Chapter

Multifocality, Multicentricity, and Bilaterality of Breast Cancer

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Abstract

Multifocal, multicentric, and bilateral breast tumours are either benign, precursor lesions or malignant neoplasms. A multidisciplinary review of these entities can offer clinicians a practical guidance for diagnostic and treatment procedures. Multiple synchronous (multifocal or multicentric) ipsilateral breast cancers (MSIBC) with heterogeneous histopathology require particular attention, since MSIBC tends toward more aggressive biology and higher rates of nodal positivity. Being independent of laterality, domination of the invasive carcinoma was observed in the bilateral and multifocal disease type. The TNM staging system for breast cancer does not include multifocality and multiplicity. Only the tumour with the largest diameter is considered for the pT category, neglecting the secondary foci which can make the treatment decision more difficult. MSIBC has a similar prognosis to unifocal cancers, but sometimes they might be negative prognostic parameters. Likewise, in comparison with unifocal breast cancer, MSIBC presents a different genetic pathway.

Keywords: Multiple synchronous tumour, multifocal, multicentric, bilateral, breast cancer

1. Introduction

The multifocal, multicentric, and bilateral aspects of breast cancer (BC) are the eternal dilemma in the scientific literature. Breast cancer is the most common tumour disease and the second leading cause of death in American women, with 268,600 new cases and 41,760 deaths in 2019 [1]. The second most common malignancy in patients with breast cancer is contralateral breast cancer [2]. Presence of another focus of breast cancer, far away from the dominant mass, was described as early as 1920 by Cheatle [3]. The appearance of such non-dominant lesions in multiple ducts of a single quadrant (multifocal), or in two or more quadrants (multicentric) was further elaborated in 1957 by Qualheim and Gall [4]. Multifocal/multicentric (MF/MC) breast cancer is occurring frequently, however, its genesis is not fully understood [5].

Previous studies evaluated histological and immunohistochemical characteristics [6, 7], revealing that most multicentric breast cancers share similar features in terms of histology and immunohistochemistry, suggesting that early-stage synchronous tumours develop from one breast cancer [6]. The heterogeneity of the focus of multiple cancers [8] is understudied in the literature, with a number of studies which have evaluated histological and immunohistochemical characteristics

of tumour foci in multiple cancers arriving at contradictory results and different conclusions [7, 9].

Multiple synchronous ipsilateral breast cancer (MSIBC) with heterogeneous histopathology is a controversial condition in a clinical context, which has been discussed and studied extensively in the literature, but lacking international consensus on itsdefinition and clinical treatment options. Current incidence of MSIBC is unknown, but, owing to improved sensitivity of medical imaging methods and the use of magnetic resonance imaging (MRI) for BC screening and staging, is showing increased occurrence. This heterogeneous disease requires special attention during treatment, given the fact that MSIBC is a much more aggressive condition which produces metastases in lymph nodes more frequently [10].

Based on current therapies for breast cancer, the treatment of this heterogeneous disease calls for joint decision making in a multidisciplinary team and in collaboration with an oncology council, where the pathologist, working with the other members of the team, influences the new concept of individual approach to treatment of MC/MF breast cancer patients with their data and explanations obtained through testing. A new rigorous view on genetic patterns of heterogeneity in each individual focus would present a more specific approach to treating MSIBC [11].

2. Terminology and classification of multifocal, multicentric, and bilateral breast cancers

Multiple synchronous tumour foci in one breast are referred to as multifocal and multicentric, but without a consensus on terminology [12]. MF/MC cancer may occur due to intramammary proliferation of a single primary BC or multiple synchronous, independent primary breast cancers [5, 13]. Recently, the definition of multifocal cancer was changed. Previous definition of multiple synchronous lesions of breast cancer stated that these could be either MF or MC, depending on where the lesion was located (in the same or different quadrants). The use of breast quadrants to define and classify cancers is now considered inappropriate, since quadrants are not part of convention which correspond to the breast anatomy [14]. Pathologists define multiple simultaneous primary lesions when there are two or more tumour foci without malignant tissue between them [15].

Multifocality is usually determined microscopically, when a greater number of morphological cancer development centres are present, which is the same micromorphological unit or lobe in the breast. Radiologists do not have a more precise definition, but tumours are usually considered multifocal when the distance between the tumour masses is less than or equal to 5 cm, and multicentric when this distance is greater than 5 cm (**Figure 1**) [16, 17]. Given that a standardised definition is not established, multifocal and multicentric breast cancers are often grouped together as multifocal/multicentric breast cancers [18]. In histological terms, BC is defined as multiple cancer when it consists of more than one clearly distinguishable tumour foci which are separated by normal and benign breast tissue or ductal carcinoma in situ (DCIS) [19].

Various time intervals are used to define bilateral synchronous breast cancer (BSBC). In 1921, Kilgore defined BSBC as breast cancer where both tumours are diagnosed simultaneously [20]. Since 1921, various time intervals were introduced, ranging from one to five years [21]. A broadly accepted definition of BSBC is the one given by Hartman and co-authors in 2007 as a tumour diagnosed within 90 days after the initial mass has occurred. Although the reported time intervals vary, bilateral BCs are considered to be synchronous when contralateral BC is diagnosed within a period of three months, and as metachronous bilateral cancers (BMBC)

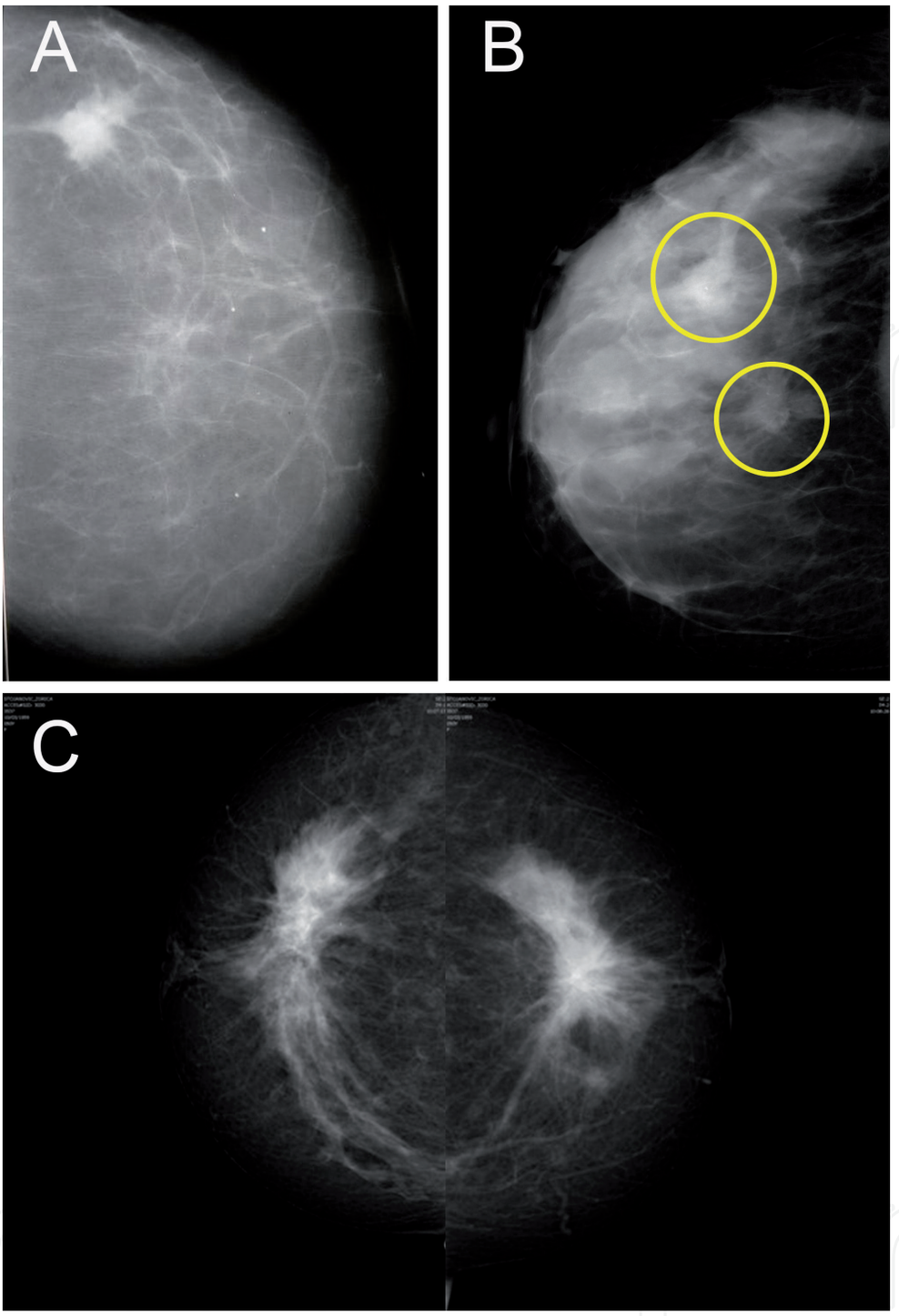

Figure 1.
Images from mammograms of ILC from three different patients: (A) stellate tumour shadow of unifocal ILC from the 58 years old patient; (B) multicentric (bicentric) ILC from the 53 years old patient; (C) bilateral synchronous ILC from the 32 years old patient. In reference [16] (the figure was taken from article; permission obtained from the copyright owner).

when diagnosed more than three months after the first diagnosis [22]. Limit values used in the literature to differentiate between BSBC and BMBC range from 1 to 12 months [23]. Before a bilateral breast cancer diagnosis is confirmed, metastatic contralateral breast cancer has to be ruled out [24].

The definitions of multifocality, multicentricity, and bilaterality refer primarily to the two most common types of breast cancer (ductal and lobular), but can also refer to certain lesions which occur less frequently in the breast. In terms of multifocality, between 10 and 20% of tubular carcinomas may present as multifocal [25, 26], and the identical frequency of multifocality is observed in cribriform

cancers [27, 28]. A thorough sampling of large areas with high DCIS grade should be performed in order not to miss the foci of the carcinoma microinvasions (or invasions). Some reports suggested that when a microinvasive carcinoma occurs, it is likely to be multifocal [29].

Certain benign lesions, such as papilloma, are rarely multiple in nature (**Figure 2**). Breast lesions which often present as bilateral are DCIS [30], Paget's disease of the nipple, radial scars and complex sclerosinglesions, gynecomastia, Burkitt lymphoma [31], while bilateral breast cancer also frequently occurs in patients with Cowden syndrome and heterozygous ATM mutation carriers (ataxia telangiectasia), as a result of submitting patients suffering from Louis–Bar syndrome to radiotherapy [31–33]. Other types of potentially bilateral-onset breast lesions are atypical ductal hyperplasia [31], phyllodes tumour [32, 34], myofibroblastoma [33], desmoidfibromatosis [35], male breast cancer [36], angiosarcoma [37, 38], liposarcoma [31], lymphoma (about 10% of the cases), pseudoangiomatous stromal

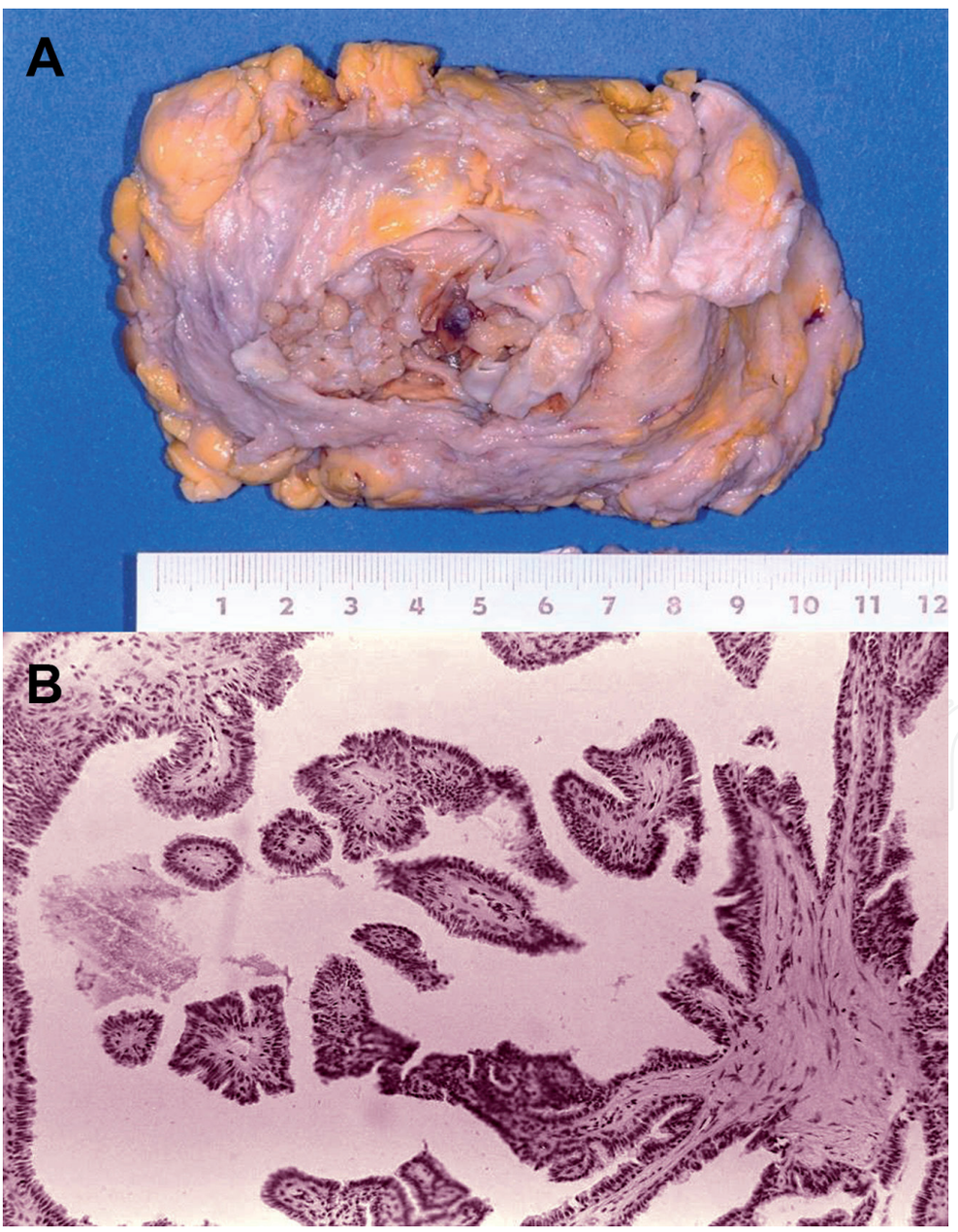

Figure 2.
Multiple breast papillomas in multilocular cyst of the 52 years old patient. (A) Macroscopic appearance; (B) microscopic appearance of breast papilloma (HE x 100) (image was taken from author's own lab).

hyperplasia [39], ductal adenoma in patients with Carney syndrome [40]. There are also lesions with unidentified bilaterality, some of which are ALK-negative anaplastic large cell lymphoma [31], mucosa associated lymphoid tissue lymphoma [41] and granular cell tumour [42]. Most patients with diffuse large B-cell lymphoma develop a unilateral condition, but there is a risk of relapse in the contralateral breast [43].

3. Epidemiology and risk factors

Based on data from the literature, there is no consensus on the factors relating to the development of multicentric carcinomas [44]. MF/MC BC incidence ranges from 6 to 77% [14]. Bilateral breast cancers are responsible for 2 to 6% of all breast carcinomas [22]. Earlier studies have shown that one of the most important risk factors for MCBC is if the first occurrence is an invasive lobular carcinoma (ILC) [45]. Low-grade invasive ductal carcinomas (IDC) are not linked with the number of tumour masses in the contralateral breast. All of these observations contradict the fact that ILC is more common among patients with bilateral and multifocal BC solely due to slower growth rates [46].

There are no differences when it comes to patient age, tumour stage, or the presence of multifocal, multicentric, and bilateral ILCs [47]. Contralateral tumour incidence, in particular synchronous ILCs, is in the 5 to 19% range, which is more than invasive ductal carcinoma of no special type [45, 48, 49]. BSBC is a rare entity with an incidence between 1 and 3%. Surprisingly, there has not been an increase in the BSBC incidence since 1980. A lower incidence of metachronous bilateral breast cancer was observed, likely due to the introduction of systemic adjuvant therapy. In the study on incidence of bilateral breast cancers in Sweden, conducted by Hartman and co-authors reported that the incidence of BSBC was approximately 100 times greater than what can be explained as coincidence or a cumulative effect of exogenous carcinogens [22],

Women with MF/MC breast cancers are often of younger age at the time of diagnosis and with positive oestrogen (ER) receptors expression than women with a unifocal condition [50]. Patients with MF/MC tumours are prevalently premenopausal and with a lower body mass index [51]. Women already suffering from BC are at two to six times greater risk of developing contralateral BC compared to the risk of other women developing their first primary BC, with the risk being inversely proportional to their age at the time of initial diagnosis [45, 52]. Average time between the diagnosis of the first BC and metachronous contralateral breast cancer varies from 3.9 to 7.7 years [22, 52].

Histological subtype of invasive carcinoma did not prove to be a predictive multicentricity factor, particularly in ILC subtypes [16, 47]. Earlier studies suggest that ILCs are much more prone to multicentric growth; but when lobular carcinoma in situ (LCIS) is excluded, multicentricity is not that common [44, 53]. When compared to IDCs, ILCs are ER and progesterone (PR) positive to a larger extent, but show lower HER2 positivity with the exception of pleomorphic lobular carcinoma [31]. Women diagnosed with MF/MC BC proportionally more frequently have positive ER receptors and lower prevalence of triple-negative tumour masses. Numerous studies documented significantly higher positivity levels of ER receptors among the BRCA2 mutation carriers in comparison to BRCA1 mutation carriers. Therefore, it is highly unlikely that ER signalisation leads to MF/MC disease [54]. An extensive meta-analysis found no connection between the ER status and sporadic MF/MC breast cancers, suggesting that the ER status does not play a part in the specific development of MF/MC disease [55]. The risk of other contralateral

primary breast cancers varies depending on the status of hormone receptors of the first tumour, age, race, and/or ethnic origin [56].

A certain number of earlier studies discovered a strong correlation with the lobular histology in the first primary breast carcinoma and the occurrence of bilateral breast cancer [57]. Women with primary breast cancer who have positive hormone receptors show twice the risk of developing contralateral BC, while women who have cancers with negative hormone receptors are at almost four times higher risk as compared to general population with regard to age and race. Women with primary tumours who have negative hormone receptors more frequently develop secondary tumours which have negative hormone receptors, especially if the initial diagnosis is confirmed before the age of thirty [56].

Women who have next of kin with BC are at 50% higher relative risk of developing bilateral breast cancer than women without family history of this condition [22]. When compared to non-carriers, women with BRCA1 mutations are at 4.5 times greater risk and with BRCA2 mutations at 3.4 times greater risk of bilateral breast cancer [58]. On the other hand, carriers of similar ATM gene variants have a lower risk of developing contralateral breast cancer [59]. Family history of breast carcinoma, younger age at the time of initial diagnosis, or mutation of BRCA1 and BRCA2 genes are linked to a higher risk of developing contralateral tumours, placing them in the higher risk group [45]. Higher prevalence of multifocality/multicentricity than expected occurs in women diagnosed with cancer who are BRCA2 mutation carriers [50].

4. Radiodiagnostics

Mammography and ultrasound are complementary methods for evaluating the size, spread, and the presence of multifocality in BC (**Figure 1**) [16, 31]. However, not all MF/MC cases will necessarily be found using these imaging modalities [60]. Radiologic BC characteristics can vary significantly. These differences often depend on the tumour grade and histological subtype. Therefore, variations in the radiologic presentation can sometimes predict the differences in the morphology and biology of the tumour. ILC often invades normal tissue without causing desmoplastic stromal response which is usually found in IDC. For this reason, ILC density is often similar to the surrounding normal fibrous and glandular tissue of the breast, which makes it inconspicuous in mammographic screening [61, 62], particularly since non-desmoplastic ILC produces metastases in axillary lymph nodes more frequently [63].

Due to the limited use of mammography in diagnosing ILC and the risks of obtaining false negative results, other methods such as sonography and MRI are used to assess the tumour dissemination [64]. Magnetic resonance imaging is more useful for diagnosing ILC, in particular multifocal lesions, although this imaging procedure may produce false positive results or overestimate the tumour stage [65, 66]. Recent literature on the role of imaging modalities in the BSBC diagnosis suggests that family history of BC, multifocal BC, or the presence of an ILC should serve as recommendations to perform an MRI with the purpose of eliminating contralateral malignancy [67].

5. Pathology report

In recent decades, pathohistology has made a huge step forward from the typical traditional documentation to the ability to modify the histochemical and

immunohistochemical methods [68], which has shed new light on some patho-histological parameters and consequently led to a new approach when it comes to recognising the criteria for classifying and grading tumours. Tot et al. support that there can be two different types of multifocal invasive carcinoma: one with multiple individual invasive foci which develop from *in-situ* lesions in different parts of the same lobe either at the same or at a different time, and one where individual foci are *in-transit* metastases of the primary focus and are not connected to the *in-situ* component [69].

When compared to unilateral BC, bilateral breast cancer is associated with significantly lower rate of the ductal type, with a higher histologic grade, HER2 positivity and metastases in lymph nodes, without differences relating to age, race, ER and PR status, or pathologic stage of the tumour disease (**Figures 3** and **4**). Synchronous breast cancer is associated with a higher rate of consistency with the ER, PR, and HER2 statuses (**Figure 4**) as compared to metachronous bilateral breast cancer, but without any difference regarding the histologic type or grade [70]. A high-grade malignancy and multifocal contralateral breast disease are inversely proportional [46], which is why patients with BSBC often develop slow-growing and low-grade carcinomas [71].

Greater size of the tumour masses and a larger number of the lymph nodes affected are also linked with multifocal carcinoma, both in unilateral and bilateral

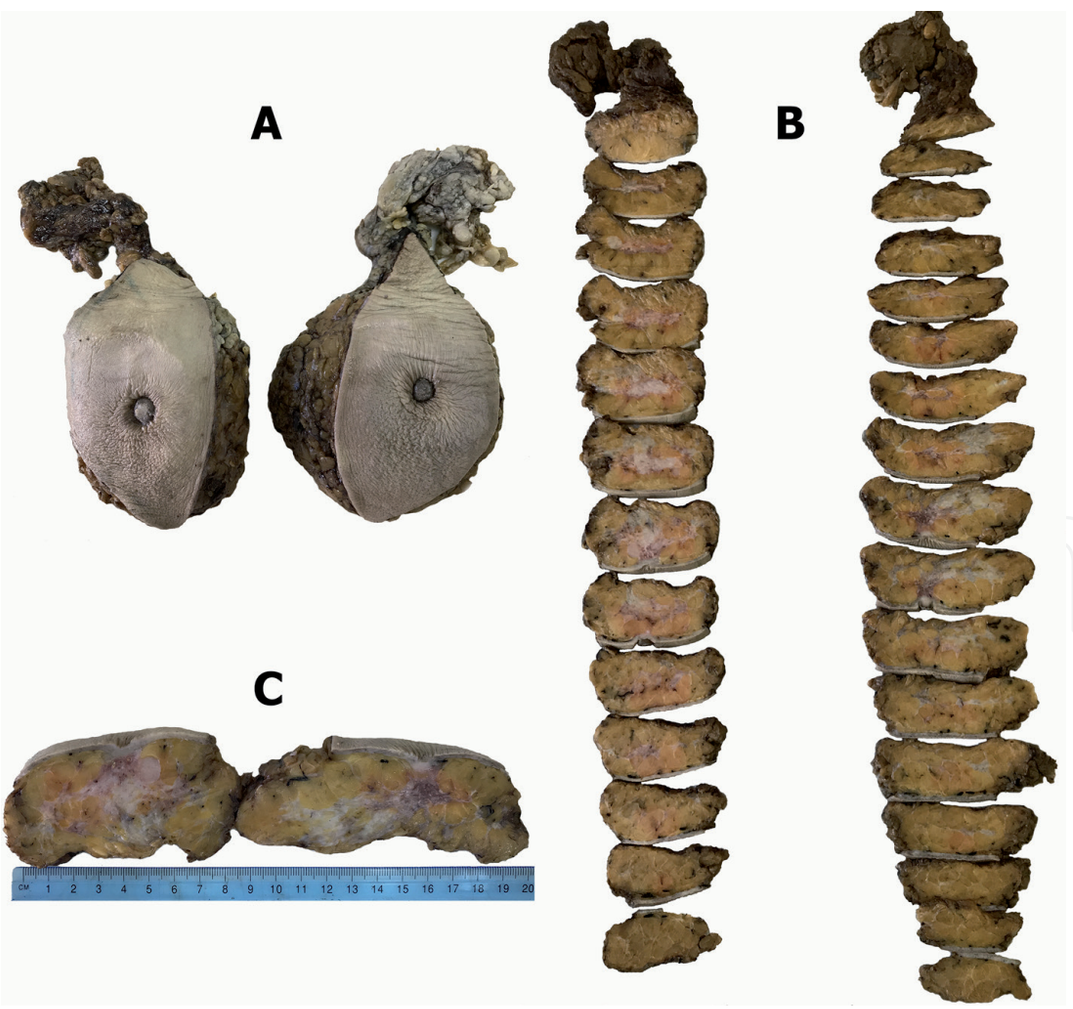

Figure 3.
Macroscopic appearance of BSBC from the 36 years old patient in stage IIIA and IIB: (A) mastectomies of both breasts with associated axillary adipose tissue; (B) macroscopic examination of the tumour infiltration zone by transverse serial sections; (C) foci of the largest tumour infiltration zones and their distance from the resection margins. (image was taken from author's own lab).

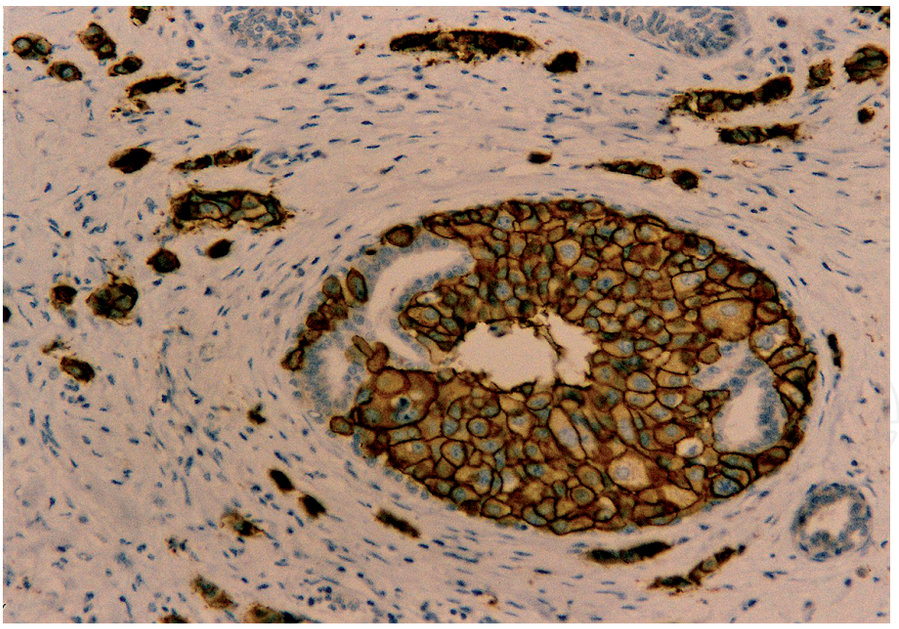

Figure 4.
Microscopic appearance of BSBC from the 36 years old patient in stage IIIA and IIB. Strong membranous expression of HER2 in invasive and "in situ" component of classical subtype of ILC (LSAB x 200). (image was taken from author's own lab).

breast cancers [46]. In unilateral BC patients with a multifocal disease, 40% present with tumour foci that have different histopathology [5, 13, 72]. Studies analysing clonal origin of the tumour focus in multifocal BC show that at least 50 to 70% of cases with different foci are genetically related [73–75], arguing that most multifocal breast carcinomas in patients with unilateral BC originated from the same precursor cell, therefore being an intramammary spread of metastases or an *in-situ* carcinoma with numerous invasive foci [14, 73].

Some studies revealed that multiple synchronous ipsilateral breast cancer (MSIBC) correlates with the known risk factors, suggesting aggressive biology, such as younger age of patients, higher grade, hormone receptor status, HER2 status, lymphovascular invasion and node involvement [76, 77]. Other factors can also play a part, such as the loss of E-cadherins, causing a loss of cell-to-cell adhesion and contributing to metastatic potential. A recent study demonstrated that MSIBC had a significant downregulation of E-cadherine expression as opposed to unifocal lesions [78].

While desmoplastic stromal response is not associated with higher frequency of metastases in axillary lymph nodes [63], there is a positive correlation between the presence of metastases in axillary lymph nodes and the number of tumour foci [77]. In multiple carcinomas, between 3 and 7% of cases can present with different histologic tumour types and/or histologic tumour grades (intratumor heterogeneity) [19, 77]. Using androgen receptor tests, it was discovered that some DCIS and LCIS develop from different cell clones [79]. If we assume that pure DCIS obtains its phenotypic diversity from different cell clones or from accumulated genetic alterations of a single clone, followed by the progression of the dominant clones to invasive carcinomas, it is possible that these represent different phenotypes in multifocal/multicentric BC with a heterogeneous DCIS component [5].

If the multifocal/multicentricBC in question develops as a consequence of lymphovascular invasion, a higher risk of further metastases is probable. Higher frequencies of lymph node involvement and higher relapse rates in MF/MC BC than in other unifocal BCs support the idea that they can occur as a result of

lymphovascular invasion, although a high incidence of metastases in lymph nodes in MF/MC breast carcinomas is also associated with larger tumours [80, 81]. When the tumour (T) stage is determined with the diameter of the largest lesion, multifocality and multicentricity can act as independent predictors of axillary lymph node involvement.

6. Heterogeneity of tumour foci

Heterogeneity is a well-known trait of malignancies. It can be observed in individual tumours or among primary BCs and synchronous metastases in lymph nodes. This should be particularly emphasised in the case of MSIBC with different biology and positive lymph nodes in the diagnosis. The status of axillary lymph nodes is the most important individual prognostic factor for BC patients; an accurate histological characterisation of nodal metastases can help clinicians select the most appropriate .treatment [11].

Studies suggest that the tumour foci in MF and MC carcinomas may manifest clonal and behavioural heterogeneity [76], irrespective of the distance between the lesions [7], that ipsilateral foci usually have identical clonality while bilateral breast cancers vary [82], and that 25% of MC carcinomas is polyclonal [83]. The studyof Nortonand co-authors focusing on multifocal ILCs, numerous genetic copies between the foci are consistent to a high degree, suggesting clonal connection between the foci on the one side, while genetic heterogeneity was observed between the foci in patients on the other side [84]. Phenotypic differences are more common in foci (**Figure 5**) that are homogeneous in terms of tumour type and grade [76]. Actually, all tumour foci are considered to have the same phenotype, although genetic or phenotypic alterations may occur during the progression of the tumour [5].

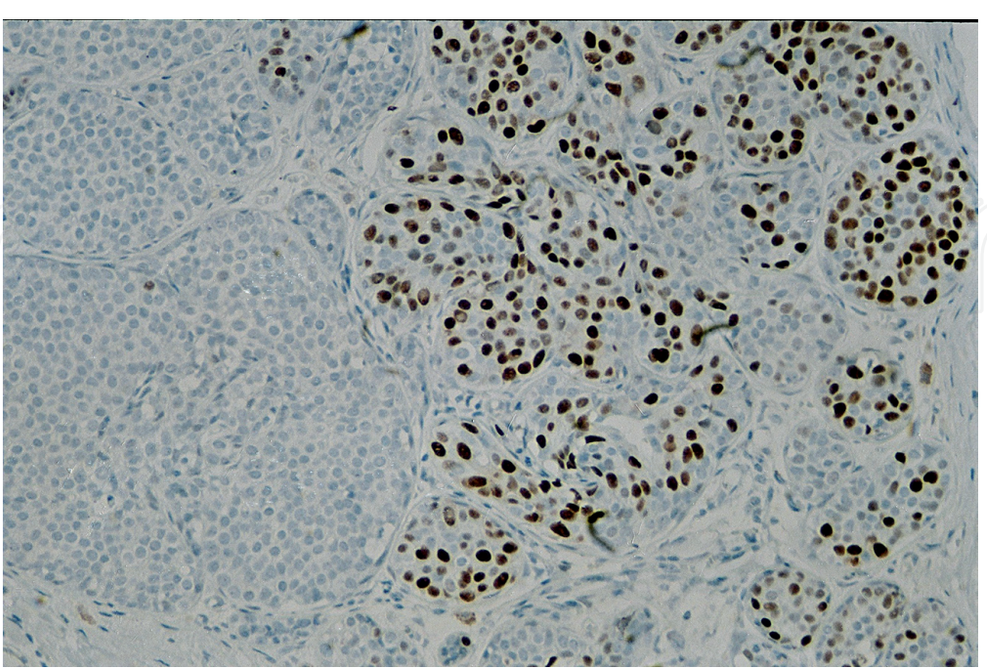

Figure 5.
Phenotypic differences in ER expression (positive nuclear staining on the right side and negative nuclear staining on the left side of tumour focus) may indicate clonal and behavioural heterogeneity of LCIS (LSAB x 200). (image was taken from author's own lab).

7. Molecular and genetic testing

It is not clear whether multifocal/multicentric BCs with different phenotypes are of independent origin due to the fact that phenotypic changes may occur during the tumour progression and dissemination [85]. A few studies, using various molecular methods, showed that bilateral breast cancers are most likely not genetically identical [86, 87]. While the presence of a different phenotype is a clear indicator of separate synchronous primary tumours, over 70% of invasive BCs classified as IDC have identical morphology, meaning that the tumours are clonally related. Using targeted gene sequencing in patients with multiple invasive ductal carcinomas of the same grade and hormone receptor status, it was determined that one third of the cases shows identical mutation profile, one third shares mutations with individual mutations in different foci suggesting identical clonal origin, and one third exhibits no common mutations. Despite common mutations not being present, common changes in copies among the lesions were found, which requires more detailed examinations with methods such as sequencing the entire genome, which would reveal common subclones with a clonal distinction in a larger number of cases [73].

The 21 gene recurrence score assay is a commercially available prognostic and predictive test that measures gene expression levels (16 cancer-related and 5 reference genes) using RT-PCR. The test generates a numeric RS on a scale of 0 to 100 to predict a ten-year risk of a distant metastasis as well as the benefit of chemotherapy in patients with an early-stage ER positive, HER2 negative breast cancer. This RS divides the patients into three risk categories: low (RS < 18), medium (RS 18 to 30), and high (RS ≥ 31). Adjuvant chemotherapy is added to endocrine therapy in patients with high RS; it is estimated that the benefit is low enough to outweigh the consequences in low RS patients [88]. The importance of genome testing for classification by risk category was recognised in the eighth edition of the AJCC Cancer Staging Manual [89], which integrates RC into BC staging. This study examines the consistency of RS in multiple synchronous ipsilateral BCs of similar histology [90].

Tsuda and Hirohashi [91]. investigated the loss of heterozygosity at 16q chromosome in multiple breast cancers and have decided to define multicentric carcinomas as those which are not related through the DCIS component and are not showing satellite nodules and can appear independently. On the other hand, Teixera et al [82], using cytogenetic analyses, concluded that the dominant origin of multiple BCs is intramammary spread from a single primary tumour, despite the fact that some cases develop as unrelated pathogenetic processes. Recently, Brommesson and co-authors compared genome similarities between synchronous multiple invasive breast cancers by means of a comparative microarray-based genome hybridisation and discovered that 5 out of 10 unilateral tumour pairs showed similar genome profiles, suggesting that some synchronous unilateral multiple tumours may have a common origin, while other develop independently [74].

8. Staging of multifocal/MulticentricTumours

Tumour classification as unifocal, MF, or MC is determined in accordance with the pathology reports. The size of the tumour is obtained from the pathology reports. In patients with MF/MC tumours, T stage is determined using two methods: diameter of the largest tumour focus (T_{max}) and by adding up the largest diameters of all tumour foci that are present in the pathological sample (T_{sum}) [51]. AJCC TNM classification defines tumour size as a measure of the largest individual

focus of MSIBC [92]. BSBC should be classified independently to permit separation of cases by histological type. (**Figures 3** and **4**). Some authors support the hypothesis that MSIBCs can be best described as summarised dimensions which reclassify tumours to higher stages [93].

According to the College of American Pathologists' recommendations, when multiple synchronous ipsilateral invasive cancers of the same histology are present, the largest invasive carcinoma is used for classification and receptor evaluation [94]. The largest tumour focus is ranked as index or first-rank tumour, and other foci as second to n-rank of additional foci by descending diameter size. The number of lymph nodes affected with macrometastases (larger than 2 mm) or micrometastases (with a diameter between 2 and 0.2 mm) is also reported, as well as the total number of lymph nodes analysed [8]. When the T stage is determined based on the diameter of the largest lesion, multifocality and multicentricity are an independent predictor of axillary lymph node involvement. However, redetermining the T stage based on the sum of diameters of all foci compensates for their difference, leaving the proportion of lymph node metastases between the MC/MF and UF tumours equal [93]. These findings suggest that the increase in the lymph node involvement (or any other relation with unfavourable outcomes) is not a consequence of the common nature of the MC and MF tumours, but rather the result of underestimating the spread of the disease using current staging systems [95].

Some investigationssuggest that the sum of the largest diameters is actually greater than the overall size of the tumour mass and that a better criterion for assessing the tendency of metastasis formation is the total volume and surface area of the tumour [81]. After reclassifying the tumours according to this model, MF/MC tumours still show increased level of lymph node involvement, suggesting that the difference is not the result of the lower stage, but rather the basically more aggressive tumour biology [95].

9. Therapeutic modalities and prognosis

Breast-conserving therapy is now an established alternative to radical mastectomy. When it comes to tumours with more than one lesion, suggested treatments are changing at the moment. Many authors continue to support breast-conserving surgery for MC/MF tumours [96]. Furthermore, when breast-conserving surgery is proposed as a treatment option for patients who carry BRCA2 mutations and have ER positive receptor status, the surgeons should bear in mind the increased incidence of multifocality and plan the surgical procedure accordingly, ensure that the complete excision is performed in one procedure, as well as minimise the consequences related to repeated surgery due to marginal involvement [50]. Oncoplastic surgery enables a more precise resection of the tumour mass and free resection margin as compared to standard quadrantectomy or lumpectomy [97].

Considering that the effect of partial breast radiation therapy is limited to the index quadrant, it is of paramount importance that patients with low risk of occult microscopic disease in the remaining breast tissue are selected, meaning that local control is not less important than whole-breast radiation [11]. It has been proven that whole-breast radiation after a breast-conserving surgery is more efficient against microscopic foci of BC, which is demonstrated by the fact that leaving it out increases local recurrence rate to 39.2% [98]. Patients under 45 who have BC and were treated with post-lumpectomy tangential field radiotherapy are at higher risk of developing contralateral breast cancer, in particular women with family history of BC [52, 99]. Adjuvant chemotherapy is also associated with reduced incidence (up to 20%) of contralateral breast cancer in women under 50, but not in female

patients of and above this age [100]. Moreover, chemotherapy is also related with a lower risk of contralateral breast cancer for a period of up to 10 years after the initial BC diagnosis [101].

It was reported that adjuvant systemic hormone ER positive therapy reduces the incidence of contralateral breast cancer by 39 to 55%, depending on the menopausal status [100], which is why detecting limit values for the ER receptor positivity is important [102]. The analysis of the study results revealed that adjuvant chemotherapy is not effective in patients with RS < 25 and above fifty years of age. However, women under 50 with BC who have RS in the medium range between 16 and 25 can still derive some benefit from chemotherapy [103].

Certain data supports the claim that multifocality/multicentricity is not an independent prognostic factor for BC. Although it is suggested that MF/MC can predict the outcome, it is a fact that the size of the tumour bears greater significance in these patients, rather than the presence of multifocality/multicentricity itself [50]. There is controversy in the literature relating to MF/MC prognosis. The rate of locoregional recurrence has increased in some studies [104], while others found no differences [95]. A 2.75 times higher risk of cancer-related death was reported in patients with MF breast cancer, irrespective of the molecular subtype [19]. In an extensive retrospective study, Weissenbacher et al. reported a lower median global survival (OS) in MF/MC patients as compared to unifocal tumours [104]. One earlier study showed that MC disease is related to higher local recurrence rates, but not MF disease (37 and 17% respectively) [105].

Histologic grade is a well-known prognostic factor for BC, with numerous studies demonstrating a strong connection with survival rates [31, 106]. The size of the tumour has been identified long ago as an independent indicator of lower global survival [107]. Two studies monitored the relation between different methods for T staging and survival. It was discovered that MF and MC tumours larger than 2 cm are accompanied by lower global survival when compared with unifocal carcinoma, but this difference vanishes if the sum of the tumour diameters is used in staging [93]. In patients with MF/MC disease, calculating the sum of diameters of multiple foci does not add any prognostic information apart from the conventionally determined T stage on the basis of the largest diameter of the largest focus [108]. A more intensive systemic chemotherapy could potentially mask an accurate prognosis which is determined by measuring the size of the tumour. The prognosis for patients with MF/MC tumours is similar to that for patients with unifocal tumours. In higher stages, the presence of lymph node positivity and distant metastases provides more significant prognostic information, while the T-stage effect on the prognosis is of little importance [51]. Most studies found increased frequency of metastases in multiple carcinomas when compared to unifocal carcinomas [77, 104], explaining the unfavourable outcome in MSIBC patients [109].

It is difficult to assess the prognosis of bilateral breast cancer, because the outcome may not be unevenly ascribed to either the first or the second carcinoma. The survival of BSBC patients seems to depend on tumours with poorer histological characteristics [110]. Women over the age of 50 with synchronous bilateral carcinoma or women who develop contralateral breast cancer within 5 years are at two- and four-times higher risk, respectively, of dying from cancer than women with unilateral carcinoma. The prognosis for women with bilateral breast cancer that was diagnosed after 10 years from the initial carcinoma is similar to that for women with unilateral BC [22]. There is no significant difference in survival for patients with bilateral BC compared to patients with unilateral tumours. However, synchronous tumours are accompanied by lower survival compared to metachronous tumours [111]. Conversely, global survival is not different in patients with bilateral BC and those with unilateral BC [112, 113].

There is a significantly higher risk of distant metastases being present in bilateral BCs [114]. Bilateral BC is associated with lower grade of the disease, patients show an absence of distant metastases prior to developing contralateral breast cancer; more importantly, no difference in the disease-specific survival (DSS) was noticed among patients with bilateral BC and unilateral BC. Bilateral BC is associated with shorter relapse-free survival (RFS), but similar DSS when compared to unilateral BC. Furthermore, BSBC is associated with favourable RFS, but has similar DSS when compared to BMBC with respect to other clinicopathologic parameters in patients with bilateral BC [70].

10. Limitations and future guidelines

The incidence of MF/MC breast cancer varies between 6 and 7%, depending on somewhat arbitrary definition of the MF/MC imaging method sensitivity and biopsy performed by the pathologist. The TNM stage does not include multifocality in the tumour classification [51]. As further progress is made in the pre-operative diagnostics, the number of identified MF and MC tumour is increasing [115]. and consequently better manuals are required for treating them [95], as well as standardised immunohistochemical procedures which would reduce the subjectivity and intralaboratory variations in the interpretation [102].

The National Comprehensive Cancer Network and American Society of Clinical Oncology recommended the use of RS as a manual for adjuvant systemic therapy in patients with ER positive, HER2 negative, lymph node-negative invasive BCs that are ≥0,5 cm in size [116, 117]. In some studies, the entity of focality was determined using histological parameters, while others use clinical and radiographic data only. Most authors do not differentiate between MF and MC tumours, and some almost universally analyse these groups together [95]. Not all patients underwent the same pre-operative radiologic assessment or surgical treatment, which may lead to inaccurate classification of the patients as having unifocal carcinomas when they actually had an unidentified MF or MC condition [76]. Oncological decisions in the systemic adjuvant therapy for BC are based on the histological criterion and immunohistochemical profile of the largest tumour focus, ignoring the smaller synchronous cancers [118, 119].

Histological characteristics of the metastases (type and grade) of axillary lymph nodes in multiple breast cancers correlate with the histological type with an unfavourable prognosis and/or highest histological grade, which may not necessarily correspond to the tumour focus of the largest diameter. For this reason, we accentuate the need to individually report on and assess every single tumour focus in multiple BCs [8]. A new classification may be required for bilateral BCs that would include the size of the tumour in both breasts [120]. TNM staging does not take the tumour biology (hormone receptor status, grade, Ki-67, genetic markers) into account. Additional studies are required about the advantage of using biomarkers to improve the accuracy of staging [51]. Despite the diameter of the largest focus being smaller than the volume of the entire tumour, the sum of diameters of all foci will be bigger than the actual tumour volume, since volume is proportional to one third of the diameter. However, using tumour diameter to assess the size is convenient in the sense of being easier to measure [81]. The use of T_{sum} in clinical practice may improve the current staging process and change the approach, in particular for patients with early stage of the disease [51].

There are certain limitations of the retrospective view of MF/MC breast cancer and information on macroscopic appearance which is no longer available. The status of ER/PR/HER2 is also not available for individual tumour foci, since in most cases

it is not evaluated for all tumour foci, meaning that the morphological nature of the MF/MC condition in these patientscannot be reviewed. Tumour characteristics of the second largest lesion are usually not tested, since most medical centres do not routinely perform immunohistochemical staining of each focus. However, certain findings indicate that the biology of the second tumour may affect the prognosis [121], which is why it is recommended to assess tumour markers in each multiple focus [9]. For instance, if the second lesion was hormone-positive or HER2-positive and the main lesion was triple-negative, the chance to administer endocrine therapy or molecular targeted therapy may be missed. That being said, there is considerable controversy surrounding the assessment of Ki-67 in the literature and, despite the efforts to standardise it, a certain degree of subjectivity still remains. Likewise, its limit value is not generally accepted [8].

Future studies observing molecular profiles of separate tumour foci in the same breast could shed light on this matter and provide clinically relevant information for therapy manual-based decisions. Another limitation is the median monitoring of under 5 years [95] and the bias of multicentric studies [120]. Failure to factor in the heterogeneity of the focus of an additional tumour could prevent the patients from taking advantage of appropriate therapies [31, 89, 122]. Most studies are retrospective or incidental in nature, which neither compare breast-conserving surgery with mastectomy nor analyse locoregional recurrence as a primary goal in MSIBC [123].

Conflict of interest

The author declares no conflict of interest.

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