Assessment of breast lesions using Doppler with contrast agents

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Summary

Objective: To evaluate the use of contrast agents on ultrasound examination of breast lesions and to analyse the capacity of this technique to achieve a differential diagnosis of benign and malignant lesions, using as a pattern a histological study of the lesions.

Materials and Methods: Seventy-two women with suspected malignant breast lesions participated in this randomised prospective study, undergoing a colour Doppler ultrasound (US). The results of the study were measured before and after the use of US contrast agents and were compared with the ones obtained from the histological study of the pieces.

Results: Malignant breast tumours showed, when using US Doppler with contrast agent, a hypervascularity pattern in 78.1% of the cases. The predominant pattern in benign tumours was avascular (11 cases, 64.7%). The intensity of the signal in the first minute was intense in 43.7% or moderate in 40.6% of the cases with malignant tumours versus the benign tumours where no signal was registered in 64.7% of the cases. A marked increase in the sensitivity and the predictive negative value of the ultrasound signal was noted with the use of potentiating substances.

Conclusions: The use of contrast agents in colour Doppler US studies improve the differential diagnosis of benign and malignant breast lesions.

Key words: Breast; Doppler; Contrast agent.

Introduction

Colour Doppler ultrasound (US) is a technique that has recently been introduced as a diagnostic method for breast lesions. The first literature references date from 1990 [1].

The first Doppler equipment only detected blood flow in highly vascular areas; therefore initially it was thought that it could be used for the differential diagnosis of malignant lesions (highly vascular) and benign lesions (with scarce vascularity) [2].

Later on, the use of higher Doppler frequencies (6-7 Mhz) improved the sensitivity of the technique to detect slow flow in small vessels, with which many benign lesions also showed colour Doppler signals, not as a result of the presence of flow in a lesion but for a diagnostic criteria [1].

The advent of US contrast agents has introduced a new focus for the analysis of vascularization because they increase the ultrasonographic differentiation when substances with acoustic impedance are used [3].

The objective was to evaluate the use of contrast agents on ultrasound examination of breast lesions and to analyse the capacity of this technique to achieve a differential diagnosis of benign and malignant lesions, using as a pattern a histological study of the lesions.

Materials and Methods

A prospective study included 72 patients who were to be subjected to a breast colour Doppler for the study of: nodules, asymmetric densities, postsurgical scars (both from benign and malignant processes) that presented a pathological palpation during follow-up.

All patients underwent: 1) clinical exploration, mammography and conventional breast US, 2) colour Doppler breast US with and without contrast agent, 3) biopsy for anatomic pathological study.

The contrast agents used were Levograf* and Levovist* (both contain 1 g of granules, 999 mg of galactose and 1 g of palmitic acid) [4]. These are untimely microcrystalline suspensions for intravenous administration; for the concentration of 300 mg/ml, an intravenous bolus of 5-10 ml was administered.

The location of vessels in relation to the tumour (peripheric, penetrating and intratumoral), the number of vessels: avascular, hypovascular (1 vessel), vascular (2 or 3 vessels) and hypervascular (more than 5 vessels) and vessel morphology, the intensity of the signal per minute, at three minutes and at the end of the signal, and type of vascular signal: dotted, tortuous, shunt, or lineal were evaluated.

An anatomic pathological study of all the cases was performed.

Exclusion criteria: patients suffering from galactosemia, coagulation disorders, severe anaemia and cardiopathologies.

Results

Seventy-two patients, aged 34-86, were included in the study. The anatomic pathological study included: malignant lesions: 32 cases (44%); benign lesions: 17 cases (23%); scars from interventions of malignant neoplasias:

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21 cases (30%); scars from interventions of benign neoplasias: two cases (3%).

Clinical characteristics: Sixty-one cases with a palpable nodule (84.7%) and 11 cases with a non palpable nodule (15.3%) were studied.

Mammography characteristics: The mammographic image obtained was a nodule in 93.1% of the cases (67 cases), an assymetric image in 2.8% (2 cases) and an image without pathological findings in 4.2% of the cases (3 cases).

Ultrasound characteristics: The ultrasound examinations were: an image with suspiciously malignant nodule was obtained in 60 cases (83.3%) and in 12 cases (16.7%) a nodule type image with no malignant criteria.

Basal Doppler: In 10 cases (13.9%) vascularization was obtained in the study of flow through Doppler and lack of vascularization in 62 cases (86.1%).

Doppler/histological study: The Doppler study without contrast agent showed an increased vascularization in 25% (8 cases) of the malignant tumours against 11% (2 cases) of the benign tumours (Table 1).

When the scars resulting from the extirpation of a neoplasia were studied, no cases were found where neovascularization was detected, independently from the benign or malignant nature of the neoplasia previously removed.

Vascularization after using a contrast agent: When vascularization of lesions was studied using potentiating substances the following results were found: 38 cases (52.7%) showed an increase in vascularization in comparison with the ten cases (13.9%) where no potentiating substances were used. In 34 cases (47.3%) no increase in vascularization was found.

Vessel localization/US contrast agent: In 26 cases more than one vessel was found (36.1%), in 11 cases (15.3%) the localization of the vessels was in the periphery and in one case (14%) perforating vessels were found.

Vessel localization/histological study: In the Doppler study with a contrast agent, of malignant tumours a hypervascular pattern was patent in 78.1% of the cases (25 cases). Being the predominant pattern of benign tumours an avascular one (11 cases, 64.7%) (Table 2).

Table 1. — *Doppler/histological study.*

	Anatomical pathology				
	Malignant	Benign	Malignant Scar	Benign Scar	Total
Doppler					
With vascularization	8	2			10
Without vascularization	24	15	21	2	62
Total	32	17	21	2	72

Table 2. — *Vessel localization/histological study.*

	Anatomical pathology			
	Malignant	Benign	Malignant Scar	Benign Scar
Peripheral	6	5		
Perforating	1			
More than one	25	1		
No vessels		11	21	2
Total	32	17	21	2

The majority of vessels peripherally localized both in benign as well as in malignant lesions. The resulting scars of the extirpation of benign or malignant neoplasias did not show any colour signal during the study.

Vessel morphology/US contrast: The most frequent vessel morphology observed was lineal in nine cases (12.5%), being the dotted-like and the tortuous-shunt morphology less frequent (1 case of each, 1.4% each case).

Vessel morphology/histological study: the results are shown in Table 3.

US contrast agent at the first minute/anatomical pathology: Signal intensity in the first minute was intense in 43.7% (14 cases) and moderate in 40.6% (13 cases) of the malignant tumours versus benign tumours where no signal was registered in 64.7% (11 cases) (Table 4).

US contrast agent at three minutes/anatomical pathology: Signal intensity at three minutes was moderate in 43.7% of the cases and acute/intense in 34.3% (11 cases) of the cases corresponding with malignant tumours versus benign tumours where no signal was registered in 64.7% (11 cases) (Table 5).

US contrast agent: No signal was registered at four minutes after perfusion of the contrast agent in any of the cases of benign tumours. On the other hand in 31% (10 cases) of the cases of malignant tumours a signal was still transmitted at six minutes, and at ten minutes two cases were found where the signal persisted (Table 6).

Diagnostic value of the test: Table 7.

A marked increase in the sensitivity and the negative predictive value was observed the the US signal of the colour Doppler study with the use of potentiating substances.

Table 3. — *Vessel morphology/histological study.*

	Anatomical pathology				
	Malignant	Benign	Malignant Scar	Benign Scar	Total
Dotted	1				1
Lineal	4	5			9
Tortuous-shunt	1				1
More than one	26	1			27
No vessels		11	21	2	34
Total	32	17	21	2	72

Table 4. — *US contrast agent first minute/anatomical pathology.*

	Anatomical pathology	
Signal intensity 1 minute	Malignant	Benign
Light	5	2
Moderate	13	4
Acute	14	
No signal		11
Total	32	17

Table 5. — *US contrast agent at 3 minutes/anatomical pathology.*

	Anatomical pathology	
Signal intensity at 3 minutes	Malignant	Benign
Light	7	4
Moderate	14	2
Acute	11	
No signal		11
Total	32	17

Table 6. — *US contrast agent.*

Wash	Anatomical pathology Malignant	Benign
3 minutes	1	2
4 minutes	5	4
5 minutes	10	
6 minutes	8	
7 minutes	4	
8 minutes	2	
10 minutes	2	

Table 7. — *Diagnostic value of the test.*

	Sensitivity	Specificity	PPV	NPV
Without contrast	25%	88%	80%	38.50%
First minute	100%	85%	84%	100%
Third minute	100%	65%	84%	100%

Discussion

The growth of malignant neoplasias, both primary as well as secondary, requires vascularity. This vascularity occurs in an anomalous, unorganised way with a faulty angiogenesis in which the medium or muscular layer of the vessels is missing. These vessels penetrate in the tumoral tissue mass in a radial form establishing contact between the arteries or even between venous and arterial blood (shunt). This results in an increase speed of the flow [5].

At the beginning of cellular multiplication, a slow growth, avascular, non-metastasizing phase is recognised. However from a cellular volume of 10 x 6 cells the vascular contribution becomes indispensable as well as part of the tumour's biology allowing the neoplastic cells to penetrate in the circulation. This vascular phase is manifested by rapid tumoral growth and the capacity to result in metastasis. Angiogenesis is fundamental both at the end as well as at the beginning of the metastatic cascade; at the beginning to allow the access of neoplastic cells to the blood flow which will facilitate their dissemination, and at the end, when a cell has survived the extravasation and has colonised the distant tissues to reinitiate the growth of new secondary tumours.

Since the initiation of the clinical use of Doppler, there has been an attempt to find signals which will allow the differential diagnosis between benign and malignant tumours [6, 7]. In order to obtain this information the colour signal is searched and analysed: localization of vessels in relation to the tumour, number of vessels and type of vascular signal. With these findings, differences can be established between benign and malignant tumours. The use of US contrast agents will facilitate early detection of tumours as well as characterization of the neoplasia. The theoretical basis is to produce a strong acoustic interphase with a reflection coefficient which will emphasize the echocontrast [8, 9].

These substances were initially used to evaluate the right cardiac images hemodynamically and then the use extended to other fields such as the study of tumoral vascularization. These prominent signal agents are introduced intravenously, do not cause undesirable side-effects and should have adequate stability for the time the study lasts. The two types of prominent signal agents used are: chemical $-ClO_4$ and the bubble contrasts (gas microbubbles, galactose microparticles and water suspensions).

The ultrasound applied to the organic tissues make them vibrate and produce heat, in the case of microbubbles vibrations are produced, as well as variations in their diameters (as a result of compensation and expansion), which will induce an oscillating frequency and harmonic frequency [10]. The magnification of the US signals is due primarily to the micrometric air bubbles which originate after the suspension of the granules in water. The palmitic acid confers stability to the bubbles for several minutes while they circulate, and also in the subsequent vascular channel, before they dissolve in the blood stream [10, 11].

Conclusions

The use of US contrast agents improves the differential diagnosis of benign and malignant lesions. This statement is supported by the findings of our study, which corroborate the literature reviewed for this burpuse [4, 6, 10, 12] such as:

First, all malignant tumours have their vascularity augmented. This enables the punction to be guided in suspicious nodules of mixed ultrasonographic differentiation.

Second, in the study of benign lesions with US contrast agents no significant differences were found between the evaluation pre- and post-injection of a contrast agent, while in the malignant tumours the number of vessels linked to the tumour increased considerably, as well as their tortousity and number of fistulas.

Third, the scars are always avascular. Therefore this methodology allows a differential diagnosis between the scar and a local relapse.

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