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The contribution of new US technologies to US differential diagnosis of nonpalpable lesions

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Background. *Gray-scale ultrasound (US) patterns are still the best indicators of the risk of malignancy and correlation with mammography and guidance to bioptical procedures are still the gold standard in breast diagnosis. But recent technological advancements in ultrasound offer new diagnostic capabilities that integrate conventional US imaging: 3D, CAD, perfusion imaging and elastography.*

Conclusions. *The US technologies allow to differentiate and grade the vascularity of breast lesions (both with conventional technologies and with contrast enhancers) and to evaluate the elastic properties of the normal and pathologic tissues (elastography). Both these technologies are on the way of becoming commercially available on medium and high-end US instruments. But they must still be considered as research tools because their diagnostic efficacy requires more widely clinical testing.*

Key words: breast, ultrasound, perfusion imaging, elastography, nonpalpable lesions

Introduction

Gray-scale ultrasound (US) patterns are still the best indicators of the risk of malignancy and correlation with mammography and guidance to bioptical procedures are still the gold standard in breast diagnosis.

But recent technological advancements in ultrasound offer new diagnostic capabilities that integrate conventional US imaging: 3D, CAD, perfusion imaging and elastography.

They allow increasing the number of signs that support the final diagnosis and open new application fields.

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Actually the tecnologies that seem to be more promising allow to differentiate and grade the vascularity of breast lesions (both with conventional technologies and with contrast enhancers) and to evaluate the elastic properties of the normal and pathologic tissues (elastography). Both these technologies are on the way of becoming commercially available on medium and high-end US instruments. But they must still be considered as research tools because their diagnostic efficacy requires more widely clinical testing.

Assessing vascularity

Although the use of contrast-enhanced ultrasonography for breast imaging is less established than other applications, it is an excit-

ing technique with great potential. The principles of contrast-enhanced ultrasonography of breast cancers are similar to those for all tumours, and are based on the detection of tumour-associated neoangiogenesis. In the breast, neoangiogenesis is characteristic of both invasive disease and in situ cancer including high-grade ductal carcinoma in situ (DCIS).

Breast tumours present with increased vascular density, irregular and often chaotic branching and penetrating vessels, and sometimes incomplete vascular walls that permit leakage of contrast agent into the surrounding tissue; this diagnostic clue for malignancy is currently used with magnetic resonance imaging (MRI). Since angiogenesis correlates with tumour grade (and presence of metastatic disease), a patient's prognosis can be partly determined from the degree of angiogenesis observed at diagnostic imaging.

Conventional vascular US

Continuous progression in ultrasound technology and related software's has greatly refined the diagnostic capability of this technique in breast pathology.

Vascular assessment has progressed enough to depict vessels in almost all the tumors and in most fibroadenomas.[1] Modern ultrasound scanners have sufficient sensitivity to detect blood flow through small blood vessels of 1 mm or less in diameter and with blood flow on the order of 1 cm/s. This allows visualization of arterioles and venules, but does not reveal flow through smaller blood vessels at capillary level.

Fibroadenomas are the most common benign tumour in the breast. Clinically, these tumours tend to be soft and mobile, and are seen mostly in younger women. On colour and power Doppler US, fibroadenomas generally have poor vascularity; vessels are peripheral, with a nest arrangement, regular and small.

In contrast, malignant tumors have numerous central and penetrating, branching vessels with irregular caliper and velocities. These patterns reflect the abnormalities that are peculiar for rapidly growing tumors: irregular and variable vessel caliber, elongated and coiled vessels, arteriovenous shunts, disturbed dichotomous branching and decreasing of caliber, and incomplete vascular wall.[2] The correlation between the vascular disorganization and the grade of tumoural anaplasia is very close.

Benign tumors may have one vascular pole while malignant tumours can have more than one.

The best results are obtained when Doppler frequency is higher than 5 MHz, pulse repetition frequency is between 600 and 800 Hz, and the area of interest is scanned with minimal compression. The relative risk for malignancy is higher when the vessels exhibit irregular morphology and irregular velocities (Table 1); these two characteristics contribute to define the "mosaic" pattern.

Informations obtained with conventional colour Doppler are very helpful for detecting small lesions and axillary nodes with large fatty infiltration of the hilum. In most of the cases vascularity allows correct diagnosis of intramammary nodes and acts as major alert for inflammations and malignancies. Ozdemir et al.[3] prospectively examined with Doppler 112 lesions (70 malignant and 42 benign) detected with mammography and sonography; Doppler studies increased the specificity of

Table 1. Malignant characteristics of the vascularity in solid breast nodules

Characteristic	Relative risk Masses < 15 mm	Relative risk Masses > 15 mm
Irregular morphology	5.8	4.7
Irregular velocities	3.2	4.3
Multiple poles	2.1	2.0
Central vessels only	2.6	3.4
Peripheral vessels only	1.2	1.4

mammography and gray scale sonography for lesions 10 mm and smaller (from 88.9% to 100%) and for those larger than 10 mm (from 70% to 96.6%).

There is some overlap, however, in the vascular properties of breast lesions. At conventional ultrasonography, false-positive results are mostly given by hypervascularized inflammatory lesions, proliferating and juvenile fibroadenomas and phylloid tumours. There are also false negatives, particularly small tubular or ductal lesions with intense fibrosis giving an avascular appearance. Intraductal carcinoma is covered by the original basement membrane and is supplied by perfusion only from capillary vessels out of the ducts; the only exception is a papillary form with fibrovascular cores.[4] In invasive carcinoma tumoural cells are accompanied by the surrounding angiogenesis, and are supplied from capillary vessels in the circumference.

Early experience in contrast-enhanced vascular assessment

Initially, contrast-enhanced ultrasonography was used in breast imaging to increase the sensitivity and specificity of color Doppler scanning.[5] The use of contrast agents markedly improved visualisation of the intratumoural vascular architecture (today similar images are obtained with conventional Doppler and accurate technique).

Using the presence of vascularity as criterion for malignancy, Moon et al.[6] found an increase in sensitivity (36% to 95%), positive and negative predictive values, but a reduction in specificity (86% to 79%) due to the hypervascularity of some benign lesions. Weind et al.[7] had already demonstrated an overlapping in the microvessel distribution between carcinomas and fibroadenomas. Ellis,[8] revaluating their results, pointed out that the higher was the grade of tumour in their series the higher the distribution ratio and that fibroadenomas and grade I tumours had no substantial difference in vascular distribution. These results confirm that frequently there is little functional difference between low-grade invasive tumours and benign tumours.

Schroeder et al.[9] have compared the different published studies with unenhanced and enhanced colour Doppler and found that the diagnostic accuracy has improved by contrast enhancement. This was mainly caused by better assessment of the vascular architecture and better depiction of the hypervascularity of malignancies.

Stuhrmann et al.[10] tested the possibility of improving the evaluation of benign breast lesions at Doppler sonography in patients scheduled for surgical resection. They measured the degree of enhancement provided by Levovist® (scored on an ad hoc 5-point scale), the number of tumour vessels, the time to maximal enhancement, and vascular morphology and course (classified as: avascular lesions; lesions with monomorphic or peripheral vessels; and lesions with irregular penetrating vessels). They observed more vessels and faster, stronger enhancement in malignant tumours compared to benign lesions, but the best distinction was afforded by vascular morphology and course, with a 90% sensitivity. However, the 81% specificity limited the clinical utility of this approach. Later reports confirmed that irregularities in the morphology and course of tumoural vessels may be highly suggestive of malignancies leading to a sensitivity of 95% and specificity of 83% or higher.[11,12] As reported by Zdemir et al.,[13] really only in the category BI-RADS™ 4 the combination of mammography-grey scale sonography and contrast-enhanced Doppler may achieve a higher specificity (71%) and positive predictive value (70%) than mammography-grey scale US (39% and 53%, respectively).

Contrast-enhanced Doppler was tested also in the difficult distinction between postoperative scar and tumour recurrence. Many studies have confirmed that contrast-en-

hanced hypervascularity may suggest recurrency.[9] Contrast-enhanced US was found to substantially reduce biopsy rates[14] and was suggested as an alternative to MRI, particularly in the first 18 postoperative months, when nodular scars or granulomas may also be vascularized with decreasing tendency parallel to the increasing age of the scar.[15]

Unfortunately most of the results originating from all the published series on breast masses did not correlate well with the microvessel density determined histopathologically, and so far this imaging modality has not translated into increased diagnostic accuracy. Since the breast is a relatively superficial organ, diagnostic biopsy is considered safe and is performed as a gold standard. Thus, there is less demand for an imaging technique to differentiate between malignant and benign lesions.

Doppler ultrasonography, even with contrast agents, enables visualization of blood vessels at the level of arterioles and venules, but does not reveal flow through the capillary bed. The relatively poor correlation between Doppler flow parameters and histopathological analysis of microvessel density confirms that Doppler US visualizes mainly tumoural macrovasculature. Therefore, there is need for an imaging modality that provides information about a lesion's microvasculature, because of the correlation with markers such as HER2 positively, lymphovascular invasion, metastatic disease and poorer prognosis.

The specificity and sensitivity of evaluating breast lesions with MRI is improved by performing quantitative imaging with the aid of contrast agents: malignant tumours show early enhancement followed by washout or plateau, whereas benign lesions exhibit a gradual increase in enhancement from early to late phases. To determine if this phenomenon is also observed during dynamic contrast-enhanced ultrasonography, Huber et al.[15] studied 47 patients with breast lesions and measured colour pixel density on Doppler US for 3 minutes after injection of Levovist®. They reported a shorter time to peak enhancement for carcinoma than for benign tumours. Different time-intensity curves have been found for carcinomas, fibroadenomas and scars.[1] Focal inflammations, due to their markedly increased vascularity, showed the same curves of malignancies. But the wash-out behaviour, although different, was adversely influenced by the continuous bubble destruction induced by the high US mechanical pressure.

Ultrasonography of the breast with new-generation contrast agents

New contrast agents are less fragile and allow use of specific softwares that reveal the perfusional flow even in the smallest vessels.[17]

Actual experience is based on the use of a blood-pool echo contrast agent. SonoVue® (Bracco, Milan, Italy) consists of microbubbles containing sulphur-hexafluoride (SF6) and encapsulated by a flexible phospholipid shell. These microbubbles have a mean diameter of 2.5 μm, with 99% smaller than 11 μm, allowing a free passage of capillaries but keeping the agent within the vascular lumen (intravascular tracer).

The microbubble suspension contains 8 μl/ml SF6 gas. The best results in the breast are obtained with bolus injections of 4.8 ml administered intravenously through a 3 ways connector, followed by an injection of 5 ml saline solution for flushing.

Due to the flexibility of the microbubbles phospholipidic shell the reflectivity of SonoVue® is very high. This results in a strong echo enhancement. Due to the poor solubility and diffusivity of SF6 this agent is also highly resistant to pressure.

Depending on the frequency and amplitude (Mechanical Index - MI) of the ultrasound wave, SonoVue® microbubbles may reflect the incident wave repeatedly without being altered (low MI continuous imaging).

The reflected wave contains harmonic frequency components caused by the non-linear bubble oscillations. Because the microbubbles are very flexible significant harmonic response is obtained even at very low MI.

Although harmonics are also generated during propagation of ultrasound waves in tissues, SonoVue® microbubbles generate echoes that are considerably larger than tissue echoes at harmonic frequencies. Contrast -specific imaging modes have been developed in order to accurately discriminate between the harmonic response from microbubbles and the response from tissue.

This results in perfusional images of the tumoural microcirculation based only on the microbubbles response. Microvascular blood velocities on the order of 0.1-10 mm/sec that cannot be detected with conventional Doppler methods can be demonstrated with this technique.

Actual experience is based on the use of Contrast Tuned Imaging (CNTi™) that is a low MI technique proposed by Esaote (Genoa, Italy) in which the fundamental echo is filtered out and only the second harmonic echo is detected by the US probe. The best perfusional imaging in the breast is obtained with MI values between 0.1 and 0.08, without reducing too much the field of view to avoid superficial artefacts and with the focal zone positioned just behind the deeper lesion margin. Perfusion is seen as an area of enhancement on the background of a nearly absent tissue signal and with minimal microbubble destruction. The resolution is rather poor in harmonic mode, and may be problematic for detecting small lesions.

Linear hyperechoic structures, like ligaments, often act as reference structures to keep the right scanning position.

CNTi™ has the capability to render the time-intensity curves. The signal perfusion intensity is monitored over time in selected tumour regions of interest (ROIs) and plotted on a final graph. Curves can be filtered and normalized according to the baseline signal intensity in the selected ROIs.

A group of European physicians is participating in the multicentre project PUMEB 04-05 (Perfusion Ultrasound Multicenter European Breast study) to determine appropriate uses of low MI contrast tuned imaging in the evaluation of breast cancers. The group is led by myself and includes R. Chersevani, E. Cassano, A. Gambaro (Italy), J. Camps Herrero (Spain), S. Paebke (Germany) ad G. Ralleigh (United Kingdom). The clinical applications of contrast-enhanced US that are being evaluated in PUMEB 04-05 are described as follows.

Lesion characterisation

There is a major difference in the behaviour of the contrast agents that are used in MRI and US; therefore both the size of the enhanced area and the time-intensity curves may differ especially in the later phases.

Tumour angiogenesis is a sequential process. During the organization of tumour-associated capillary networks neovessels progressively acquire their distinctive structural and functional characteristics.[18] Their lining is formed by fenestrated endothelial cells limited by a discontinuous basement membrane; as a result the neoangiogenetic vessels are more permeable then the normal ones.

Vascular endothelial growth factor (VEGF) is the cytokine that directly stimulates endothelial cell division and migration; it strongly increases the permeability allowing the extravasation of plasma proteins and resulting in the formation of an extravascular gel conducive to neovascular growth.[19]

In contrast-enhanced MRI the actual tracers cross the tumour microvessels and extravasate in the extravascular tumoural space; this capability is responsible of the major capability of MRI to differentiate different angiogenetic properties and to assess changes in angiogenesis during neoadjuvant therapy.[20]

On the contrary the diameter of SonoVue® microbubbles keeps the agent within the vascular lumen (intravascular tracer). Therefore the area of the perfusion and the correlated time-intensity curves strictly correspond to the neoangiogenetic vascular bed, and not to the extravascular tumour space.

Some new characteristics issue from CNTi™ clinical use:

- Avascular lesions (adenosis, fibrotic changes, scars) do not exhibit internal perfusion;
- Fibroadenomas usually have only a peripheral rim of perfusion;
- Some fibroadenomas have a diffuse perfusion and a peripheral rim during the latest phases (75 sec and more);
- The perfused area in malignancies is always larger that the vascular area seen with contrast-enhanced Doppler. Cospicuity differs mainly in infiltrating tumours with acoustic shadowing and in lobular carcinomas growing without mass;
- Tumoural perfusion may be non homogeneous, mainly in larger or treated tumours;
- Tumoural perfusion slightly differs in the same patient with different injections; this might be related to the differences induced by the manual injection and/or the correlation with the cardiac cycle;
- Tumoural perfusion is lower in older patients (60 years and after);
- Time-to-peak is usually shorter for malignancies (20-25 secs) than for benign lesions (30 secs and more);
- Time-to-peak is slightly increased for in situ and low grade invasive carcinomas;
- Time-intensity curves in invasive tumours, probably due to the presence of important arteriovenous shunts, exhibit a very rapid wash-out;
- Time-intensity curves in benign lesions or in situ carcinomas have a longer plateau and/or a less steep gradient during the washout phase.

Many of these characteristics seem to correlate very well to the different vascular arrangements of breast pathologies. This is only a preliminary experience and must be supported by larger series of cases; but it gives an idea of the potentials of US perfusion imaging. No doubt that biopsies offer more reassuring informations but we must foresee if these possibilities will have an impact on some breast clinical and imaging problems, and the new therapies.

Evaluation of lesions first identified with MRI

Currently, MRI is the most sensitive technique for detecting breast cancer; although specificity is high, biopsy is still required for nonpalpable lesions evident only on MR images. Expertise to perform MRI-guided biopsy or localization presently exists only in few centers; moreover MRI-guided procedures are time consuming and a rate of technical failure of 20%.

MRI-detected lesions may be localized with "second-look" US to obtain additional information or to guide real time biopsy. LaTrenta et al.[21] identified 23% of 93 suspicious, nonpalpable and mammographically occult lesions with a median size of 0.9 mm. The likelihood of carcinoma was higher among lesions with a US correlate (43% carcinoma) than lesions without a US correlate (14% carcinoma). Conventional US, however, may be ineffective in locating the malignant lesion in patients who have multiple benign cysts or fibroadenomas.

With dynamic contrast-enhanced US, it may be easier to locate the malignant lesion on the basis of an enhancement time course similar to that observed at MRI. This application is important because it may permit accurate guidance for biopsy.

Detection of lymph node metastases as alternative to sentinel lymph node procedure

Today, most patients with breast cancer un-

dergo local resection or mastectomy, as well as axillary lymph node dissection if a sentinel lymph node (SLN) procedure has provided evidence of malignancy. This procedure involves biopsy and histopathological analysis of the first draining (sentinel) lymph node, identified by following the clearance through the lymphatic system of a radioactive or coloured dye injected into the breast near the tumour.

Use of the SLN procedure is justified by the knowledge that when the sentinel node is negative for malignancy, there is very low likelihood that the tumour has metastasized to the axillary nodes; in this case many surgical groups now avoid axillary dissection.

In general SLN is an accurate procedure, but pitfalls exist. Studies correlating the results of SLN biopsy with axillary dissection in more than 3.000 patients have shown that SLN biopsy has a technical success rate of 88%, sensitivity of 93%, and accuracy of 97%.[22] Veronesi et al.[23] have found 32% of positive SLNs in 516 patients with primary breast cancer in whom the tumour was less than or equal to 2 cm in diameter; in 34% the SLNs were seeded only by micrometastases (foci ≤ 2 mm in diameter).

Sonography can usually identify enlarged reactive or metastatic nodes. In vitro studies demonstrate that metastatic disease is often indicated by an enlarged and round shaped node, the absence of an echogenic hilum, a marginal bulging or a small hypoechoic area within the echogenic cortex.[24,25] Doppler studies show a reduced vascularity inside the metastatic deposits; in case of massive metastatic infiltration the remaining vessels are displaced at the periphery of the node.[26] Conventional US have a great potential; both specificity and positive predictive value are high.[27] US guided biopsy can confirm a positive diagnosis[28] and these patiens can be immediately scheduled for nodal dissection.

US actual resolution is within the range of macrometastases (3 mm or more); this situation is expected in around 20 to 25% of all the breast cancer patients.

Some new characteristics issue from CNTi™ clinical use:

- Normal or reactive cortex has always an intense, homogeneous perfusion;
- Marginal bulgings without lack of perfusion may reflect normal morhologic variability;
- In the early phase of metastatic seeding the node is highly reactive, with diffuse and homogeneous enhancement;
- CNTi™ has not enough resolution to depict micrometastases (≤ 2 mm in diameter) but small deposits larger than 3 mm are clearly seen as non perfused "black" areas not always predictable on the basis of conventional imaging and Doppler;
- In case of massive infiltration the perfused not involved area is always larger than shown with conventional imaging and Doppler;
- In case of enlarged nodes with Doppler massive vascularity the behaviour of the perfusion progression may suggest different pathologies.

Many imaging groups dealing with a large number of breast cancers have already appreciated the accuracy and the advantages offered by sonography in assessing the nodal status.[27] Nodes can be assessed in a very early phase and US can guide very precisely a needle in the suspicious areas.

Perfusion imaging offers an unique capability in picking up the metastatic areas in all the different nodal locations that may be involved by breast carcinoma. Small deposits, 3 mm and more, located in the normal cortex are easily discovered and are precisely assessed with biopsy. False positives may be related to small fibrotic changes or granulomas. In case of enlarged nodes that exhibit poor vascularity on conventional Doppler the needle is guided in the metastatic areas that are usually smaller than with conventional imaging. In other cases the intense but inhomogeneous speckled enhancement in the early ar-

terial phase that seems to be mostly related to lymphomas,[29] is accurate enough to readdress the patient.

Perfusion imaging actually increases the already high positive predictive value of US in nodal assessment. When a node is positive on US and biopsy the patient is scheduled for axillary dissection and a SLN procedure is avoided. This happens in around 20% of patients with breast cancer. Imaging impact is very high because of the reduced cost of the diagnostic procedure and the better scheduling of the operation room.

Monitoring the response of advanced breast cancers to neoadjuvant therapy

Advanced breast cancers (ABC) include local recurrence, disseminated disease or locally advanced breast cancer (LABC). In this last stage the tumour in the breast is usually more than 5 cm across or it has destroyed the superficial fascia and invaded the subcutaneous lymphatic network, or it has spread to the axillary nodes or to other nodes or tissues near the breast.

Neoadjuvant therapy includes standard cytotoxic and /or hormonal manipulation. About 75% of these LABC regress with cytotoxic treatment allowing surgery with disease free margins. In more than 50% of these patients there is no tumour left or only microscopic tumour.[30] In the responsive area cancer tissue is transformed to xanthogranulomatous lesion with the infiltrations of macrophages and lymphocytes.[4] It is replaced by myxomatous fibrous tissue and then by cicatricial tissue. The cases with a high proportion of intraductal component have lower response,[4] the larger number of residual cancer cells are found within the ducts and preserve their proliferative activity. In all the tumours there is a consistent reduction in mitotic activity and in global microvessel density. Complete response to neoadjuvant chemotherapy is documented also for axillary nodal metastases. Kuerer et al.[31] reported complete axillary conversion in 23% of patients. Arimappamagan et al.[32] found a complete response in 22% of patients; in 10% conversion was complete for both axilla and primary tumour.

The management of ABC is really an expanding field. Many trials are now going on to evaluate also the potentials of novel combinations or new cytotoxics like anthracyclines and taxanes, or the effects of monoclonal antibodies like excerptin. Future developments will include host response modifiers like agents which suppress angiogenesis.

The challenges for breast imaging lie in the ability to incorporate technologies to ensure both accurate staging and effective monitoring of tumour response.

Mammography and conventional US have limited efficiency; they usually measure the tumor response evaluating the changes of its diameter, morphology and echopattern. MRI seems to be the most accurate imaging modality.[33,34] The correlation between tumour diameter measured by histopathology and MRI is very high; a clear reduction in size is usually seen only after the third cycle. Size reduction is usually associated with a decrease of the contrast enhancement parameters.

MRI is not universally available. Optimisation of an ultrasonographic protocol to monitor treatment outcomes would be advantageous clinically and economically.

Huber et al.[35] have already documented an increased US efficiency when colour Doppler flow imaging is added to conventional US. A good efficiency has also proved for very short interval monitoring of the neoangiogenetic vascularity of inflammatory lesions undergoing antibiotic therapy.[5]

More recently Pollard et al.[36] have documented the potentials of a destruction-replenishment US technique in monitoring the antineoangiogenetic effects of therapy in rat models.

Preliminary experience with CNTi™ demonstrates that contrast-enhanced Dop-

pler may give false negative vascular patterns while perfusion imaging still registers important residual intratumoural vascularity.

Actually perfusion US must be considered as the only alternative to MRI; moreover it offers the possibility of guiding further biopsies on the residual areas. In the future, with the clinical introduction of new therapies, it will be very important to understand if monitoring should be restricted to the tumoural vessels or also the extravascular bed. This decision will determine the choice in favour of perfusion US or MRI.

Evaluation of microcalcification in DCIS

Patients with DCIS usually present with clinically occult screen-detected microcalcification, which is biopsied using stereotactic guidance. Stereotactic biopsy can significantly underestimate (by approximately 8-20%) the presence of invasive disease necessitating delayed axillary node sampling and multiple operations.[37,38]

Investigators have previously demonstrated that large clusters (>10 mm) of microcalcifications are visible with high frequency US.[5,39] In addition DCIS may manifest as a hypoechoic mass, acoustic shadowing and/or intraductal abnormality. Abnormal vascularity has previously been demonstrated using Power Doppler in areas of DCIS.[40]

Currently, areas of microcalcification are biopsied during lengthy stereotactic procedures. The ability to guide biopsy by contrast-enhanced US would render the procedure more comfortable for the patient and would permit clinicians to excise the most intensely vascularised lesions; this may translate into an improved detection of invasive foci within areas of DCIS. High-grade DCIS is associated with increased microvessel density next to the arm, negative ER and positive HER2 status, and poor prognosis. Contrast-enhanced ultrasonography may contribute in the evaluation of these patients by stratifying lesions, describing tumour biology, and providing information regarding prognosis and the likelihood of success with systemic therapies. The use of SonoVue® during CNTi™ may be a useful adjunct to mammography and percutaneous biopsy in assessment of these lesions.

Future developments

Future developments are needed both for technology and contrast agents.

Probably large matrix transducers will help in acquire larger 3D volumes and CAD will increase the recognition of small enhancing lesions, therefore allowing helping screening procedures. But tracers must change in their properties, with both longer recirculating time and higher resolution without movement artefacts.

Two major interests are linked to US perfusion imaging.

First the capability to vehiculate drugs or other components within the microbubble. They will be targeted and linked to specific tissues; or they will be monitored up to the peak perfusion within the tumour, or even benign pathologies like inflammations. Fusion with molecular imaging and optical probes might be part of this future. The same transducer will use higher energies to destroy the microbubbles or to partially fragment their shells and to release the drug in the proper time. The same perfusion US imaging will monitor the effects of therapy.

Second improvement will be the capability of new contrast agents to enter the lymphatic stream and to fully replace radiotracers in the SLN procedure.

Some of these future applications are already working within ongoing projects on animal models.[41-47]

Assessing elasticity

During last years a new diagnostic strategy has emerged which uses US to assess tissues

differences in elasticity or stiffness. A weak repetitive movement of the transducer produces a feeble compression on breast tissues that are different in the way they can be compressed. Thus they produce a variable distortion in the backscattered waves that are collected during and post tissue compression. The computerized analysis of the distortion of the echo signal gives information related to the elasticity of normal components of breast tissue and pathological lesions. A way to differentiate them not related to sonographic parameters is than available and complementary to conventional real time US.[48,49]

Presently the elastosonographic unit is a conventional US unit with an elastographic modulus and the same transducer is used to perform both exams. An oval adaptor is applied on the top of the array in order to allow a perpendicular contact between array and skin. Strain data are converted into a colour scale imaging that is superimposed on B-mode imaging. Colours range from red, corresponding to soft tissue, to blue, the stiff one. Ex vivo specimen studies suggest that the degree of stiffness may correlate with the malignancy of the lesion. Benign lesions are less soft than breast tissue and cancer is very stiff. Moreover what seems to characterise breast carcinoma is the tendency to be visible on elastosonography on a wider area than that of B-mode.[50.51]

Actually no significant in vivo clinical experience with elastography is reported in the literature. We assessed in vivo elastographic behaviour of breast lesions and the potential application of this new technique. We evaluated 107 known breast lesions previously studied with B-mode and eventually with some other cases were benign controls unvaried for more than two years on US controls.

On the basis of the elastographic behaviour showed by the lesions, we distribute the patterns into a five scores classification: three-layered presentation of the lesion (score 1); totally soft lesion (score 2); soft and stiff mixed behaviour of the lesion (score 3); totally stiff lesion (score 4) and stiff area larger than that represented in B-mode exam (score 5). This classification is slightly different from the previous one reported by Ito et al.;[52] it seemed to us to be easier to apply to the kind of lesions we studied in our clinical setting. In the first score we classified 45 cysts (28 simple, 17 complicated), 3 fibroadenomas 1 granuloma. Six fibroadenomas, 3 mycrocyst-microcalcifications plaques and 1 scar were found in second score. Several different benign lesions, mostly fibroadenomas, fell in score 3. Two fibroadenomas (1 calcified), 1 carcinoma and 1 papilloma were put in score 4. Score 5 included mostly carcinomas (12) and 1 case of benign fibrosis.

The number of lesions is too small to allow a definite evaluation of the potential role of elastosonography. Nevertheless, apart the expected overlap seen in the intermediate scores, we found a sharp distribution of the lesions in score 1 and in score 5. These findings suggest the chance of distinguishing solid from liquid or simil-liquid lesions presenting with a score 1 pattern. The three-layered pattern is efficient especially in cases of complicated cysts, difficult to evaluate on B-mode exam.

A second interesting finding is the appearance of some lesions, subsequently proved to be cancers, as stiff larger areas compared with the size evaluated on B-mode.

Some aspects other aspects attracted our attention. First the size of some of the malignant lesions (less than one centimeter in diameter). Second, two cancers that presented as hyperechoic area or iso-hipoechoic area with strong posterior enhancement. The corresponding elastographic pattern was a clear blue stain. These cases suggest a complementary role of elastography, especially in cases that are not easy to manage with B-mode and colour Doppler.

In our experience the diagnostic limitations were represented by the overlap among multiple benign lesions with intermediate

elasticity patterns. Technical limitations were found in 4 cases of in which the breast was incompressible, because of a large haematoma or because the whole gland was extremely fibrous and firm. In one case the lesion lied in the lower part of an involved breast close to mammary sulcus and the scanning space was insufficient for a correct movement of the transducer.

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