyping that multiple breast lesions may exhibit distinct clonal patterns at the molecular level [35, 36].

In fact, some authors described quite a different picture. Poulsen et al. [37] presented a case report in 1981 of a patient with two foci of invasive ductal breast cancer in the same breast: one tumor was ER positive, while the other was ER negative. Panahy et al. [38] studied hormone receptor distribution in normal and cancerous breast tissue from nine patients harboring ER-positive cancers and identified—in four patients—multifocal tumors with a varying phenotype for ER and PgR status; multiple tumors were reported to be somehow different in regard to histological criteria, too, but no further detail on the histology of foci was reported. In one case, all three cancer foci were ER positive/PgR positive, but other cases showed multifocal tumors of more than one soluble receptor phenotype. One case had both ER-positive/PgR-positive and ER-positive/PgR-negative tumors, while another case had an ER-positive/PgR-negative and an ER-negative/PgR-positive tumor. A third instance combined two distinct ER-positive/PgR-positive tumors with, remarkably, a second phenotype (ER negative/PgR negative) on a further focus. Interestingly, in addition, variability was also seen in different regions of large tumors.

In order to analyze whether biological features that play a role in the choice of adjuvant treatment of breast cancer are differently expressed in distinct foci of invasive multiple breast cancers with a single histological feature, we prospectively studied the expression of biological markers connected with adjuvant therapy and prognosis over a series of 113 cases [39]. In particular, ER and PgR status, proliferative index Ki-67 (measured as Mib-1 staining), and the amplification of HER2 were

Table 2.1 Overview of diverging expression of biological parameters among different foci in 113 multiple breast cancers (modified from Buggi et al. [39])

	ER-positive minor focus/ ER-negative main focus	ER-negative minor focus/ ER-positive main focus	Total
Divergent ER status	2 cases (1.7 %) PgR-positive minor focus/ PgR-negative main focus	3 cases (2.5 %) PgR-negative minor focus/ PgR-positive main focus	5 (4.4 %)
Divergent PgR status	10 cases (8.8 %) High-grade minor focus/ low-grade main focus	8 cases (7.7 %) Low-grade minor focus/ high-grade main focus	18 (15.9 %)
Divergent grading	3 cases (2.6 %) “High” in minor focus/ “low” in main focus	18 cases (15,9 %) “Low” in minor focus/ “high” in main focus	21 (18.6 %)
Divergent Ki-67 staining	8 cases (7 %) Amplified in minor focus Not amplified in main focus	9 cases (7.9 %) Not amplified in minor focus Amplified in main focus	17 (15 %)
Divergent HER2 expression	4 cases (3.5 %)	7 cases (6.2 %)	11 (9.7 %)

ER estrogen receptor, PgR progesterone receptor

assessed. The expression of all these features was prospectively assessed in each, and every tumor focus of multiple lesions and mismatches among foci were present in 4.4–18.6 % of cases, according to the parameter considered (see Table 2.1).

In detail, mismatches in ER status were present in 4.4 % of cases: in two cases (1.7 %) out of five, a smaller focus was positive and the main focus was negative, while in the remaining three cases (2.5 %), a smaller focus was negative and the main focus was positive. For PgR status, mismatches were present in 18 cases (15.9 %). For tumor grading, 21 (18.6 %) mismatches were found, with a minor focus displaying a higher grade in comparison to the main nodule in 3 cases (2.6 %). Proliferative index Ki-67 differed in 17 (15 %) cases, with eight cases (7 %) in which a “high” index was reported in minor foci only. A mismatch in HER2 amplification was present in 11 (9.7 %) cases showing amplification exclusively in a minor focus in four cases (3.5 %).

The specific biological parameters were chosen because they are known as key elements in planning adjuvant treatments and their specific combination is an issue in the indication to hormonal therapy, chemotherapy, target therapy, or associated treatments [40, 41]; actually, in our series, extending the biological characterization to each tumor focus led to identifying heterogeneous characteristics over the foci and therefore to issuing different indications to adjuvant treatment in 14 (12.4 %) patients out of 113 as compared with what would have been prescribed if the status of the main focus only were taken into account.

2.8 Closing Remarks

Findings such as those reported in the experiences cited above need consistent confirmation, but nevertheless they allow to obtain some insight into biological heterogeneity among foci of multiple breast cancer. As previously claimed, the design of a rational therapeutic strategy for breast cancer should begin with a clear understanding of the biological basis of multicentricity and multifocality; given this, questions of definition and therapeutic strategy would follow logically [2].

Future efforts will be required in order to confirm preliminary data, but if present findings will prove consistent, a thorough assessment over all tumor foci of biological features that play a role in the adjuvant treatment decision-making process may eventually lead to optimal therapy tailoring.

References

1. Fisher B. Role of science in the treatment of breast cancer when tumor multicentricity is present. *J Natl Cancer Inst.* 2011;103:1292–8. doi:[10.1093/jnci/djr240](https://doi.org/10.1093/jnci/djr240).
2. Khan S. The many questions that surround multicentric and multifocal breast cancer. *Breast J.* 2010;16(3):219–21. doi:[10.1111/j.1524-4741.2010.00929.x](https://doi.org/10.1111/j.1524-4741.2010.00929.x).
3. Holland R, et al. Histologic multifocality of Tis, T1-2 breast carcinomas. *Cancer.* 1985;56:979–90.
4. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer.* 1996;74:820–4.
5. Connolly JL, Harris JR, Schnitt SJ. Understanding the distribution of cancer within the breast is important for optimizing breast-conserving treatment [editorial]. *Cancer.* 1995;76:1–3.
6. Tot T. Clinical relevance of the distribution of the lesions in 500 consecutive breast cancer cases documented in large-format histologic sections. *Cancer.* 2007;110(11):2551–60. doi:[10.1002/ncr.23052](https://doi.org/10.1002/ncr.23052).
7. Luttges J, Kalbfleisch H, Prinz P. Nipple involvement and multicentricity in breast cancer. *J Cancer Res Clin Oncol.* 1987;113:481–7.
8. Katz A, Strom E, Buchholz T, Theriault R, Singletary E, McNeese M. The influence of pathologic tumor characteristics on loco regional recurrence rates following mastectomy. *Int J Radiat Oncol Biol Phys.* 2001;50(3):735–42.
9. Pedersen L, Gunnarsdottir KA, Rasmussen BB, Moeller A, Lanng C. The prognostic influence of multifocality in breast cancer patients. *Breast.* 2004;13:188–93. doi:[10.1016/j.breast.2003.11.004](https://doi.org/10.1016/j.breast.2003.11.004).
10. Patani N, Carpenter R. Oncological and aesthetic considerations of conservational surgery for multifocal/multicentric breast cancer. *Breast J.* 2010;16(3):222–32. doi:[10.1111/j.1524-4741.2010.00917.x](https://doi.org/10.1111/j.1524-4741.2010.00917.x).
11. Teixeira MR, Pandis N, Bardi G, et al. Discrimination between multicentric and multifocal breast carcinoma by cytogenetic investigation of macroscopically distinct ipsilateral lesions. *Genes Chromosomes Cancer.* 1997;18:170–4.
12. Dawson PJ, Baekey PA, Clark RA. Mechanisms of multifocal breast cancer: an immunocytochemical study. *Hum Pathol.* 1995;26:965–9.
13. Andea AA, Bouwman D, Wallis T, Visscher DW. Correlation of tumor volume and surface area with lymph node status in patients with multifocal/multicentric breast carcinoma. *Cancer.* 2004;100:20–7. doi:[10.1002/ncr.11880](https://doi.org/10.1002/ncr.11880).

14. American Joint Committee on Cancer. Summary of Changes: Understanding the Changes from the Sixth to the Seventh Edition of the AJCC Cancer Staging Manual. <http://www.cancerstaging.org/staging/changes2010.pdf>. Accessed 30 April 2012.
15. Fisher ER, Gregorio R, Redmond C, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4). Observations concerning the multicentricity of mammary cancer. *Cancer*. 1975;35(1):247–54.
16. Spinelli C, Berti P, Ricci E, Miccoli P. Multicentric breast tumour: an anatomical-clinical study of 100 cases. *Eur J Surg Oncol*. 1992;18:23–6.
17. Egan RL. Multicentric breast carcinomas: clinical-radiographic-pathologic whole organ studies and 10-year survival. *Cancer*. 1982;49:1123–30.
18. Gallager HS, Martin JE. The study of mammary carcinoma by mammography and whole organ sectioning. Early observations. *Cancer*. 1969;23:855–73.
19. Lagios MD. Multicentricity of breast carcinoma demonstrated by routine correlated serial subgross and radiographic examination. *Cancer*. 1977;40:1726–34.
20. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227–32.
21. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233–41.
22. Ho A, Morrow M. The evolution of the locoregional therapy of breast cancer. *Oncologist*. 2011;16:1367–79.
23. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five national surgical adjuvant breast and bowel Project protocols of node-negative breast cancer. *J Clin Oncol*. 2009;27:2466–73. doi:10.1200/JCO.2008.19.8424.
24. Millar EK, Graham PH, O'Toole SA, et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. *J Clin Oncol*. 2009;27:4701–8.
25. Nguyen PL, Taghian AG, Katz MS, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. *J Clin Oncol*. 2008;26:2373–8.
26. Rakowsky E, Klein E, Kahan E, Derazne E, Lurie H. Prognostic factors in node-positive breast cancer patients receiving adjuvant chemotherapy. *Breast Cancer Res Treat*. 1992;21(2):121–31.
27. Vlastos G, Rubio IT, Mirza NQ, Newman A, Aurora R, Alderfer J. Impact of multicentricity in patients with T1-2, N0-1, M0 breast cancer. *Ann Surg Oncol*. 2000;7(8):581–7.
28. Litton JK, Eralp Y, Gonzalez-Angulo AM, Broglio K, Uyei A, Hortobagyi GN, Banu Arun B. Multifocal breast cancer in women <35 years old. *Cancer*. 2007;110:1445–50. doi:10.1002/cncr.22928.
29. Cabioglu N, Ozmen V, Kaya H, Tuzlali S, Igci A, Muslumanoglu M, Kecer M, Dagoglu T. Increased lymph node positivity in multifocal and multicentric breast cancer. *J Am Coll Surg*. 2009;208:67–74. doi:10.1016/j.jamcollsurg.2008.09.001.
30. Weissenbacher TM, Zschage M, Janni W, Jeschke U, Dimpfl T, Mayr D, Rack B, Schindlbeck C, Friese K, Dia D. Multicentric and multifocal versus unifocal breast cancer: is the tumor-node-metastasis classification justified? *Breast Cancer Res Treat*. 2010;122:27–34. doi:10.1007/s10549-010-0917-9.
31. Sobin LH, Gospodarowitz MK, Wittekind CH, editors. Union for International Cancer Control. TNM classification of malignant tumours. 7th ed. New York, NY, USA: Wiley-Blackwell; 2009.
32. Andea AA, Wallis T, Newman LA, Bouwman D, Dey J, Visscher DW. Pathologic analysis of tumor size and lymph node status in multifocal/multicentric breast carcinoma. *Cancer*. 2002;94(5):1383–90. doi:10.1002/cncr.10331.
33. Lester SC, Shikha Bose S, Chen YY, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med*. 2009;133:1515–38.

34. Garimella V, Long ED, O’Kane SL, Drew PJ, Cawkwell L. Oestrogen and progesterone receptor status of individual foci in multifocal invasive ductal breast cancer. *Acta Oncol.* 2007;46:204–7. doi:[10.1080/02841860600897884](https://doi.org/10.1080/02841860600897884).
35. Tse GM, Kung FY, Chan AB, Law BK, Chang AR, Lo KW. Clonal analysis of bilateral mammary carcinomas by clinical evaluation and partial allelotyping. *Am J Clin Pathol.* 2003;120:168–74.
36. Smeds J, Warnberg F, Norberg T, Nordgren H, Holmberg L, Bergh J. Ductal carcinoma in situ of the breast with different histopathological grades and corresponding new breast tumour events: analysis of loss of heterozygosity. *Acta Oncol.* 2005;44:41–9.
37. Poulsen HS, Jensen J, Hermansen C. Human breast cancer: heterogeneity of estrogen binding sites. *Cancer.* 1981;48:1791–3.
38. Panahy C, Puddefoot JR, Anderson E, Vinson GP, Berry CL, Turner MJ, Brown CL, Goode AW. Oestrogen and progesterone receptor distribution in the cancerous breast. *Br J Cancer.* 1987;55:459–62.
39. Buggi F, Folli S, Curcio A, Casadei-Giunchi D, Rocca A, Pietri E, Medri L, Serra L. Multicentric/multifocal breast cancer with a single histotype: is the biological characterization of all individual foci justified? *Ann Oncol.* 2012;23:2042–46. doi:[10.1093/annonc/mdr570](https://doi.org/10.1093/annonc/mdr570).
40. Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol.* 2009;20:1319–29. doi:[10.1093/annonc/mdp322](https://doi.org/10.1093/annonc/mdp322).
41. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ, Panel members. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol.* 2011;22:1736–47. doi:[10.1093/annonc/mdr304](https://doi.org/10.1093/annonc/mdr304).

Cell and Molecular Biology of Breast Cancer

Schatten, H. (Ed.)

2013, VIII, 383 p. 55 illus., 51 illus. in color., Hardcover

ISBN: 978-1-62703-633-7

A product of Humana Press