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High-resolution ultrasound and power-Doppler - advances in pre-invasive diagnosis of solid breast lesions: our one-year experience

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The purpose of the study was to evaluate high-resolution ultrasound (HRUS) and power-Doppler (CDE) in the differentiation of malignant from benign solid breast lesions.

Patients and methods: HRUS and CDE examinations of solid breast masses were carried out in 25 women. Gray-scale criteria of malignancy and benignity were considered. The vessels of the lesion were classified as penetrant, peripheral and non-detectable with CDE. Final diagnose was obtained cytologically and/or with biopsy.

Results: HRUS detected more frequently irregularity of contours, heterogeneity and posterior attenuation than "classic" ultrasound. Lateral shadows in carcinomas were seen in a considerable number of cases, but this did not have any impact on the accuracy of diagnosis. HRUS facilitated the visualization of small carcinomas intraductal calcifications and papillomas. CDE detected flow in 15/25 lesions, of which 8 were malignant. Penetrant vessels were observed in 6/8 carcinomas and only in 2/17 benign changes;6/11 fibroadenomas were avascular, and 4/11 with peripheral vessels. In 3/6 other benign lesions, the flow was shown with CDE.

Conclusion: HRUS and CDE can successfully help in differentiation malignant from benign solid breast mass, and are a good adjunct to mammography and physical examination in the pre-invasive phase of diagnostic process.

Key words: breast neoplasms; ultrasonography, mammary; ultrasonography, Doppler; high-resolution ultrasound

Introduction

Breast sonography performed until few years ago with 5-7.5 MHz transducers was mainly confined to the differentiation between cystic and solid nature of the lesion and, to some extent, to characterizing solid mammary nodules.[1] High-frequency transducers (up to 13

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MHz) constructed in the last decade allow perfect spatial and contrast resolution, with the former being well lower than a millimeter. Therefore, non-palpable lesions of a few millimeters can be detected, whereas palpable ones more precisely characterized. This "high-resolution ultrasound" (high definition ultrasound, HRUS) was "born" approximately at the same time as the power-Doppler (color-Doppler energy, CDE) was introduced as a new mode of color-Doppler imaging. Although sonography has, as yet, an uncertain place among other differential diagnostic steps and is considered by many as a secondary technique,[2] HRUS and CDE available in most modern US machines enable preinvasive work-up of breast lesions with more sensitivity and specificity, sparing thus many unnecessary biopsies of benign lesions.

Tumor vascularization and power-Doppler

Each tumor larger than a few millimeters depends, during its growth, on the proliferation of new vessels in its periphery, and produces substances (angiogenetic factors) that stimulate neoangiogenesis.[3,4] In breast carcinomas, an increased number of the vessels is evident. Their diameter is enlarged. The structure of its wall, as well as the architecture are aberrant (AV-shunts, sinusoids), with a consecutive abnormal function.[5] The abnormality of such vessels is a clue to the features of Doppler signals gained from malignant breast masses, or from their close surroundings.[6]

B-mode, regardless of its high resolution, cannot visualize small intratumoral vessels because of their microscopic dimensions. The detection of such vessels on the basis of flow is thus a great advance, firstly, enabling a precise positioning of sample volume and acquisition of spectral flow signal and, secondly, imaging of their distribution and architecture, especially with CDE.

Although there are many inconsistencies and overlapping of results, and as malignancy cannot be ruled out only due to the absence of flow signal in the mass, the majority of authors agree that vessels are more numerous, and velocities higher in malignant than in benign masses. Some authors also report of the increase of pulsation indices.[6-8]

"Conventional" color-Doppler imaging (CDI, color-Doppler velocity, CDV) detects and displays blood velocity and its variance. Since 1993, a new color Doppler ultrasound technique has become available. It provides information of total amplitude or energy of signal, rather than velocity and direction of flow (Figure 1).

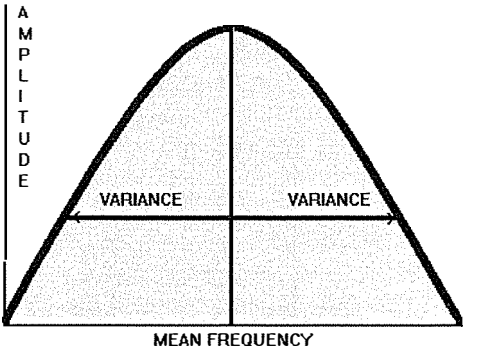

Figure 1. shows typical Doppler signal spectrum: variance is marked with arrows. Energy is proportional to the area under the curve under the curve, which is shown shadowed.

The new mode is termed power-Doppler, color Doppler energy (CDE), "ultrasound angiography" or amplitude color-Doppler sonography, which is the most exact term.[1] The flow is coded in hues of a single color, e.g. yellow, rather than blue and red (+green) as with standard CDI, and the color saturation of a pixel is related to the number of red blood cells in a unit of volume (voxel), regardless of their vector sum. When the resultant velocity is zero, as within the areas of capillaries randomly distributed in a voxel, related pixels on CDI will not be coded at all. On the contrary, CDE displays nearly all the amount

of circulating blood in these low-flow areas, which results in improved sensitivity.[9,10] Thus, directional averaging in each pixel is substituted with the summing of amplitudes, and randomly distributed tissue capillaries altogether contribute to the signal strength. Hence, an overwhelming "blush" in good vascularized organs, such as kidneys, will be apparent.[11] There is no angle-dependence of signal which is one of the basic principles (and limitations) of CDI.

Patients and methods

In the period from April to November 1997, we examined 25 women with breast lesions, aged 16 to 68 years (mean 42.2). The gray-scale morphology of the lesions was assessed with "classic 7.5 MHz" and high-resolution ultrasound machine, with their compressibility and mobility additionally evaluated, then CDI performed (searching for eventually high velocities), and finally power-Doppler (CDE) examination carried out. Some patients were seen because of breast complaints (palpable mass, discomfort, nipple discharge), others were routinely examined prior to initiation of hormone replacement therapy. All but one were out-patients. Every patient had undergone mammography, either in our hospital or in another institution, less than 30 days before ultrasound was recommended because of mammographically suspected abnormalities. Final diagnoses were obtained mainly by fine-needle aspiration cytology (FNAC) and, in 2 cases, by open surgical biopsy.

All ultrasound examinations were done and images checked by one breast radiologist (Z.B.), and occasionally reviewed by another (I.D.).

Scanning was carried out with three machines: General Electric-CGR RT 2800 equipped with linear-array 7.5 MHz transducer, and General Electric-Logic 400 MD and -Logic 500 MD ultrasonic units with multifrequent (7-13 MHz) transducers with a length of 38 and 50 mm, respectively. The latter two probes enable superior imaging in the near field, thus no distance silicone pad was required. It is especially suitable for radial examination technique, with satisfactory visualization of pyramidal architecture and ductal system. Color-Doppler velocity mode ("frequency mode") and color-Doppler energy mode ("amplitude mode", power-Doppler) are available in both.

Besides the optimization of standard gray-scale scanning parameters, special attention was given to the optimization of Doppler presets. Color Doppler velocity receiver gain was turned down until a few specks of color remained in the color box, i.e. background color "noise" was just suppressed. The color box was adjusted to include the lesion and some adjacent normal surrounding tissue. Thus defined region of interest was then scanned slowly until a persistent color signal was apparent. Power-Doppler gain was adjusted according to recommendations of Bude et al.[10-12] we would, however, like to stress that we did not strictly stick adhere to the articles referred to. We increased the gain until a clear and persistent color signal representing intralesional vessel appeared, or, if such was absent, until the background became almost uniformly colored.

The gray-scale criteria used in the evaluation of solid breast lesion were as follows: *Typical benign lesions* were smoothly marginalized, with linear borders and homogeneous fine-granulated echotexture, hypo- or hyperechoic, ovoid shaped with the long axis parallel to the chest wall (depth/width ratio, D/W>1), and with enhanced acoustic through transmission. Conversely, *typical malignant features* included ill-defined, spicular or lobulated margins, of round or ovoid shaped with the long axis perpendicular to the chest wall (D/W <1, "taller than wide"), hypoechoic and sometimes heterogeneous

echotexture, posterior acoustic shadowing, sometimes with obvious central microcalcifications, broken tissue planes or distorted breast architecture.[13,14] If any of malignant characteristic mentioned above was present, the lesion was considered malignant, until proven otherwise. When all criteria of benignity were strictly adhered to, the lesion was considered benign. Arbitrarily, when most of benign characteristics were present, the lesion was defined as "probably benign" or "indeterminate".[15]

Similar to the methodology of Raza and Baum,[16] the appearances of vascular pattern in the lesion were categorized into 3 groups: *(a) penetrating vessels* - one or more blood vessels arising at the edge of the lesion, coursing toward the center, with an irregular branching pattern, *(b) peripheral vessels* - one or more blood vessels of predominantly uniform appearance, parallel to the edge of a mass, linear or arcuate, without significant branching, and *(c) no detectable vessels* - no vessels were reliably detected, or, in other words, color signals were not so constant to distinguish them definitely from noise. Centrally located vessels were seen occasionally, but this vascular pattern was often indistinguishable from *(a)*, especially within small lesions, and therefore it was not included as a distinct category.

Doppler images were obtained in peak-systolic phase when the vascular signal was the most excessively enhanced, tracing vascular architecture to the largest extent.

All the examinations were performed with the lowest transmitted energies that allowed good visualization, as recommended in manuals. Scanning performed in the most erratic manner that was possible not to insonate the same tissue volume for a too long time. Medical Ethics Committee approved of the examinations referred to in this study.

Results

Of 25 solid nodules, 17 (68%) were benign and 8 (32%) were malignant. The negative-to-positive biopsy ratio was 2.13 : 1.

Table 1. shows morphologic features detected in our patients by HRUS. Certain characteristics were seen in larger percentage with HRUS and than were detectable with conventional sonography.[16,17]

CDE was performed on all masses included in this study. Six of 8 cancers showed penetrating vessels (Figure 2), one showed peripheral vessels, and in one case, no flow was detected. This latter one was a very small carcinoma (6 mm), which was diagnosed as carcinoma even with repeated FNAC. In the group of fibroadenomas, no detectable vessels were found in 6 cases. One or more peripheral vessels were seen in 4 cases and a penetrating vessel was found in one lesion. Six lesions were found to be benign breast tissue with some dysplastic changes. In 3 cases of this group, no significant flow was detected, in two cases, vessels were found at the periphery, and in one, circulation was observed arising from the intramammary lymph node.

Table 2 is a concise presentation of the results. We detected flow in the mass in 15/25 (60%) cases, while in 10/25 (40%) lesions no flow was found. Penetrating vessels were most frequent in carcinomas and in 2 benign masses; but not all cancers demonstrated vascularization. In benign lesions, the vessels, if detected, were situated predominantly peripherally. Sometimes, in a hyperechoic boundary, they remind of (pseudo) capsule. In 10/17 (59%) of nodules, no flow was detected with CDE, although they were all solid.

Table 1. Morphologic features detected with HRUS (bold figures) in comparison with "low frequency ultrasound". Some characteristics were seen in larger percentage with HRUS than with conventional sonography. These figures were marked with apostrophe (')

Diagnose %	Carcinomas	Fibroadenomas	Other benign lesions
Irregularity of contours	88 **88**	18 **36'**	33 **50'**
Inhomogeneity	75 **88'**	18 **27'**	33 **67'**
Posterior attenuation	13 **25'**	0 **18'**	0 **33'**
Lateral shadowing	13 **25'**	54 **54**	16 **16**

Table 2. CDE features of solid breast lesions

Vascular pattern	Penetrant vessels	Peripheral vesseles	Vessels undetected	Total
Carcinoma	6	1	1	8
Fibroadenoma	1	4	6	11
Other benign lesions	1	2	3	6
All diagnoses	8	7	10	**25**

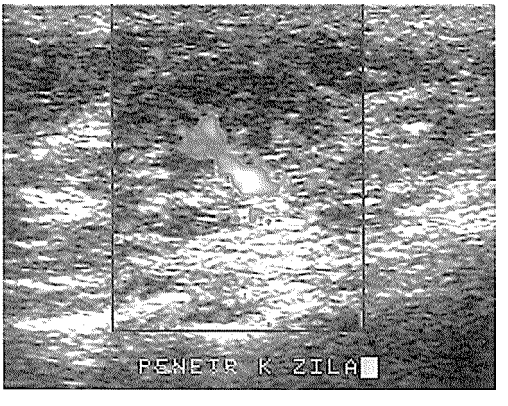

Figure 2. Penetrating vessels visualised by CDE.

Discussion

Considering the aggressiveness of aspiration tissue-sampling techniques (FNAC, core-biopsy) and open surgical biopsy as well as their costs, additional characteristics differentiating between benign and malignant lesions that can be detected in the pre-invasive phase of diagnostic process, could eliminate some financial load and patientsę sufferings. If negative predictive values (NPV) for malignant characteristics of the mass were high enough to substantiate recommendations for surveillance rather than biopsy, ultrasound would become a more capable tool in diagnostics, not restricted to distinguish only cystic from solid. Stavros et al.[15] classified prospectively 750 solid breast lesions as benign, indeterminate, or malignant using gray-scale sonography criteria, and calculated a NPV of 99.5% for malignancy. This is unexpectedly an encouraging result in spite of using state-of-the-art equipment and strict diagnostic criteria for benign masses; nevertheless, corroboration by other investigators is still required. The advantages of HRUS are undoubtedly proved [16,17] and our experiences are very similar.

In our material, we detected irregularity of contours as a typical sign of malignancy[15] in a larger number of carcinomas than other authors who employed low-frequency probes.[16,17] As the spiculation is a sign with very high positive predictive value (PPV) for malignancy,[15] its accurate sonographic disclosing is of great value. This is particularly relevant in the dense breast where mammography may be of limited value in the evaluation of the mass. However, in a considerable

number of benign lesions, irregularity of contours was displayed more frequently than with low frequency probes. This may result in false positive results, especially when dealing with fibroadenomas. But, as they predominate in younger population group and are not so characteristic for malignancy, neither is there any overt spiculation, but only microlobulation of the contour,[17] we prefer a non-aggressive (but not passive) approach, especially if no risk factors in patient's history are present.

We discovered *heterogeneity* in a large proportion of "other benign lesions", predominantly as a heterogeneous group that includes some regions of fibrocystic changes and areas of architectural distortion. Stavros et al. did not consider this feature as a separate category, but discussed about shadowing and punctate calcifications as signs of malignancy. Hence, we detected no clear (micro)calcifications in any masses analyzed: we might have not paid sufficient attention to this feature, probably also because microcalcifications were present in only one third of carcinomas. Undoubtedly, the detection of tiny calcifications has not been exclusively related to mammography; it can as reliably be done with HRUS, especially when situated in hypoechogenic mass. The lower their dimension, the lower the sensitivity for their detection.[15]

Posterior attenuation is the feature that has no decisive strength when dealing with breast tumors, unless confused with shadowing. It may serve as a clue for the diagnosis of fibrous dysplastic changes, which can explain some palpatory resistencies that are otherwise not suspected of malignancy. We were often faced with this feature, however, it was rather a practical difficulty in penetrating to deeper parts of the voluminous breasts than a reliable diagnostic sign.

Lateral shadowing was earlier referred to as a sign supporting benign diagnosis (fibroadenoma), but we detected it also in malignant tumors, and it was often asymmetric. The detection of this considerably unspecific sign is not significantly influenced by HRUS, and Stavros at al. did not even point it.[15]

Precise imaging of the ductal system is one of the leading advantages of HRUS. Although fairly time-consuming and of limited accuracy, when scrutinizingly performed radially, HRUS may compete with galactography/ductography at least in its lack of contrast agent and invasiveness. On the other hand, it may be of valuable help in the characterization of an intraductal lesion detected by the latter. Thus, it is possible to detect primary intraductal growth as well as *duct extension* of proliferative process within or/and around the lumen which courses toward the nipple. This was to a very limited extent also possible with low-frequency US. The frequencies between 10-13 MHz are optimal for this task. Moreover, scrutinize scanning, with an optimal focus adjustment, may reveal small intraductal papillomas, microcalcifications, and other intraductal masses with a possibility of precise needle guidance. In some cases, an intraductal location of calcification detected by HRUS, without presence of solid mass may be a decisive factor to consider them rather benign than suspected of malignancy. From our experience it is obvious that we should be cautious not to overestimate the significance of intraductal masses because, in many cases, they were proved to be an insignificant detritus, sites of atypical duct branching or just a tortuous duct seen in the scanned plane, as if the mass was contained within it. This may nullify advantages of HRUS by provoking many false positives resulting in additional FNACs or biopsies. When ductography cannot be obviated, the ducts dilated with contrast agent are better visualized with HRUS, and the lesion then punctured.[18]

We believe that the probe length of 38 mm, although adequate for scanning the subareolar region and axilla, may be too small for

the radial scanning technique of the breast, because of insufficient orientation in lobar/ductal anatomy; we therefore suggest a probe footprint of 50 mm as ideal for this task.

Until recently, investigations in the field of Doppler spectral analysis have not yielded unequivocal criteria for distinguishing malignant from benign solid breast lesions.[6-8] Cosgrove et al.[18] used a semiquantitative scoring system involving analysis of an average number of vessels per square centimeter and average density of color pixels. Although they found color Doppler signals in 98% of cancers, they did not prove correlation of color Doppler scores with the conventional prognostic indicators such as lymph node status or survival.[19] Birdwell et al. employing power Doppler used similar methodology.[20] They characterized breast masses with <10%, 10-25%, 25-50% and >50% of flow in a scanned area as avascular. They concluded that the presence of color in a solid breast mass was a non-specific finding, and that assessing of the extent of vascularity appears to be of limited value in the evaluation of solid breast masses. The authors found approximately equal numbers of malignant and benign masses among avascular lesions, and a quarter of malignant masses showed no color flow, although a sensitive method (CDE) was used. In their material, however, there was a significant number of small carcinomas as well as large fibroadenomas. The theory of the prevascular phase in tumor growth may explain the small amount of detected blood flow in the invasive carcinomas smaller than 2 cm, as well as good vascularity in large fibroadenomas.[21-22] We can assume that the presence of acoustic shadowing may limit the acquisition of Doppler signal and may have accounted for the avascular assessment of carcinomas with surrounding fibrosis as the dominant morphologic feature.

We studied the morphology and the pattern of distribution of vessels within the mass in an attempt to find the characteristics of malignant and benign lesions. In our study, carcinomas predominantly had penetrating vessels. Benign lesions had no detectable vessels in 59% of cases (cysts were excluded from our material) or had vessels around the periphery of the mass. In fibroadenomas vessels, if detected, were situated mainly in the peripheral parts. Sometimes, in a hyperechoic boundary, they looked like (pseudo)capsules. In one larger fibroadenoma (34 mm), an overt penetrating circulation (with a borderline spectral finding) was shown, and in one palpable intramammary lymph node with a diameter of 1 cm, hilar vascular pattern, which was categorized as "penetrant", was depicted. Later, FNA revealed the real nature of the mass, and retrospectively, when reviewing MOD recordings, we concluded that the vessel that we describe as "penetrant" was, in fact, a normal hilar vessel of the reactive lymph node. Unfortunately, we did analyze Doppler spectra in this case. In our work, we did not strictly analyze the morphology of the vessels, but in some carcinomas an examiner experienced in angiography would be amazed at a glance of a chaotic and irregularly branched vessels. The morphology was especially apparent when an individual vessel was kept well extended through the scanned plane, and the gain decreased so as to prevent the leakage of the color out of the lumen of the vessel. Such tortuous vessels depicted by standard color Doppler would be fairly confusing because of inconstant angle of insonation, and sometimes aliasing, and because of power Doppler homogeneous coding. Also, slow flow just near the wall was not eliminated and the lumen was filled with color in its real width.

We detected the flow in the mass in 15/25 (60%) cases, while in 10/25 (40%) lesions, no detectable flow was found. In comparison to some recent studies,[20] there was a considerable number of vascular lesions. Possibly, we were too rigid in eliminating some flow sig-

nals, assuming that they were related to noise. We might have falsely extended our experiences with classic color Doppler, and in some situations, decreased the gain too much. Perception of weak tiny signals of flow through an overwhelming homogenous color may sometimes be exhausting; we therefore preferred to avoid it. Another possible reason may be the attenuation of the ultrasonic beam by some lesions with abundant fibrosis, which obscure the acquisition of Doppler signal.

As we had no strict criteria to differ peripheral from penetrating vessel, we put some lesions with strong signals, even just beneath the capsule, in the latter group to avoid false negative result which we consider more dangerous than false positive one.

Motion artifacts were strong near the heart, especially when the breast was very small, and lesions situated deep close to the thoracic wall. Some patients were even unable of breathholding, or were also anxious and restless, which made the examinations more difficult. The use of ultrasonic contrast agent would theoretically help to overcome this problem, enabling the utilization of lower gain and higher pulse repetition frequency, but cost/benefit ratio remain questionable. Nevertheless, careful and patient scanning is, in the majority of cases, satisfactory to obtain images of acceptable quality.

In many centers of our country and also elsewhere, HRUS and CDE, if available, should be applied prior to FNA or biopsy, in order to further characterize the undeterminate solid lesion and to increase the specificity of the diagnostic process. It must be emphasized that this excellent sonographic technique, including radial technique, with the best scanners and transducers, as well as strict observing of relevant criteria for benign lesions, is highly recommended. With this approach, the population with benign solid breast lesions that does not require invasive work-up, can be identified with considerable accuracy. This could result in improved care and reduction of patient's discomfort, morbidity and health care cost.

Conclusions

1. HRUS can successfully help to distinguish many benign from malignant solid nodules in the breast. The chance to detect some malignant feature in a lesion are better with the application of HRUS than with conventional, lower frequency probes.
2. Assessment of internal vascular architecture of the lesion is a new approach in Doppler analysis, different from spectral waveform analysis; it may possibly add new determinants of biological nature of breast lesions. Further prospective studies on larger patient population are required.
3. When combined with, and in addition to mammography and clinical examination, HRUS and CDE increase accuracy of preinvasive differentiation of solid breast nodules.

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