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REVIEW ARTICLE

The lobar approach to breast ultrasound imaging and surgery

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Abstract Breast cancer is a lobar disease in the sense that, at the earliest stages, the cancer is structurally confined to a single sick lobe. The subgross morphology of breast carcinoma is often complex, as multiple invasive foci are frequently present and the ductal system often contains an extensive in situ component. Adequate preoperative visualization of all of the malignant structures within the affected breast and preoperative mapping of the lesions in relation to the surrounding normal structures are essential for successful image-guided breast surgery and therefore are key factors in assuring adequate local control of the disease. We advocate use of the lobar approach in ultrasound imaging (ducto-radial echography) and breast-conserving surgery based on the lobar anatomy of the breast, the sick lobe theory, our extensive clinical experience with the approach, and favorable long-term patient outcomes. Despite abundant evidence demonstrating the advantages of the lobar approach, the number of breast centers using it in practice is still limited. In this review, we aim to call attention to the advantages of the lobar approach from the theoretical, imaging, and surgical points of view.

Keywords Breast anatomy · Breast cancer · Sick lobe theory · Lobar ultrasound · Breast-conserving surgery

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Introduction

Classical anatomical studies first described the lobar morphology of the breast over a century ago [1]; however, these observations had no influence on the development of breast imaging techniques or management of breast cancer patients until recently. Despite confirmation of the morphological findings some decades ago [2], only very few clinicians recognize the value of a morphology-based surgical approach, and consideration of the lobar morphology in diagnosis and treatment of breast diseases remains very limited [3, 4]. The introduction of mammography screening allows detection of breast carcinoma at early stages, thereby increasing the number of small and early-stage lesions. The associated challenges underscore the necessity of correlating these imaging findings to anatomy and pathology. Pioneering work in establishment of the lobar approach to modern breast ultrasound [5–8] led to the adoption of this special method by a limited number of institutions. In parallel with the rapid development of breast imaging techniques, the growing body of knowledge about the molecular pathology and genetics of breast carcinoma has overshadowed the previous, clinically important observations regarding the complexity of breast cancer subgross morphology [9–11]. The recently published "sick lobe theory" [12] has now unified these genetic, embryological, and morphological perspectives into a framework that offers a possible explanation for the lobar distribution of early breast carcinoma lesions. This concept also provides a theoretical basis for the utility of the lobar approach in modern breast ultrasound imaging and for ultrasound-guided lobar breast-conserving surgery, which are the main topics of this review.

Theoretical background (the sick lobe theory)

Breast cancer is a lobar disease in the sense that the earliest stages of cancer development are confined to a single lobe within the breast [12]. The sick lobe theory holds that the affected lobe was mal-constructed during embryonic development and is thus characterized by increased sensitivity to endogenic and exogenic oncogenic stimuli. This sensitivity may be caused by committed progenitor cells with increased genetic instability within this lobe, as compared to the healthy lobes. The progenitor cells give rise to differentiated progenies, both epithelial and myoepithelial, that participate in the continuous renewal of the parenchymal structures within normal breast tissue. Committed progenitor cells carry genetic changes that were acquired during embryonic development [13, 14].

Accumulation of mutations over decades of postnatal life can result in complete malignant transformation of the committed progenitor cells within a sick lobe. Over time, these malignant progenitor cells and their progenies can eventually replace the normal epithelial and myoepithelial cells within the sick lobe and take over their functions. During the "in situ" phase, these cells are still able to retain the normal ductal-lobular morphology (although the lobules and the ducts become distended and distorted by the accumulation of the malignant cells and their products), the biphasic (epithelial-myoepithelial) cell differentiation, and to produce the basement membrane that delineates the parenchyma from the stromal elements. Additional mutations may lead to partial or total loss of these qualities of the progenitor cells and their progenies: the ductal-lobular compartments, the myoepithelial cells, and the basement membrane eventually disappear. Intense interaction between the parenchymal and stromal elements, and the epithelial-mesenchymal transition of some parenchymal cells lead to invasive malignant growth [15, 16].

The genetic constitution of the cells is most vulnerable and unstable during cell replication. Malignant transformation of committed progenitor cells may be considered to be biologically timed in the sense that the number of cell cycles required for such transformation is approximately the same in all such cells [13, 14]. As the committed progenitor cells may be either evenly or unevenly distributed within the sick lobe, malignant transformation of the cells could appear at a single discrete locus, simultaneously at several loci, or at many different points within the entire lobe. Consequently, the development of cancer in situ within the sick lobe may be unifocal, multifocal, or diffuse. Similarly, invasive growth may appear at a single locus, at several distant loci, or over a large area within the breast tissue [15, 16]. The volume of breast tissue involved in this process is observed to be variable; it can be many cubic centimeters in size from the beginning of the process and can expand via invasion beyond the limits of the sick lobe at more advanced stages.

In summary, most breast carcinomas exhibit complex subgross morphology. Approximately one-third of invasive cases are unifocal, with a single invasive focus and an in situ component within and/or in the vicinity of this focus. Another third of the cases are characterized by the presence of a single invasive focus, but associated with a diffuse or multifocal in situ component. The final third of the cases exhibit a multifocal invasive component. Almost half of these cases are extensive in which the individual foci occupy a tissue volume of greater than 4 cm in the largest dimension [15, 16]. The lobar nature of breast carcinoma is easiest to observe at in situ or early (millimetric) invasive phase.

Lobar ultrasound of the breast lesions

Echographic anatomy of the breast

In contrast to the traditional method, in which the structures of the breast are visualized starting from the outer surface and moving toward the thoracic wall, we advocate the lobar approach, in which imaging starts from the echographically most important structure, the acino-ductal axis of the lobe. The lobes are positioned around the nipple in a corolla, like the petals of a daisy. Upon ultrasound examination, the lobes exhibit a hyperechogenic membrane-like surface, keeping their more-or-less homogeneous content inside. The upper and the lower surfaces show connective spicules, which correspond to the insertion of the upper and lower Cooper's ligaments. These ligaments are connected to the upper and lower layer of the subcutaneous and pectoralis fascia, with more pronounced ligaments evident in the upper part of the lobes. The upper layer of the superficial fascia is linked to the skin through small connective structures that lie perpendicular to the skin, the retinacula cutis. Comparison of lobar echo-anatomy with large-format histological slides reveals a perfect correlation between all the structures described above (Fig. 1).

The inner surface of this acino-ductal axis is covered by the epithelial cell layer, either comprising normal epithelial cells or showing alterations of a benign or malignant nature. Because the ducts and the lobules are usually less than a millimeter in size, they are barely visible with imaging techniques (mammography, MRI, and echography) in their

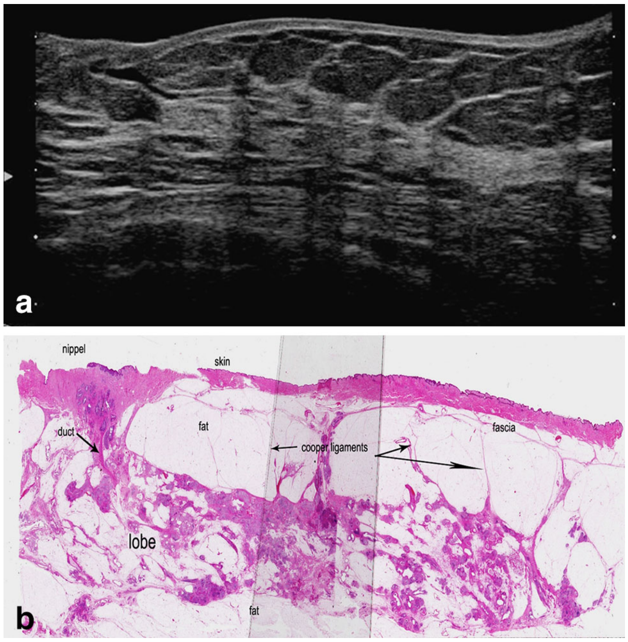

Fig. 1 **a** Radial echographic scan obtained in routine practice. The nipple is located at the *upper left* corner of the image, the lobe is hyperechogenic and its echogenicity is accentuated at the right extremity of the scan. The superior Cooper ligaments linked to the subcutaneous fascia are perfectly visualized. **b** Large-format histology section illustrating a breast lobe (reconstruction of two large-format slides; the lobe measures 14 cm in length). Note the perfect imaging—histological correlation of the designated structures

normal state and consequently are often overlooked. Upon development of epithelial hyperplasia or duct-ectasia or pathology, the size of these structures increases and they become echo-visible. Epithelial hyperplasia (termed "usual ductal hyperplasia," "UDH") corresponds to the benign and limited proliferation of the epithelial and myoepithelial cells, which distend the involved lobules and ducts, altering their internal acoustic impedance. However, the echo-structure of hyperplasia appears similar to that of the fatty tissue. Identification of hyperplasia is facilitated by the intra-lobar localization of these hypoechogenic structures, which helps distinguish them from perilobar fat. Discrimination between usual ductal hyperplasia and atypical ductal hyperplasia (ADH) is not possible using echography (Fig. 2).

In summary, the breast ultrasound examination should begin with visualization of the lobar anatomy. The examiner must investigate the entire lobe: all of the ducts and lobules within the lobes, if they are individually visible, as well as the Cooper's ligaments. Investigation of the cutaneous and subcutaneous covers, which are clearly visible on echography together with investigation of the ligaments, is essential for the early detection of millimetric cancers. The anatomical survey should also include examination of the deeper levels (pectoral muscle) and of the latero-

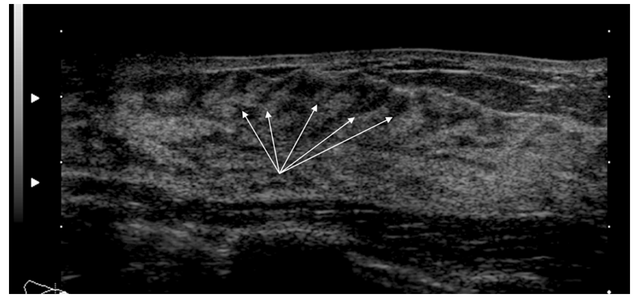

Fig. 2 Radial echographic scan of the breast with lobular and ductal epithelial proliferations within the lobe. Note the numerous hypoechogenic lobules located at the upper part of the lobe (*arrows*) contrasting to the hyperechogenic background of the lobe

sternal, subclavicular, and axillary regions to check for any atypically located lobes and lymph nodes [7, 17–19].

The lobar ultrasound examination technique

Because of the intra-lobar position of the ducts and the radial distribution of the lobes around the nipple, a ducto-radial ultrasonic scanning technique is required, as pioneered by Teboul [17, 18, 20].

Before starting the examination, the equipment must be adjusted as follows: the decibels must be increased to the maximum level and the general gain lowered, so as to achieve a sharp contrast for investigation of the epithelial structures. The High-Frequency linear probe must be as long as possible (10 cm for the L.53L from Hitachi) to rapidly achieve a 'panoramic' visualization of all of the lobes. Adapting a dedicated water bag to the probe allows improved superficial analysis (of the skin, fascia, and ligaments) and provides optimal contrast resolution. Orthogonal, anti-radial scanning is used only in pathological cases, to obtain measurements in two perpendicular planes.

The patient is typically positioned on her back with her arm raised above her head, although the examination can also be carried out with the patient sitting. The examiner must not neglect to move the patient during the examination to examine the breast with the patient in both outward and inward side-lying positions.

The optimal B mode ultrasonic picture is obtained with the probe held in a strictly horizontal position, perfectly perpendicular to the skin. To achieve this, one needs to move the patient into an oblique lying position, so as to avoid displacing the probe laterally. This also applies to the use of elastography, whether using the 'Strain: SE' technique or the 'shear wave: SWE' technique.

The nipple and periareolar zone are investigated before scanning the lobes. This scan is performed around the nipple in a clockwise fashion, lobe by lobe, and is followed by a complementary external analysis of the upper half of the breast and exploration of the axilla.

No pressure on the probe is required, but as the course followed by the duct is not strictly linear, the application of slight lateral pressure on the probe during the examination is useful in order to position the ductal axis well within the ultrasonic beam.

To facilitate interpretation of the results and exam-to-exam monitoring, all of the ultrasonic slices are arbitrarily positioned with the nipple in the upper left section of the screen, with the distal extremity of the lobe to the right and the skin parallel to the upper section of the screen. The examination thus becomes operator-independent, and views can be duplicated exactly during further checkups.

Developmental and physiological considerations

The development of the breast occurs in several stages. The first lobes to become fully developed during and after the puberty are located in the upper outer quadrants of the breast. The lobes around the nipple are next to develop, followed by the lobes in the lower, inner quadrants.

During and after menopause, the involution of the breast is characterized by fatty infiltration of the lobes, between the regressively disappearing ducts and lobules. This process begins in the lobes of the lower inner quadrants (which are the last to develop during adolescence) and affects the upper outer lobes last. This explains the observation that cancer is more frequently detected in the upper outer quadrants, as they consist of more epithelium over a longer period of time. These age-dependent changes in lobar morphology are variable, as involution may happen before the age of 40 in some women and persistent lobes may still be observed in others at the age of 70, often in association with hormone replacement therapy. Thorough knowledge of normal anatomical variation and physiological changes is necessary in order to understand and interpret the morphological and echographic characteristics observed in the mammary gland in each individual patient (Fig. 3).

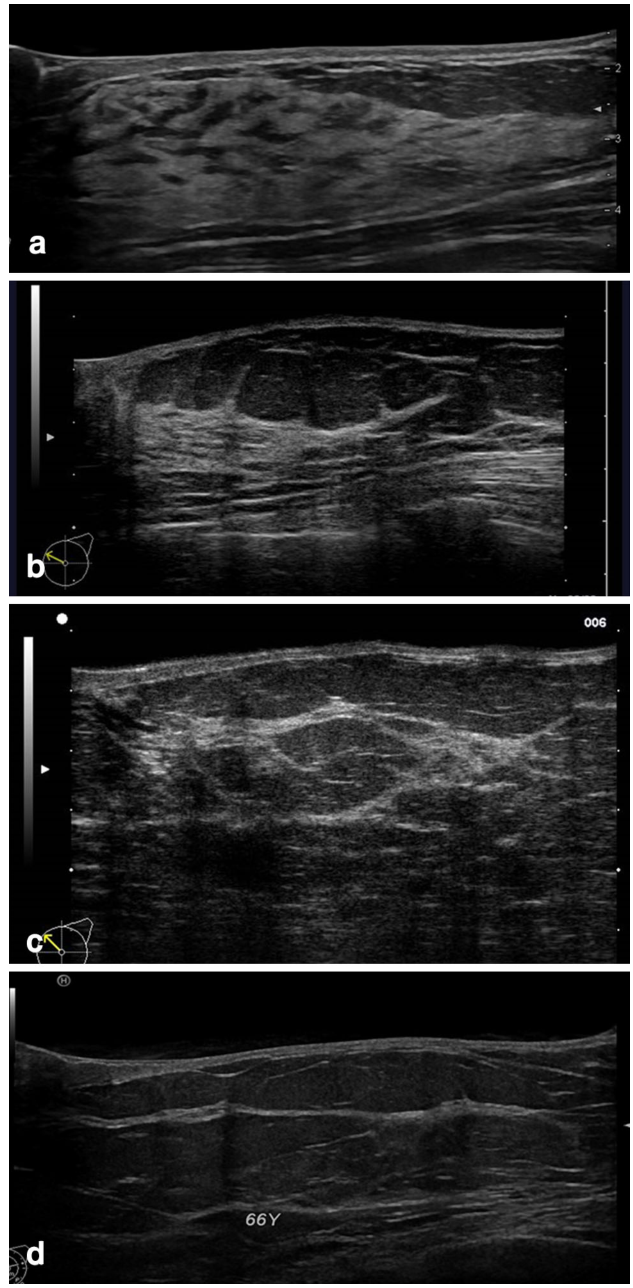

Fig. 3 Radial echographic scans illustrating the age-related gradual involution of the breast lobes. **a** Lobe of a young female. Note the scarcity of fatty tissue around the lobe and the hypoechogenic areas corresponding to hyperplastic ductal and lobular structures; **b** early lobar involution with fatty replacement of the structures of the lobe leading exaggeration of the superior and inferior Cooper ligaments. **c** A lobe of a postmenopausal woman with advanced lobar involution with fatty replacement. The inferior ducts disappear, and only the upper part of the lobe persists. **d** Residual postmenopausal lobe characterized by linear hyperechogenic structures within a fatty environment

Cancer development within the lobes

The sick lobe theory connects breast carcinogenesis to an anatomically well-defined structure, the breast lobe. The lobes cannot be seen on mammography, but are visible using ultrasound. The traditional method of ultrasound imaging produces orthogonal slices of the breast and is not appropriate for visualization of the lobes; only the ducto-radial echography approach, which we advocate, is able to visualize the lobes and their content. Using this technique, we often find the early-stage cancers located at the meeting point between the ductal axes and the axis of the Cooper's ligaments [11]. We note that these cancers are, in contrast to benign tumors, often taller than they are wide. This phenomenon is due to a complex interaction between the supportive connective tissue and the cancer cells [9].

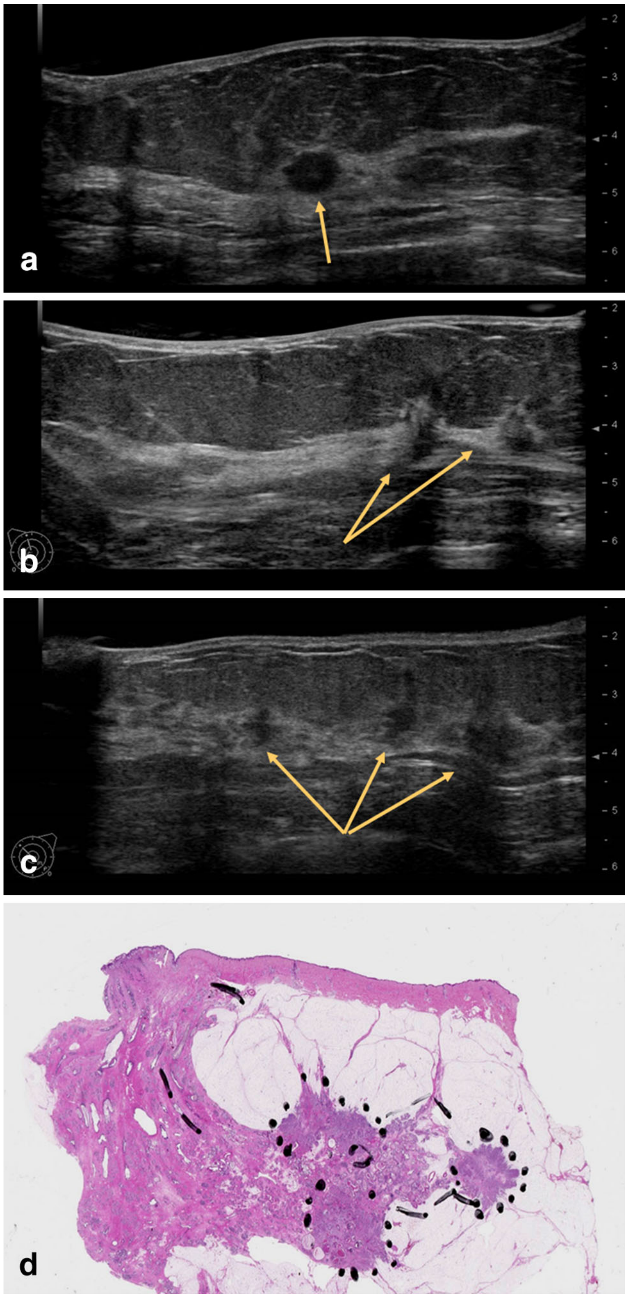

Fig. 4 Radial echographic scans of the breast. **a** Unifocal millimetric ductal carcinoma at the section point of the axis of a superior Cooper ligament and the ductal axis. Note the hypoechogenic solid nodule with spiculations (*arrow*). The reaction of the surrounding connective tissue is still limited due to the small (less than a centimeter) tumor size. **b** Bifocal lobular carcinoma located in two different lobules. Note the small taller-than-wide hypoechogenic lesions located at the distal extremity of the sick lobe (*arrows*). **c** Multifocal ductal carcinoma: the largest (oldest) focus is located at the distal extremity of the lobe, the younger ones between the nipple and the distal cancer (*arrows*). Note the connective tissue reaction being more evident at the lobe's extremity around the largest lesion. **d** Large-format histology section illustrating a multifocal invasive carcinoma with three foci (*dotted lines*) and in situ lesions filling the lobe (*dashed-line* marked area)

The surprisingly high proportion of multifocal, multicentric, and diffuse breast cancers [21] warrants a complete re-evaluation of the traditional radiological approach to imaging breast cancer and provides a compelling case for adoption of ductal echography as the preferred method to detect the multiple foci (Fig. 4). Even ductal echography may fail to reveal every intra-lobar focus of millimetric size; although the sensitivity of the method is high, small invasive foci will remain undetected by imaging, despite best efforts, and will be revealed only by histological examination.

Implications for treatment

Based on decades of experience with ducto-radial echography [19] and our research, we are motivated to advocate for a shift from the conventional diagnostic approach to the lobar approach. Breast cancer develops not as a single tumor, but as a lobar disease [12]. The lobes are individual units, and the spread of cancer cells from one lobe to the other is extremely rare, if it occurs at all. However, simultaneous involvement of several lobes in the same breast is possible (multicentric cancer). It is important to delineate such rare multicentric cases from the much more common multifocal cancer, in which the multiple tumor foci are localized within the same lobe.

The breast radiologist bears profound responsibility, as the findings from the preoperative imaging determine the choice of treatment. Proper preoperative mapping of the disease comprises both the precise localization of the lesions within the breast (expressed as clock location and distance from the nipple, measured in centimeters) and the detailed assessment of the number of lesions, their size, their relation to one another and to normal structures, and an assessment of the extent of the disease. In addition, the imaging approach has to be multimodal, meaning that a synthesis of information gathered by different modern breast imaging modalities (mammography, ultrasound, MRI) should be used to compensate for the limitations of each of the individual methods and to provide the best possible basis for therapeutic decision-making.

Lobar ultrasound and breast-conserving surgery

Lobar ultrasound is also a useful tool to assist and guide breast surgeon at each step of the operation: preoperatively, during surgery and during postoperative examination of the excised surgical specimen.

Back in the early 1980s, influenced by the work of Townsend and Craig [2] and also by own studies comparing ultrasound images with whole-breast cross-section tissue slices, Durante and his co-workers at the University of Ferrara, Italy, [3, 4] initiated the routine use of ultrasound in the operating theater. Understanding the need to strictly follow the lobar anatomy of the breast during the surgical intervention, and understanding the lobar nature of breast carcinoma, they started to systematically perform ultrasound examination in a radial and anti-radial fashion immediately before each operation in order to visualize the ductal system along the major axis and, using a special draft, indicated every scan clockwise (Fig. 5).

This step proved to be useful, as it provides the operating surgeon with an immediate, first-hand view of the morphology and disease progression and an opportunity to double-check and fine-tune the surgical plan that was based on the preoperative imaging findings and biopsy results. This surgeon can confirm all of the relevant parameters: the distance of the lesions from the nipple, skin, and fascia, tumor size, extent of disease, extent of the in situ component, multifocality, multicentricity, some lymph node involvement, tumor vascularity, and elasticity. Careful evaluation of the findings from preoperative imaging studies is crucial to the decision-making process regarding the type and extent of the surgical intervention that will be adequate in every individual case. The echographic image clearly shows the lesion, its relation to anatomical landmarks, the extent of the disease, and the structure of the adjacent tissue, thereby delineating the tissue that the surgeon needs to remove (Fig. 6). The imaging facilitates accurate placement of marks on the skin to show the limits of the sick lobe and to indicate the direction of the most advantageous incision. The surgeon should always follow the Langer lines during the operation, and the breast tissue resection should follow the lobar anatomy. The resection is performed directionally from the periphery to the rear-nipple region, where the major ducts are closed. A slight modification of this method is also proposed by Dolfin [22].

Lobar ultrasound provides very sensitive detection of small invasive tumor foci. Within the Ferrara series of 406 consecutive breast cancer cases that were surgically treated with lobar breast-conserving surgery, 241 (59 %) of the tumors measured <10 mm in size. Lobar ultrasound has

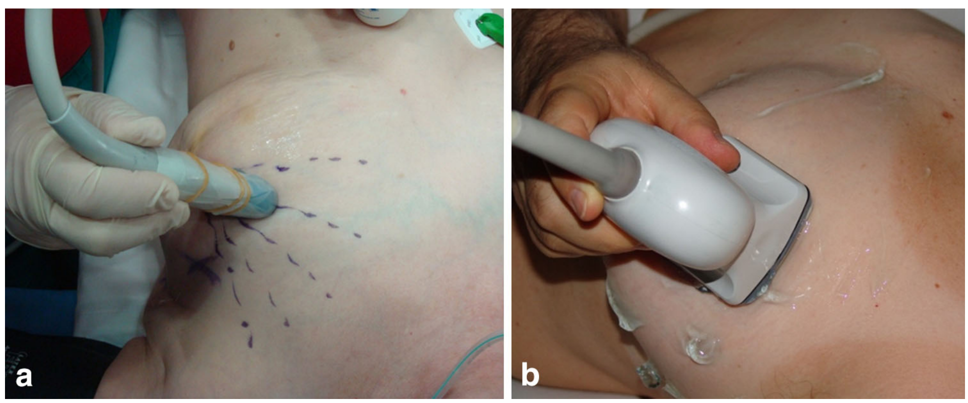

Fig. 5 Scanning technique with 2D (**a**) and 3D (**b**) transducer in radial fashion (lobar approach)

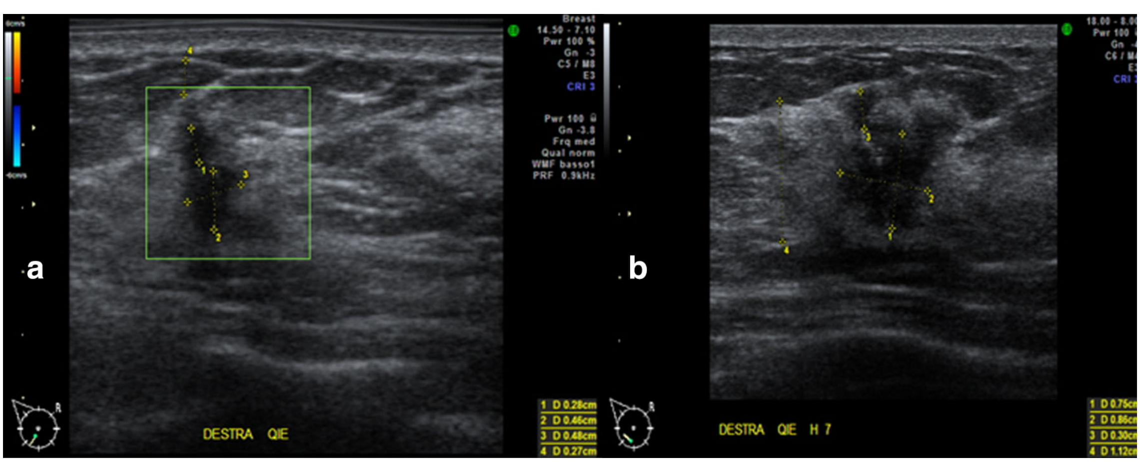

Fig. 6 The pre-surgical anti-radial scan provides an opportunity to assess the extent of the disease, determine the optimal way of resection of the tissue, and to adjust the surgical plan as appropriate. In this case, the tumor is located at 7 o'clock (**a**) and lobar resection from 6:30 to 7:30 (**b**) will yield an adequate lateral margin

substantial impact in determining margin status, which is a key factor in achieving adequate local control of the cancer. The human breast is a subcutaneous organ lying completely within the superficial and deep layers of the superficial pectoral fascia. The radial imaging approach provides better display of the anatomy and the lesions within the ductal system, as well as their relation to fascia. The integrity of fascial layers is extremely important in regard to preoperative estimation of the feasibility of radical breast-conserving surgical intervention that also achieves clear superficial and deep surgical margins.

The frequently observed multifocality of invasive and/or in situ tumor components may cause failure to surgically remove all of the foci despite obtaining seemingly clear circumferential margins. Intraoperative radial ultrasound examination, on the other hand, guides the surgeon to more comprehensively find individual tumor foci even if they are located distant from the dominant mass and provides the opportunity to modify the surgical plan in progress if necessary, and consequently to reduce failure rates. The surgical specimen produced may comprise one or more lobes, depending on the dimensions of the tumor foci and the volume of the breast tissue they occupy. From our viewpoint, removal of the entire diseased lobe is not a more aggressive surgery, but, rather, an anatomically justified approach to curative resection.

After the operation, ultrasound examination of the removed specimen enables the surgeon to visualize the presence of the lesion within the specimen, and to determine its distance from the surgical margins. Finding inadequate margins during immediate examination of the excised mass allows the surgeon to immediately perform a complete resection if necessary (Fig. 7).

Accurate and thorough pathological assessment of the removed surgical specimen provides valuable feedback to the surgeon regarding the quality of the preoperative radiological assessment and the adequacy of the surgical intervention. Unfortunately, the conventional histopathology work-up of specimens as practiced in most pathology laboratories does not allow visualization of any of the anatomical structures in relation to the lesion, rather, it is focused on the lesions in isolation. Fragmenting the specimen into 2-cm tissue blocks results in complete loss of the relationship to every anatomical landmark and makes it practically impossible to relate the histological slides to the radiological images.

Fig. 7 Ultrasound examination of the surgical specimen immediately after its removal in the operation theater

Margin status is a key factor in assessment of the adequacy of the resection. Negative margins can only be obtained if the tumor has been removed with sufficient tumor-free tissue surrounding it. Surgical interventions that follow the lobar anatomy seem to be more successful in this respect than the traditional approach, which is based on margin width. Local recurrences, which are a negative prognostic parameter as well as an emotionally devastating event for patients requiring additional treatment, are very rare after lobar surgery. Utilizing the lobar resection approach at the University of Ferrara, only 3 local recurrences were observed in the same quadrant of the breast in a cohort of 1094 consecutive patients who had surgery for breast cancer between 1988 and 2006, after 7, 8, and 11 years follow-up, respectively.

Lobar versus non-lobar approach

Both the size of the tumor and multifocality of the invasive component are powerful morphologic prognostic parameters. Numerous studies have shown that patients with invasive breast carcinomas that are <10 mm in size experience excellent long-time survival outcomes [23]. There is an increasing body of evidence showing that multifocality negatively influences both disease-free and overall survival [24, 25]. Lobar ultrasound, based on the lobar anatomy of the breast and on the lobar character of breast carcinoma, visualizes not only the pathological lesions but also the lobe environment in which they are located. In our experience, this approach is more efficient at detecting millimetric breast carcinomas and multiple foci of such size than macroscopic examination, mammography, or standard ultrasound.

The current trend toward increasingly less extensive breast surgery, with the minimal adequate margin requirements specified in guideline recommendations [26], results in high rates of reoperation, up to 60 % at some institutions, and up to 10 % local recurrence rates [27]. The experience of Durante et al. [3, 4] clearly shows that detailed preoperative radiological mapping of the disease, together with intraoperative lobar ultrasound imaging and immediate postoperative sonographic examination of the specimen, substantially reduces both the reoperation rates and the local recurrence rates [28–40].

Conclusions

Breast cancer is not a lump but a lobar disease. Involvement of the breast lobe is often patchy or diffuse, resulting in multifocality and an extensive ductal in situ component in many cases. Following the lobar anatomy during imaging and surgery provides the advantage of identifying and removing the entirety of the diseased tissue with wide margins and it minimizes the rates of local recurrence. The additional investment of time and effort to apply the lobar approach to breast imaging and surgery is repaid in improved patient outcome.

Conflict of interest Dr. Amy, Dr. Durante, and Dr. Tot have no financial interest or other relationship with any manufacturer of any product or provider of any service mentioned in this article.

Ethical standard Additional informed consent was obtained from all the patients for whom identifying information is included in this article.

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