MORPHOLOGIC ASSESSMENT OF BREAST TUMORS USING COLOR DOPPLER US

Ei Ueno¹, Eriko Tohno¹, Hiroko Tsunoda-Shimizu²
and Isamu Morishima¹

¹ Institute of Clinical Medicine, University of Tsukuba
² Kinu Medical Association Hospital, Japan

Advances in technology has enable the use of Color Doppler to assess the morphology of breast tumors. We usually evaluate breast tumors according to: (1) vascularity, (2) pattern of vessel pathway, (3) regularity of pathway, and (4) color tone of the vessel.

(1) VASCULARITY

The vascularity of the tumor is semi quantitatively assessed as hypervascular, vascular, hypovascular, or avascular.

Although we are now attempting a quantitative evaluation of vascularity in cubic cm, counting Doppler signals, in general, the vascularity is subjectively evaluated by the examiner. Hypervascular and vascular represent malignant, while hypovascular and avascular tumors are regarded as benign.

(2) PATTERN OF VESSEL PATHWAY

The patterns of vessel pathways are differ according to the breast disease. Four patterns are distinguished.

(i) Plunging

In the plunging pattern, where afferent vessels follow a direct pathway into the tumor, as the carcinoma infiltrates and involves the surrounding tissues, drawing them into itself, a specific finding for carcinoma is that the vessels enter the tumor at an angle of approximately 90 degrees from the tangent plane.
(ii) Surrounding marginal artery

In this pattern, the vessel runs along the surface of the tumor, since arteries associated with an expansive growth, such as a fibroadenoma, are pushed out of the tumor mass by itself. The feeding artery enters the tumor indirectly. We call this artery the surrounding marginal artery.

(iii) Penetrating artery

Sometime, an artery penetrating the tumor is observed on color flow imaging. This pattern results from the existing artery being encased by carcinoma, and is not neovascularization; therefore, this pattern permits the diagnosis of carcinoma.

The following arteries are judged to be the penetrating type as well:

- Blue color arteries seen on the deep side of the tumor (efferent arteries)
- Red color arteries seen on the superficial side of the tumor (efferent arteries)
(iv) Spotty Color
In this pattern, Doppler signals are recognized only as spotty color, not as linear imaging. Since the vessel pathway of a benign tumor is regular, the signals are hard to show a spotty pattern. A multiple spotty pattern indicates malignancy.

(3) REGULARITY OF PATHWAY
The pathway of vessels in malignant and benign tumor differs. In the malignant tumor, the pathway is tortuous, whereas in the benign tumor, the pathway to the tumor mass is straight.

| Straight | Tortuous |

(4) COLOR TONE OF VESSEL
The color tone of the malignant tumor of vessel is variegated, with a mosaic pattern, while the color in the benign tumor vessel is a monotone.

| Mosaic   | Monotone |

There are three cause of mosaic pattern in carcinomas as follows:
(i) Aliasing

Aliasing, this is the main cause of the mosaic pattern in malignant tumors. As color Doppler equipment for superficial organs is set in the low-velocity mode, the aliasing phenomenon readily occurs in the scanning of a tumor that has a high-velocity flow, such as carcinoma; therefore, the mosaic pattern is seen in malignant tumors.

(ii) Tortuous vessel pathway

As the vessel pathway in carcinoma is tortuous, Doppler signals fluctuate, even if the flow velocity is constant.

(iii) Fluctuation of the inside diameter of the vessel

The inside diameter of the vessel is subject to the influence of invasion and compression, and thus fluctuates. This fluctuation causes various flow velocities in the tumor.

Summary

The color Doppler diagnostic criteria of for breast tumors are summarized in Table 1.

<table>
<thead>
<tr>
<th>VASCULARITY</th>
<th>VESSEL PATTERN</th>
<th>REGULARITY</th>
<th>COLOR TONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALIGNANT</td>
<td>hypervascular</td>
<td>direct</td>
<td>tortuous</td>
</tr>
<tr>
<td></td>
<td>vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENIGN</td>
<td>hypovascular</td>
<td>indirect</td>
<td>straight</td>
</tr>
<tr>
<td></td>
<td>avascular</td>
<td>surrounding</td>
<td></td>
</tr>
</tbody>
</table>

References

NEW APPROACHES USING CONTRAST AGENTS FOR BREAST TUMOUR DIAGNOSIS

Jeffrey C. Bamber¹, Frank G. Füchsel²,³, Vijay Jayaram³, David S. Bell¹, Gerald Gui², Eleanor Moskovic², Nigel L. Bush¹, Jonathan Austin¹, Susannah Bloch¹, Ronald Adler⁴, Robert Eckersley³, David O. Cosgrove³

¹Joint Department of Physics, Institute of Cancer Research and Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, UK;
²Imaging Department and Breast Unit, Royal Marsden Hospital, London, UK;
³Imaging Department, Hammersmith Hospital and Imperial College, London, UK;
⁴Department of Ultrasound, Cornell University, New York, USA

Introduction

Early diagnosis of breast cancer is critical for its effective management. Mammography is the best screening technique and is now widely used for detection of suspicious changes. Both X-ray and conventional ultrasound mammography are used to characterise screening-detected and symptomatic breast lesions but their poor specificity necessitates many biopsies for lesions that prove to be benign. Improvements in ultrasound to reduce the benign biopsy rate would have a major impact on clinical practice by reducing unnecessary cost and trauma.

The blood vessels supplying malignant tumours are thought to have unique haemodynamic as well as morphological characteristics that are known to be useful in x-ray angiographic diagnosis. Tumour vascularity is a prognostic indicator that is independent of histological grading, hormone receptor status or clinico-pathological staging. Changes in tumour neovasculature produced by radio and chemotherapy are important determinants of clinical response while the relative resistance of hypoxic portions of tumours is a well understood limitation of radiotherapy. Chemotherapy regimens directly targeted to malignant neovascularization are being explored: if they come into clinical use, direct methods of following their effects non-invasively would be valuable.

Doppler methods and colour image quantification

Doppler ultrasound is an established means of studying vascular anatomy (using colour Doppler) and haemodynamics (using spectral Doppler). It has the important advantages of being non-invasive and relatively cheap, but only larger vessels can be interrogated and the haemodynamic analysis is limited to simple features such as the spectrum of blood velocities. Quantitative measurement is hindered in tumour studies because the orientation of the vessels is generally not known. Nevertheless a method that we developed for computer analysis of colour Doppler images has revealed features that improve the discrimination of benign and malignant solid breast masses [1,2].
Contrast agents

A large number of microbubble-based contrast agents have now been developed for ultrasound. Following intravenous injection, they are confined to the vascular bed and produce a marked increase in ultrasound blood signal intensity, even when diluted in the systemic circulation [3]. The enhancement of Doppler signals is striking and allows a more complete display of the vascularisation, especially with Doppler imaging. Our early studies suggested that Levovist ™ enhances the demonstration of the complex morphology of malignant neovascularization on colour Doppler scanning and that subjective observations may improve diagnostic accuracy [4]. These observations seem to have been born out in more recent work by others [5].

Transit-time analysis

An entirely new class of Doppler ultrasound features can be gleaned from analysing the time course of the signal enhancement during transit of an injected bolus of microbubbles, using them as tracers [4,5]. If the echogenicity of microbubble agents is proportional to their concentration, the data can be subjected to transit time analysis using techniques similar to those developed for radioisotope tracers [6] to give a number of dynamic features that may give unique insight into the pathophysiology of the neovascular circulation. To facilitate this the colour Doppler image quantitative analysis software that we developed was modified to quantitate Power Doppler, which maps the signal strength that is more directly related to contrast agent concentration.

A cannula is inserted into a vein in the antecubital fossa and, following one or more Levovist ™ injections, colour Doppler imaging with the probe held steady over the area of maximum vascularity within the lesion is video recorded until enhancement subsides, or at least for 5 minutes. The entire Doppler power sequence of full colour video images is then digitised at between 5 and 7 frames per second for quantitative analysis. The system developed for this work (CQ ™ , Kinetic Imaging Ltd., Liverpool, UK, kinetic@btinternet.com) is now commercially available.

To date about 70 patients have been assessed with repeat injections (2-4 injections) using this method. All patients underwent excisional surgery, which provided the histopathological diagnosis. Patient tolerance to the method was good and previous findings were confirmed in that subjectively there was value of contrast enhanced scanning in distinguishing between benign and malignant lesions. Early results for transit-time analysis suggested that features typical of malignancy might be a rapid wash-in, prolonged enhancement and a multiphasic wash-out pattern, whereas benign tumours were better characterised by the lack of a sharp initial rise, shorter enhancement duration and a monophasic wash-out pattern. We have now seen these features in only 50% of all lesions. In 50%, repeatability of quantitative features of transit-time curves was poor and appeared to be related to 3D vascular heterogeneity. Difficulties in the interpretation of functional analysis were mainly observed in non-invasive cancers, intermediate or low-grade
malignancies and hypovascular benign lesions. Overall degree of enhancement appeared to remain a useful feature.

**Three dimensional ultrasound and tumour vascular morphology**

Prognostic indices and measures of therapeutic response are important factors in the clinical decision making process for patients with malignant soft tissue masses, including breast cancer. Using CQ™ in a quantitative Doppler imaging study of various histologically proven soft tissue masses we have shown that measures of three dimensional vascular heterogeneity and mean displayed vascular volume increase with histological grade of the tumour. Based on the vascularity estimates, two distinct groups can be defined (P< 0.0001); one group corresponds to high-grade lesions in which tumour angiogenesis is expected to be important in predicting biologic behaviour. The method also seems to be very good at identifying metastatic lymph nodes, even before they have suspicious features in grey scale ultrasound, and for classifying reactive lymph nodes as benign due to their lower values for displayed vascular volume.

This work is currently being extended using (a) contrast agents to more completely depict the vascular morphology of tumours and (b) an electromagnetic space tracker to record the position and orientation of the probe as it is swept across the tumour volume. The segmentation provided by CQ™ enables us to volume render combined colour Doppler and grey scale anatomy of breast tumours and show that 3D presentation can greatly aid interpretation of complex vascular patterns. Current work aims to determine the degree to which 3D presentation facilitates more effective identification of vascular morphometric diagnostic criteria and whether this results in improved differentiation between benign and malignant masses.

**Microbubble signature imaging**

To obtain better flow information at the microvascular level and from other situations where there is no measurable Doppler shift, we are studying the physics of ultrasound scattering from microbubbles with a view to identifying unique bubble echo signatures. The hope is that such signatures may localise and quantify the contrast material, even in the absence of a Doppler shift due to blood flow. Imaging at the second harmonic has a similar objective but does not uniquely distinguish between echoes from bubbles and tissues. The consequences of success would include more complete imaging for a better 3-D feature analysis and quantification of blood volume in tumours (capillaries and other regions of very slow flow), improved tracking for transit-time analysis, and ability to study lymphatics and breast ducts.

Numerical solutions of the “Raleigh-Plesset” and other equations have been calculated to predict the characteristics of the scattered wave as a function of frequency, time, pressure amplitude and bubble radius. Early results have led us now to follow-up two potentially
promising signatures based on the observations that at moderate pressure amplitudes, excitation at a frequency of the second harmonic results in a strong non-linear response at the fundamental, whilst at higher pressures (similar to those used in diagnostic imaging) chaotic bubble oscillations are observed. Related work is underway elsewhere on other bubble signatures and new flow analysis methods, including methods that are associated with the destruction of bubbles in the ultrasound field (e.g. so-called stimulated acoustic emission or loss of correlation, and analysis of refill-kinetics) and with further development of the harmonic imaging process (e.g. so-called wide-band harmonic or pulse-inversion methods).

Conclusion

New ways of utilising contrast agents for providing information not previously available from an ultrasound examination are being explored. For transit-time analysis, the rate of flow image data acquisition is much higher than with previous isotope or magnetic resonance studies. In principle this should also allow a good signal-to-noise ratio to be achieved, so that a kinetic analysis may be applied to the time course of signal power at every position in the Doppler image. Thus high-resolution functional imaging studies without the use of ionising radiation are now possible with ultrasound. Early results however, indicate that the difficulty of maintaining a fixed scan plane within a heterogeneous vasculature volume currently acts to limit the reliability of Doppler intensity-time curves. Further improvement will probably require extension to 3D and application of methods for tissue tracking, with a corresponding sacrifice of temporal resolution. If these methods are successful, it will become possible to study spatial heterogeneity of perfusion characteristics in breast lesions. Future work will also include correlation of quantitative transit-time and morphometric features with histological features of the microvasculature, and the investigation of mathematical models of tumour vasculature for predicting the shapes of transit-time curves. Microbubble signature imaging has to yet undergo considerable development but should eventually substantially improve the quality of both functional and morphological analysis of breast tumour vasculature.

References


CONTRAST ENHANCEMENT OF BREAST WITH NODULAR AND DIFFUSE ALTERATIONS

Giorgio Rizzatto, Roberta Cherevani, Donatella Macorig, Rosaria Perrone, Piero Pellegrini.

Department of Diagnostic Imaging, General Hospital, Italy

Many sonographic patterns are non-specific, with a frequent overlap between benign and malignant findings. Morphology of the margins is considered the most reliable pattern to clarify the type of growth of a solid nodule: expansive or infiltrating. All the other patterns (shape, attenuation, homogeneity, calcifications) may not increase the diagnostic confidence; therefore it is increasing the use of fine needle aspirations or core biopsies performed under ultrasonic guidance.

Color flow mapping (CFM) and power Doppler did not change this behaviour. Early attempts used the criteria of the presence of flow within and around a nodule to indicate a tumor and the absence to indicate a benign lesion (3, 7, 9, 11). The results turn out to be conflicting; the main limitations described for CFM are that this technique is machine and operator dependent and that there is a large portion of benign breast nodules that exhibit some vascularity.

CFM sensitivity and specificity are still under investigation because of the persisting upgrade of this technology. More recent clinical use shows that high frequency CFM has not a definite role but helps to search for rapidly growing benign nodules, inflammatory lesions, tumors with benign patterns but with vascularity (figure 1), and multifocality; most of these possibilities are enhanced by the use of contrast media (2, 10).

Fig. 1. Medullary carcinoma with "benign" findings on conventional imaging. Irregular, sepiginous vessels after enhancement.
Preliminary reports on the use of ultrasound enhancers showed an increased vascularity for malignant lesions and suggested an increased diagnostic confidence (6,8). Increased vascularity has been also identified in benign nodules with higher adenomatous component (fig. 12); they usually grow rapidly. The aptitude to indicate benign nodules inclined to grow rapidly is important, considering the high rate of juvenile fibroadenomas larger than 1.5-2 cm or multiple. Earlier excision will result in saving troublesome controls and in more cosmetic surgery (10).

More recent papers confirm that the differential diagnosis of breast tumors is increased with enhanced Doppler analysis. Schroeder et al. (12) found a significant improvement in sensitivity and specificity (p<0.01). Typical signs of malignancy are irregular vessel calibers, serpiginous courses, penetration of the tumor's margin, and irregular reticular vascularization. The most specific parameter turns out to be the morphological pattern and course of vessels, with a sensitivity of 95% and a specificity of 83% (13). An increasing number of vascular poles is also a convincing finding (4). Quantitative assessment of different parameters increases the diagnostic confidence (1), and the possibility to have a more reliable method to monitor vascularity during and after therapy. After microbubble contrast agent injection, carcinomas and benign lesions behave differently in degree, onset, and duration of doppler enhancement.

Still there are many limits, and pathologic analysis remains the gold standard. The goal in using contrast media will be attained when they will be able to help in searching for cancer in dense or difficult breasts on mammography, or they will rate vascularity according to pathologic parameters and they will be accepted as the standard in monitoring the effects of therapy (figure 2).

Fig. 2. After the first cycle of adjuvant chemotherapy enhanced power Doppler clearly shows significant residual vascularity.
References


SENSITIVITY AND SPECIFICITY OF COLOR AND POWER DOPPLER US IN DIAGNOSIS OF BREAST TUMORS

Eriko Tohno 1 M.D., Ei Ueno 1 M.D.,
Hiroko Tsunoda-Shimizu 2 M.D. and Isamu Morishima 2 M.D.

1 Institute of Clinical Medicine, University of Tsukuba
2 Kinu Medical Association Hospital, Japan

Purpose
Following the development of ultrasound equipment, especially the improvement of Doppler sensitivity, the sensitivity and the specificity of color Doppler US in diagnosis of breast diseases have changed. The purpose of this study is to reassess those, using a state of the art machine.

Materials and Methods
The subjects of this study are the cases of breast diseases which were proven histologically either by operation, open biopsy or core biopsy, between June 1998 and December 1998 at Tsukuba University Hospital and had had ultrasound examination including color Doppler study prior to those. The materials include 42 malignant cases and 16 benign cases. The histological diagnoses are shown on the table 1.

Table. 1   Histological Diagnoses  (Total 58 Cases)

<table>
<thead>
<tr>
<th>MALIGNANT</th>
<th>BENIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma</td>
<td>Mastopathy</td>
</tr>
<tr>
<td>Medullary carcinomma</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>DCIS</td>
<td>Fibroadenoma</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>Intraductal papilloma</td>
</tr>
<tr>
<td>With predominant IDC</td>
<td>Phyllodes tumor</td>
</tr>
<tr>
<td>Syringomatous carcinoma</td>
<td>Normal breast tissue</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>42</td>
<td>16</td>
</tr>
</tbody>
</table>

The ultrasound examination was performed by LOGIQ 700 by General Electric Co. equipped with a high frequency transducer for the superficial organ. The color Doppler study was performed by both velocity and power modes in almost all cases and vascularity was assessed at the time of examination.
In this study we have summarized the vascularity according to the histological results, the sizes of the lesions and the behaviors of the posterior echoes.

**Results**
The vascularity was divided into four categories; avascular, hypovascular, vascular and hypervascular subjectively by the examiners. The numbers of the benign and malignant cases in each categories are shown on the fig.1.
All of the malignant cases had some vessels in or around the lesions and 78.5% of the lesions were hypervascular. In contrast, benign lesions were less vascular compared to the malignant lesions.
The vascularities according to the sizes of the lesions are shown in the fig.2 and 3.
Fig.4 shows the relationships of vascularity and histological diagnosis in benign cases.
In cases of the lesions, which formed masses, the lesions can be divided according to the posterior echoes into three; accentuating type (ACC type), intermediate type (INT type), and attenuating type (ATT type). The vascularities of malignant lesions in each type are shown in the fig 5.

**Discussion**
When Doppler study was first introduced in the diagnosis of breast diseases, the presence of vessels meant malignancy and absence meant benign diseases (1). Following the development of ultrasound equipment, especially by the improvement of Doppler sensitivity, it is now well recognized that benign diseases often appear to be vascular (2). Our study reconfirmed this. To evaluate the specificity, however, is difficult because we are now trying to avoid benign biopsies so the benign cases, which were biopsied, had somewhat unusual appearances in some aspects including Doppler results. But breast cancers are more vascular than benign diseases. And 100% sensitivity in our study means that avascular lesions could be followed up. Some authors tried to quantify vascularity (3,4), but it is not easy and takes some time. So we used subjective evaluation about vascularity of the lesions.
An interesting result was that in benign lesions no relation was found between the vascularities and the size of the lesions or the histological diagnosis although the number of each disease was quite limited.
Among malignant lesions vascularities of attenuating type tumors was slightly less than other types. This is probably because scirrhous type cancers were included in this type and they tend to encase the vessels.
**Conclusion**
The absence or presence of vessels on color Doppler images cannot be anymore used in differentiating between benign and malignant breast diseases. The size, behavior of posterior echoes and morphological features or use of contrast agents (5) should be considered.

**References**


