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REVIEW

Radiological–Pathological Correlation in Diagnosing Breast Carcinoma: The Role of Pathology in the Multimodality Era

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Abstract Breast carcinoma is a lobar disease, as the simultaneously or asynchronously appearing often multiple tumor foci originate from a single sick breast lobe. In its initial phase, the spatial pattern of malignant transformation may be lobar (targeting the entire lobe), segmental (targeting a segment) or terminal (targeting distant terminal ductal-lobular units) within the sick lobe. All these variations are properly characterized by the following parameters: the extent of the disease (the volume of the tissue containing all the actually present malignant structures within the breast), the distribution of the lesions within this tissue (unifocal, multifocal or diffuse, separately for in situ and invasive component), the size of the tumor (corresponding to the largest diameter of the largest invasive focus) and the exact localization of the lesion(s). In addition, intra- and intertumoral heterogeneity have to be noticed, if evident. Combining the results of different imaging modalities (mammography, ultrasound, magnetic resonance imaging) the radiologist may compensate the limitations of individual methods. This multimodality approach leads to more accurate radiological size measurement, more accurate assessment of the distribution of the lesions and disease extent. This represents a challenge for pathologists as the traditional histopathology method based on fragmentation and sampling of macroscopically suspicious lesion(s) is clearly insufficient for modern postoperative radiological–pathological correlation. There is a clear need for more complete examination of the excised tissue and for a three-dimensional reconstruction of the finding, preferably using continuous large tissue slices and two and three-dimensional large-format histological sections. Discordant results may still appear as a consequence of failure in radiological–pathological correlation or related to certain tumor subtypes as invasive lobular carcinoma of diffuse type, low grade in situ lesions or micropapillary ductal in situ carcinoma.

Keywords Breast · Breast cancer · Sick lobe hypothesis · Pathology · Radiological–pathological correlation · Large section technique

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Introduction

Breast carcinoma is a lobar disease, as the simultaneously or asynchronously appearing often multiple tumor foci originate from a single sick breast lobe [1]. The malignant transformation may target the entire sick lobe, its segments or its terminal units (TDLUs), simultaneously or with time difference [2]. High-grade ductal cancer in situ (DCIS) tends to diffusely involve the entire lobe as it develops not only in the terminal unites but also in a single lactiferous duct and its branches. Sometimes in DCIS, the malignant transformation is restricted to a segment of the sick lobe and is unifocal. Low-grade DCIS, lobular neoplasia and other borderline lesions tend to involve distant terminal units simultaneously or with varying time difference giving rise to multifocal lesions. Thus, in its initial phase, the spatial pattern of malignant transformation may be lobar, segmental or terminal [2].

Invasive carcinomas may also appear as a single focus, as multiple individual foci or as a diffuse growth of tumor cells, all in different combinations with in situ component. By the time, the invasive foci may coalesce, new tumor foci may develop and the intra-mammary (intravascular and

interstitial) spread of the cancer cells may lead to a more complex morphology of the advancing malignant tumor no longer respecting the borders of the sick lobe and obscuring the lobar nature of the disease [3]. The varying shape and size of the breast lobes [4] and the possibility of presence of more than one sick lobes within the same breast ("multicentric" carcinomas and some low-grade lesions may be multilobar [5]), as well as intratumoral and intertumoral heterogeneity makes the morphology of breast carcinoma even more variable.

Irrespective to the applied imaging method, an individual case of breast carcinoma can be properly characterized by the following morphological parameters: the extent of the disease (the volume of the tissue containing all the actually present malignant structures within the breast), the distribution of the lesions within this tissue (unifocal, multifocal or diffuse, separately for in situ and invasive component), the size of the tumor (corresponding to the largest diameter of the largest invasive focus) and the exact localization of the lesion(s). In addition, intra- and intertumoral heterogeneity have to be noticed, if evident [6].

Tumor size is one of the basic morphological prognostic parameters, which is directly related to the disease specific survival [7]. The extent of the disease is rather a "surgical" parameter, defining for the surgeon the volume of the breast tissue to be excised and is related to the rate of local recurrences: extensive lesions recur up to ten times as often as the non-extensive after breast conserving surgery [1, 8]. The distribution of the lesions is not only a morphological but also a biological parameter as multifocal invasive tumors have doubled while diffuse invasive carcinomas tripled risk of vascular invasion and lymph node metastasis compared to unifocal tumors [3]. Similar to the results of other related studies [9, 10], one third of the invasive carcinomas are multifocal in our material, and if combined with the distribution of the in situ component, less than 40% of the tumors remain unifocal. More than half of the breast carcinomas in our material are extensive [3].

While most breast carcinomas are detected by mammography screening, and the clinically detected cases are also initially characterized by radiological methods, correlating the radiological findings to pathology outcome is essential in avoiding false negative and false positive results and in getting experience considering the capabilities and limitations of different imaging modalities involved, pathology included. Preoperatively, the detected lesions have to be characterized as benign or malignant (by judging the radiological parameters and the morphological findings in preoperative biopsies), in situ or invasive (using core biopsies of different thickness). The radiological size of the lesion has to be measured. This determines the need for eventual neo-adjuvant therapy. The radiological distribution and the extent of the lesions in malignant cases influence the surgeon in choosing between breast-conserving surgery and mastectomy. The postoperative radiological–pathological correlation serves as quality control of the preoperative judgement, and also may indicate the need for additional surgical intervention and adjuvant therapy.

Mammography

The basic method of screening for breast carcinoma is efficient in detecting mass lesions and is even better in detecting microcalcifications. Most of the malignant breast tumors appear on the mammogram as mass lesions with or without microcalifications (about 80%), the rest manifesting as microcalcifications only [7]. Mammography has an accuracy in detecting mass lesions over 80% as reported in comparative studies [11, 12], which varies dependent on histological tumor type. Detection of some subtypes of invasive lobular carcinoma with mammography represents a challenge even for experienced radiologists: in one study as low detection rate as 34% was reported, contrasting to detection rate of 81% in ductal carcinomas in the same series [12].

Although pure DCIS may manifest as mass lesion or architectural distortion on the mammogram, 75% of the DCIS cases are detected by finding microcalcifications [13]. Taking into account pure DCIS and the in situ component of invasive carcinomas, the detection rate of the in situ cancer by mammography is relatively low, as only 25% of low-grade DCIS and 50% of high grade DCIS cases are calcified (Tot T, unpublished data). Consequently, the in situ component and the extent of the disease are underestimated by mammography in many cases, especially if the DCIS is of low grade. Micropapillary DCIS represents a problematic subtype of in situ cancer, which may manifest clinically with nipple discharge allowing proper characterization of the process with galactography; it also may produce typical snake skin-like microcalcifications, but it also may remain clinically and radiologically silent, even if extensive and of high grade [13]. Lobular carcinoma in situ and some borderline lesions (atypical hyperplasia, columnar cell change) are not visible on the mammogram if they are not calcified.

Breast Ultrasound

Breast ultrasound is the most useful adjunctive method in examining women with dense breasts, or examining the dense portion of the breast. Hand-held ultrasound examination aids at and has been manufactured for characterizing palpable and non-palpable breast lesions. This imaging

modality has the clear technical advantage in guiding preoperative needle biopsies and is the first "second look method" when lesions are detected by mammography or MRI. It is very efficient in discriminating solid and cystic lesions and in demonstrating intracystic papillary tumor growth.

Further, ultrasound is the best predictor of real tumor size when compared to clinical examination and mammography [14] however, determining the tumor size in cases of invasive lobular carcinomas is less reliable than in cases of ductal carcinomas even with this method [15].

Multifocal, multicentric and contralateral breast carcinomas are more frequently detected with ultrasound compared to the detection rate of mammography, especially if modern whole-breast ultrasound [16] or three-dimensional automated multislice ultrasound is used. Ultrasound is also more effective than mammography in detecting invasive lobular carcinomas, and is also better in detecting their multifocality [17]. However, MRI may still demonstrate additional tumor foci after ultrasound examination of these tumors [18].

Microcalcifications may be seen on ultrasound, but this technique is inferior to mammography in this aspect. Thus, in situ carcinomas or the in situ component of the invasive tumors may be relatively easily missed on ultrasound examination.

A modern 3D automated ultrasound unit has been manufactured as an adjunctive screening tool to examine the dense portion of the breast in women with considerable amount of fibroglandular tissue.

Magnetic Resonance Imaging (MRI)

This method detects cancers by rapid contrast enhancement after injection of gadolinium, which is dependent on underlying vascular factors. MRI is characterized by higher sensitivity compared to ultrasound and mammography in detecting mass lesions, but benign lesions may give false positive enhancement decreasing the specificity of this method. In one study, the sensitivity for detection of index lesions was 83% for mammography, 70.8% for ultrasound and 98% for MRI [11]. In addition, the high efficacy of MRI is not dependent on density of the breast tissue. The sensitivity of MRI is less dependent on tumor type than the sensitivity of mammography and ultrasound. In some studies, MRI detected invasive ductal and lobular carcinomas with the same high sensitivity of 95% and 96%, respectively [11]. In our experience, however, invasive lobular carcinoma foci may be more frequently missed on MRI than ductal tumors. False negative MRI findings in cases of lobular invasive carcinoma have also been reported in the literature [19].

MRI is less sensitive in detecting DCIS than in detecting invasive cancer. The detection rate of DCIS is related to the grade of the in situ tumor: high-grade (grade 2 and grade 3 together) DCIS was detected by MRI in 92% of cases, low-grade DCIS in only 53% in one study [20]. In our experience, micropapillary in situ carcinoma may be totally silent on MRI even if extensive and high-grade (Fig. 1).

MRI is not a purely morphological method but combines the kinetic features of contrast enhancement within the

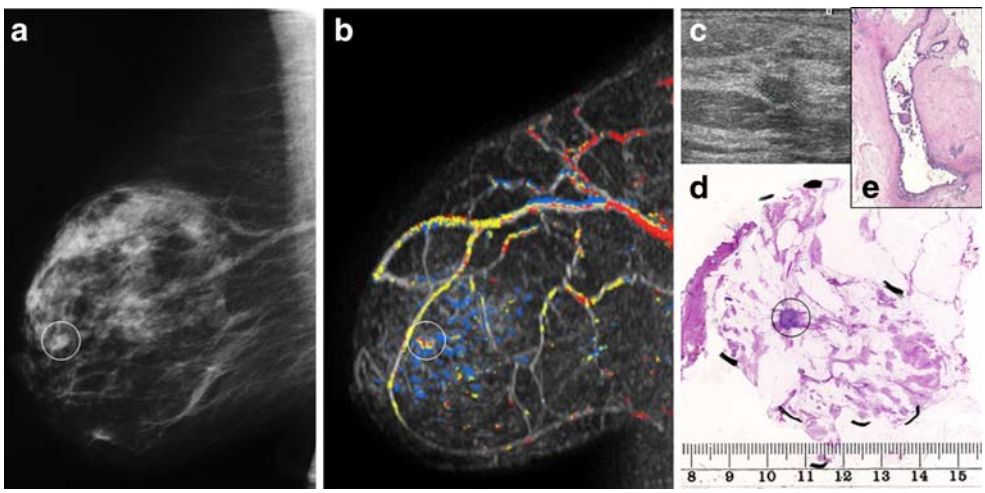

Fig. 1 Selected images demonstrating a case of a radiologically solitary 6×4 mm suspicious lesion with non-specific microcalcifications detected with mammography screening in an asymptomatic 72 year-old women. **a** Mammography image (the lesion is *encircled*), **b** MRI image, the lesion is *encircled*, Note the non-specific enhancement around the lesion, **c** the corresponding ultrasound image demonstrating the solitary lesion, **d** large-format histopathology image demonstrating a 9×9 mm invasive carcinoma (*encircled*) and an additional area of a 70×50 mm high-grade micropapillary ductal carcinoma in situ (*marked* by the pathologist), **e** microscopic detail of the in situ component. The radiology images are courtesy of Drs Laszlo Tabár, Nadja Lindhe and Mats Ingvarsson, Mammography Department, Central Hospital, Falun, Sweden

tissue with morphologic appearance of this enhancement on the image. This allows analysis of the relation of the dynamic MRI features and prognostic parameters as tumor grade or proliferation rate [21]. On the other hand, MRI imaging patterns in DCIS (like "linear or linear branching pattern, dotted, granular or homogeneous segmental pattern, and focal spot-like pattern) [20] closely resembles the pathohistological growth patterns (lobar, segmental and terminal) in earliest stages of cancer development within the sick lobe.

Comparative Evaluation of Different Breast Imaging Modalities

Due to high sensitivity of the conventional breast imaging methods (mammography and ultrasound) MRI offers no additional diagnostic value in up to 80% of cases, but in about 20% it gives additional information influencing therapeutic decisions [22]. MRI detects multifocality in up to 38% of the analysed cases [22], which is comparable to the results of whole organ histopathology studies. MRI is also more efficient in determining the extent of the disease: in one study mammography underestimated tumor extent in 37%, ultrasound in 40% and MRI in 12.5% compared to histologic findings; in multifocal and multicentric cases mammography detected all the multiple foci in 35%, ultrasound in 30% and MRI in 100% with a false-positive rate of 12.5%, 14% and 23%, respectively [11].

While mammography can effectively discriminate most in situ carcinomas from invasive lesions (microcalcifications from mass lesions) and ultrasound mainly verifies mass lesions, MRI demonstrates rather the extent of the malignant process than separately its invasive and in situ component.

Multimodality Approach, a Challenge for the Pathologist

Characterizing breast tumors using all the discussed imaging modalities in the same case allows the radiologist to combine the results and compensate the limitations of individual methods. In this multimodality approach, critical summation of the results of the individual examinations leads to more accurate radiological size measurement, more accurate assessment of the distribution of the lesions and disease extent. Pathology is expected to be at least as accurate as the radiology methods as it is based on direct examination of the tissue and the lesions and not on analysis of their images. This represents clearly a challenge for pathologists as the traditional histopathology method based on fragmentation and sampling of macroscopically suspicious lesion(s) is clearly insufficient for modern postoperative radiological–pathological correlation.

There is a clear need for more complete examination of the excised tissue [23, 24], and for a three-dimensional reconstruction of the finding, preferably using continuous large tissue slices and two and three-dimensional large-format histological sections (Fig. 2). This method has been repeatedly described in details [6, 7, 25–27], its advantages have been scientifically evidenced [27, 28], and its suitability for routine breast pathology has also been proven [1, 3, 6, 7, 23, 25, 26, 29].

An obvious advantage of mammography is to be able to produce specimen mammogram verifying the presence of the preoperatively detected lesions in the specimen, assessing the radicality of the surgical intervention and guiding the pathologist in preparing the tissue for histological examination. Ultrasound may also be used to sonographically visualize and localize lesions within the specimen, especially if they are not palpable and not visible on the mammogram [30]. A whole-specimen ultrasound image is, however, much less informative for the pathologists in radiological–pathological correlation than the specimen radiogram. As a contrast dependent method, MRI is not suitable for imaging of the operative specimen. Thus, the pathologist has to compare the specimen radiogram and the macroscopical findings to the preoperatively seen ultrasound and MRI images when he or she creates histological slides demonstrating the detected lesions. Understanding all the details in the radiology reports and understanding the capabilities and limitations of different imaging methods is the minimum needed for competent cut up of the breast specimen.

To determine the correct tumor size, the pathologist has to compare the macroscopic size (the largest diameter of the

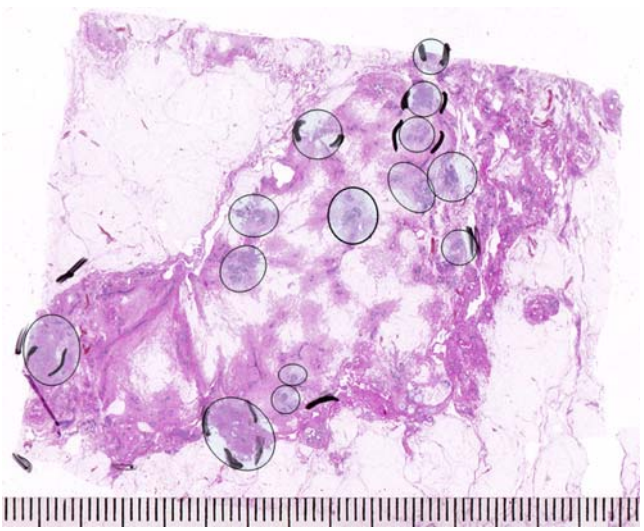

Fig. 2 Large-format histology section demonstrating an extensive multifocal invasive carcinoma

largest invasive tumor focus) on cross-section slices of the unfixed specimen to radiological tumor size. Ultrasound measurement, and especially measurements on MRI are highly accurate; MRI generates images of the tumor in different stereoscopic views and through computer assisted analysis measures tumor size in different projections. The values of tumor size measurement with ultrasound and MRI are usually very similar and guide the pathologist in creating whole mount histological sections of the tumor in proper plane. The histological tumor size should be measured on large sections containing a cross section of the entire tumor at the level of its largest diameter. Often several large sections are needed demonstrating the tumor at different levels to achieve this goal, otherwise, there is a considerable risk of underestimating the tumor size at histological examination. Measuring together multiple tumor foci separated from each other by non-malignant tissue or including extensions of the tumor and not only the tumor body leads to overestimation of the tumor size at histological examination [3, 31]. On the other hand, there is still a possibility that the radiological tumor size is underestimated, thus histological tumor size should be the endpoint if it is larger or equal to the radiological size.

Similar is the situation concerning the distribution of the lesions and extent of the disease. The individual radiology methods may underestimate or overestimate these parameters; however, the combination of the results in multimodality approach gives accurate values in most cases. MRI and whole-organ ultrasound are very accurate in finding the foci in multifocal cases, MRI also defines the extent very accurately. Large-format histopathology may also underestimate the extent of the disease if the slices were cut in inadequate plane or in case of taking insufficient number of slices for embedding. Continuous (9×8 cm) large histological sections at 2 to 4 consecutive cross section levels from the specimen usually assure adequate demonstration of the findings being representative for about a 2 cm thick tissue slice.

Discordant results may be a consequence of any failure in detailed radiological–pathological correlation or erroneous interdisciplinary communication pre- and postoperatively, but also a result of biological characteristics of some tumors. More discrepancies are expected in cases of invasive lobular carcinoma, especially its diffuse type [32] with regard of tumor size, number of individual tumor foci and disease extent. Low-grade DCIS, lobular neoplasia and borderline lesions are often occult on the mammogram, on ultrasound as well as on MRI that may lead to considerable discrepancies in determining the disease extent. Micropapillary DCIS, as discussed above, may also be radiologically silent. Radiology methods, especially MRI may overestimate multifocality and disease extent because of false positive findings. Therefore, MRI guided biopsy verification or a second look ultrasound biopsy is central in preoperative assessment of breast carcinomas in multimodality approach.

In Conclusion

- Conventional histopathology is far insufficient in defining tumor size, distribution and disease extent in breast cancer in a considerable number of cases.
- Modern breast imaging, especially in multimodality approach, is very accurate in assessing these parameters and represents a real challenge for pathology.
- Using multiple large histology sections represents a prerequisite and detailed radiological–pathological correlation the only proper way in adequate demonstration and evaluation of morphological findings in modern breast pathology.
- Low-grade in situ lesions, micropapillary DCIS and invasive lobular carcinoma are the most frequent causes of discrepancies in radiological versus pathological assessment of these parameters, in addition to failure in radio-pathologic correlation.
- As all the imaging methods may underestimate or overestimate the key parameters in breast carcinomas, there is a clear need for correct pathology background in validating these methods. The role of breast pathology has never been as central and important as in the era of rapidly developing modern breast imaging.

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