

Videodensitometry in the Examination of Focal Breast Lesions after Injection of an Ultrasound Contrast Agent

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Abstract. *Background:* The present investigation aimed at assessing the possibility of distinguishing between malignant and benign breast lesions by measuring the signal intensity in vessels of the suspect lesions over time after administration of the ultrasound contrast agent Levovist[®]. *Materials and Methods:* Levovist[®] was administered intravenously to 21 patients with breast cancer and 12 patients with a benign breast lesion. In the subsequent ultrasound investigation (Color Power Angiography) the resulting increase in brightness over time in the vessels of the lesions was measured using the videodensitometry method. From the calculated time-brightness curves, the time to maximum brightness (T_{max}), time to 90% of maximum brightness ($T_{90\%}$), maximum brightness and other time and brightness parameters were determined. The data were analyzed by means of the Mann-Whitney-Wilcoxon test. Additionally, the sensitivity and specificity were calculated for a sequence of cut-off levels for $T_{90\%}$, T_{max} maximum brightness and wash-in wash-out parameters. *Results:* The differences between the benign and the malignant lesions for the parameters T_{max} and $T_{90\%}$ were statistically significant. The malignant foci showed a significantly more rapid in-flow of the contrast agent ($p=0.006$) than the benign lesions. The wash-in wash-out time for Levovist[®] was significantly shorter for the malignant lesions than for the benign lesions ($p=0.02$). The time difference in attaining maximum brightness was not significant ($p=0.14$). The

specificity and sensitivity made a more precise differentiation between benign and malignant tumors possible. *Conclusion:* The use of a contrast agent in Doppler ultrasound enhances the diagnostic reliability in distinguishing between malignant and benign lesions, justifying the use of a contrast agent with a high specificity (92%) such as Levovist[®]. However, invasive pre-operative methods such as punch biopsy are not, thereby, rendered unnecessary. It is possible that the combination of Levovist[®] and videodensitometry will make it possible to increase the specificity of breast cancer diagnosis.

Breast ultrasound is a standard procedure for the differential diagnosis of breast cancer. For more than 20 years, Doppler sonography has been used as a method to characterize the blood flow in tumor vessels. The goal is to obviate biopsy as a future diagnostic procedure, by achieving a reliable diagnosis through improved sonographic techniques.

Based on the development of color Doppler, tumor angiogenesis can be observed by means of sonography. Additional methods of imaging, among them the so-called "power Doppler", were developed, which were able to record not only the frequency, but also the intensity of the signal from which conclusions could be drawn about the blood flow (1-4). Contrast agents ("signal boosters") were then developed, which were designed to enhance the effectiveness of these techniques (5, 6-9) by strengthening the ultrasound signal.

One of these signal boosters is Levovist[®]: Levovist[®] was registered in Germany in 1996 as an echocontrast agent which survives transit through the lungs and has become a necessary agent for ultrasound contrast medium (USCM)-supported sonographic examination of tumor vascularization (10-13). Unfortunately, Doppler sonography does not permit quantitative measurements, making the evaluation of the images highly subjective (8). Color Doppler/Doppler duplex are preferable, as it permits objective measurement.

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Table I. *Histological classification of the malignant breast lesions.*

TNM classification	No.	UICC classification	No.
pT1	7	I	7
pT2	2	IIa	1
pT3	3	IIb	1
pT4b	4	IIIa	3
pT4d	6	IIIb	10
pN0		8	
pN1		14	
Invasive ductal		20	
Invasive lobular		2	

(n=22; mean age (years)=58.1±11.5)

Videodensitometry offers the possibility of increased objectivities quantification, since the wash-in and wash-out of the contrast medium can be measured and plotted as a time-brightness (signal intensity) curve, which yields information about the blood flow in tumor vessels (14, 15).

In 1997, the Charité University in Berlin, Germany, began using the contrast agent Levovist[®], with promising results (10). The aim of the present study was to find out whether computer-aided videodensitometry after Levovist[®] injection would achieve more reliable discrimination between malignant and benign breast lesions.

Materials and Methods

Thirty-three patients with breast lesions were examined. The criterion of suitability was evidence of blood vessels in the lesions by means of power Doppler. None of the patients suffered from hypertension or diseases of the arterial vessels. Twenty-seven of the patients' breast lesions were palpable; a non-palpable lesion was detected in 6 patients. In all thirty-three patients, both mammography and breast ultrasound were performed.

Levovist[®] was injected following examination by means of videodensitometry. The imaged tissue was then extirpated for histological investigation. Histology showed 12 benign lesions; 21 patients were found to present with tumor (Tables I, II).

Ultrasound examination and the contrast agent. All examinations were performed using the ultrasound equipment (HDI 3000, ATL, Bothel, USA) with a wide-band linear transducer L10-5 (frequencies used: B-mode-scan, 10 MHz). Adjustment of the equipment for color imaging of the blood flow was carried out as follows: a pulse repetition frequency (PRF) of 700-1,000 Hz and a medium color filter (25-100 Hz) were selected. The color gain was adjusted so that the maximum brightness of the color signal outside the native vessels was in the lower range of the selected color map. Due to the special characteristics of the videodensitometer, the B-mode gain had to be turned down completely immediately before the Levovist[®] injection (Figure 1).

The ultrasound contrast agent Levovist[®] was then injected into the left cubital vein as a bolus (5-10 s) at a concentration of 300 mg/ml (7 ml solution).

Table II. *Histological classification of the benign breast lesions.*

Classification	No.
Fibroadenoma	3
Intracystic or intraductal papilloma	3
Mastitis nonpuerperalis	2
Fibrotic scar	1
Breast hyperplasia	2

(n=11; mean age (years)=47.6±12.4)

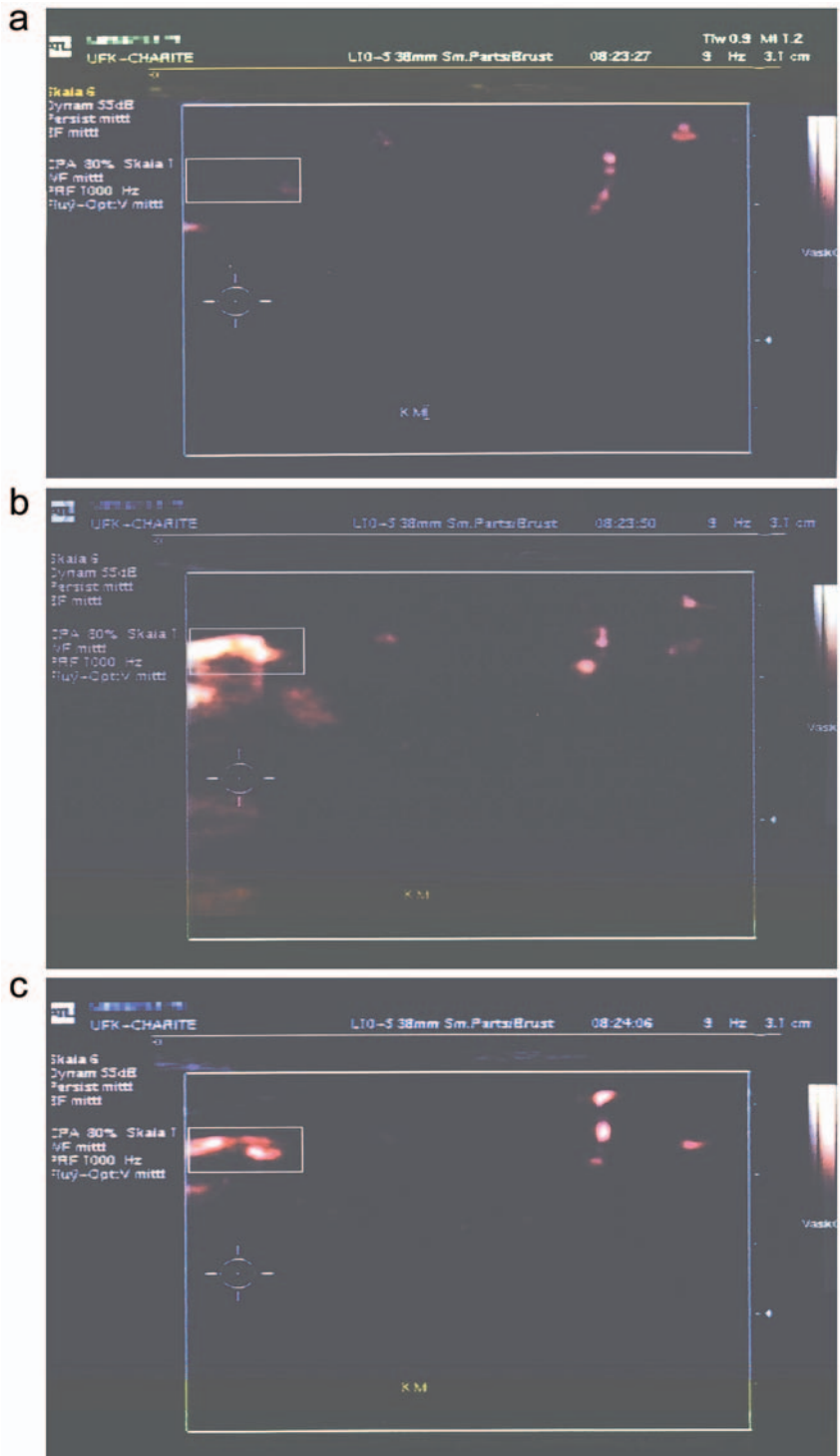
Videodensitometry. The entire investigation, including the enhancement resulting from the USCM was recorded on S-VHS video-tape. The videodensitometry of the video-tape was carried out by a doctor who had no knowledge of the histological results. The videodensitometer is based on a personal computer outfitted as follows: 33 MHz Intel'486 microprocessor, Dash 16 Videodigitizer board with an eight-bit greyscale (Keithley, USA). The digital data was analyzed by means of densitometry. The analysis was based on the following:

a) The additive color mixture procedure leads to a brighter or darker color depending on the relative weights of the individual color components. If all color components have the maximum value 255, the resulting color is white; if all colors have the minimum value of zero, the resulting color is black. The densitometry technique requires that the information-bearing pixels of the CPA (Color Power Angiography) signals be evaluated and separated from the non-information-bearing B-images. This means that the evaluation software has to have an algorithm for filtering the image information. To this end, our group developed a special application on the basis of the Game SDK (Software Development Kit) from Microsoft[®].

b) The grey color of the B-image always consists of equal proportions of red, green and blue (RGB) to filter out the color CPA-image from the B-image. This is done by setting a rectangle about the areas with relevant information (region of interest, ROI). It is only within this rectangle that the image information is filtered and evaluated.

c) The evaluation program counts the pixels and calculates the sum of all the RGB values within the ROI. The average brightness of a single pixel within the imaged area is then calculated from the sum of all the RGB values and the number of pixels. If a whole video sequence is analyzed in this manner, an ordered series of values for the average brightness is obtained. These values are then entered into a time-intensity graph to give a curve that shows the flow of information of one or several vessels over the period of observation. After administration of an ultrasound contrast agent, the vessel being investigated becomes brighter and the colored area larger (so-called "color blooming"). The number and the brightness of the information-bearing pixels increase, which leads to an increase in the average brightness, with the undesirable color blooming effect being minimized by use of the average brightness.

Measurements of the brightness were made within a rectangular ROI defined by the investigator during the time of the wash-in and wash-out of the contrast agent, over a period of at least 120 sec. After looking at the digitized video, the investigator placed the ROI as close as possible around a pixel area which had shown the effect of the contrast agent over an extended period of time and which was minimally disturbed by



Figures 1a-c. Videodensitometry of a breast cancer lesion stage IIb (pT3, pN1, G3 MO receptor positive).

movement artefacts. If breathing or other movements of the patient during the course of the investigation led the pulsation pixel area to "slip" out of the ROI, the ROI had to be enlarged or a different pixel area chosen.

The measured and calculated parameters were defined as follows (Figure 2):

a) Time parameters: $T_{10\%,1}$, time to reach 10% of the maximum brightness (left side of the peak); $T_{90\%,1}$, time to reach 90% of the

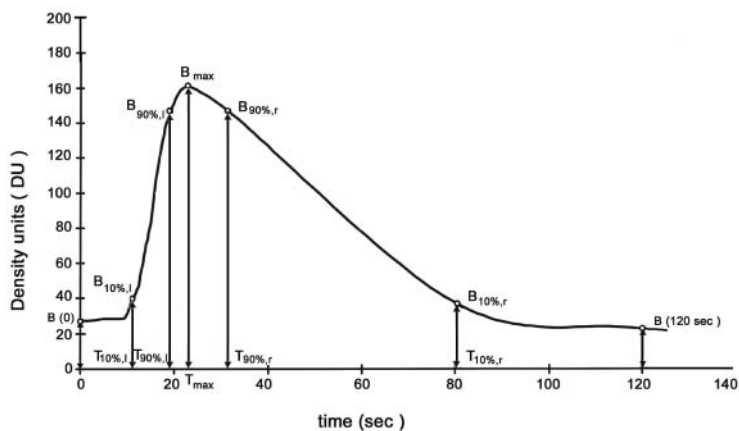


Figure 2. Time-brightness curve and definition of characteristic time and brightness parameters.

maximum brightness (left side of the peak); T_{max} , time to reach maximum brightness; $T_{10\%,r}$, time from maximum brightness back to 10% of maximum brightness (right side of the peak); $T_{90\%,r}$, time from maximum brightness back to 90% of maximum brightness (right side of the peak).

b) Brightness parameters: $B_{(0)}$, minimum brightness intensity; B_{max} , maximum brightness intensity; $B_{(120s)}$, brightness 120 sec after injection of contrast agent.

c) Calculated parameters: "time and brightness parameter", $T_{max} \times B_{max} / (B_{max} - B_{(0)})$; "wash-in-wash-out time parameter", $(T_{90\%,l} - T_{10\%,l}) / (T_{10\%,r} - T_{90\%,r})$.

Statistical analysis was done by means of the Mann-Whitney-Wilcoxon test ($p < 0.05$). The sensitivity and specificity were calculated for a sequence of cut-off levels and an optimal cut-off time level for attaining the maximum specificity for each parameter was determined.

Results

The mean age of the patients with breast cancer was 58.1 years, and those with benign lesions was 47.6 years. The mean size of the malignant tumors was 22.5 mm (± 13.4), and that of the benign tumors was 19.8 mm (± 12.3).

In the case of malignant lesions, the mean time parameters reached 10% of maximum brightness ($T_{10\%,l}$) after 10 sec and 90% of maximum brightness ($T_{90\%,l}$) 18.5 sec after USCM injection. In comparison, for the benign lesions the 10% maximum was reached 16.5 sec and the 90% maximum 26 sec after USCM injection. In the case of breast cancer, the maximum USCM enhancement was reached 22 sec and for benign lesions 35 sec after USCM injection (Table III).

The videodensitometer measurements made after administration of Levovist with respect to the time parameters $T_{90\%,l}$, T_{max} and to all the calculated parameters differed significantly between breast cancer and the benign lesions (Table III). In the case of breast cancer, the median times to maximum brightness ($p < 0.006$) and to 90% of maximum of brightness ($p < 0.005$) were

Table III. Measured and calculated parameters: median and range. Evaluation by the Mann-Whitney-Wilcoxon test.

Parameters	Breast cancer (n=22)	Benign lesion (n=11)	p-value
$T_{10\%,l}$	10 sec. (8-14)	16.5 sec (9.5-21.5)	0.08
$T_{90\%,l}$	18.5 sec. (14-22)	26 sec (21.5-40.5)	0.005
T_{max}	22 sec (18-25.9)	35 sec (23-44)	0.006
$T_{10\%,r}$	28 sec. (22-36)	44 sec (28-53)	0.6
$T_{90\%,r}$	81 sec. (56-100)	73 sec (59-119)	0.99
$B_{(0)}$	26 DU (9-34)	14 DU (4.5-36.5)	0.3
B_{max}	166.5 DU (122-202)	147.5 DU (71-175.5)	0.14
$B_{(120s)}$	15 DU (6-35)	22 DU (7.5-61.5)	0.36
$T_{max} \times B_{max} / (B_{max} - B_{(0)})$	26 sec	42.8 sec	0.003
$(T_{90\%,l} - T_{10\%,l}) / (T_{10\%,r} - T_{90\%,r})$	0.19	0.32	0.02

(DU=density units)

significantly shorter than for the benign lesions. The ratios of the Levovist® wash-in to wash-out times in the breast cancer patients were significantly smaller than in the benign lesion patients ($p=0.02$).

The measured CPA brightness was not significantly higher in the cancer than in the benign lesions, either prior to the administration of Levovist® ($B_{(0)}$) or in the measurement of the maximum brightness after injection of the contrast agent (B_{max}). The measured values corresponded to both the observers' subjective impressions of the S-VHS tapes and the time-brightness curves (compare Table III and Figures 3 and 4).

Figures 1a-c. The color power images of a breast cancer lesion in a patient with a stage IIb tumor after UICC (pT3 pN1 G3 M0 receptor-positive). The CPA image prior to injection of the ultrasound contrast agent (the greyscale

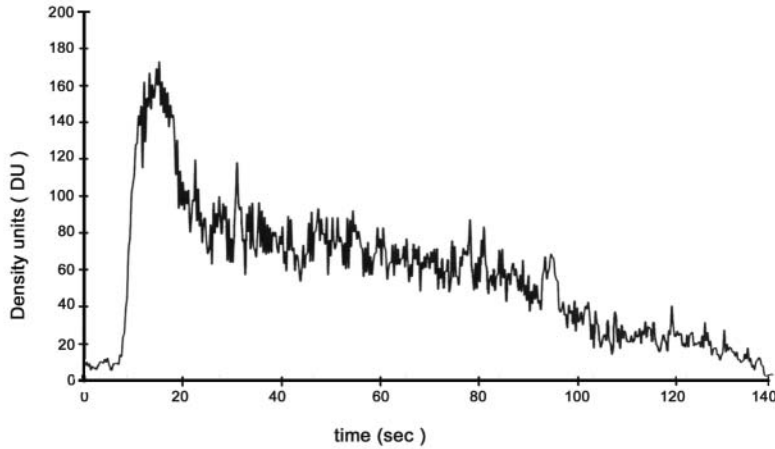


Figure 3. A typical videodensitometry curve for breast cancer.

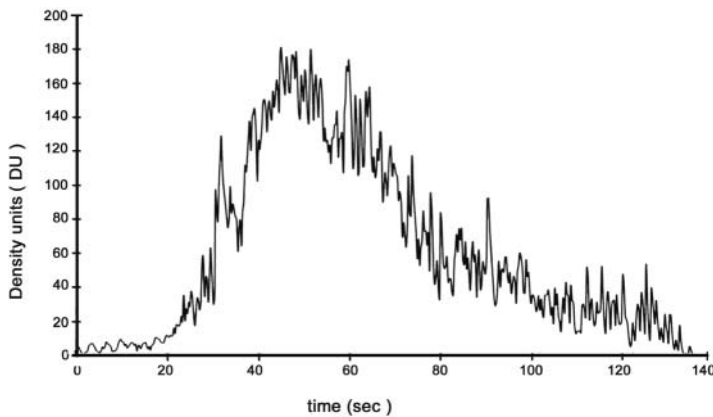


Figure 4. A typical videodensitometry curve for a benign lesion (fibroadenoma).

image was suppressed). After administration of the contrast agent, the change in CPA brightness in the blood vessels was measured in the region of interest (ROI) at the upper left border of the image. The effect after injection of the ultrasound agent, both the brightness and the area of the CPA signal increased. After a minute, the decreasing effect (wash-out) of Levovist® was observed.

In order to evaluate the usefulness of the parameters for differentiation between benign and malignant lesions, the sensitivity and specificity were calculated for each parameter which showed significant differences between the two groups (Table IV and Figures 5 and 6).

The parameter with the highest specificity was the "time-and-brightness parameter" (specificity: 92%; sensitivity: 73%; cut-off value: 28.4 sec) followed by the measured parameter $T_{90\%,l}$ (specificity: 92%; sensitivity: 64%; cut-off value: 20 sec). T_{max} showed a specificity of 91% and a sensitivity of 67% for a cut-off value of 28 sec and the calculated "wash-in wash-out" parameter had a specificity of 75% and a sensitivity of 68% for a cut-off value of 0.23.

Table IV. Sensitivity and specificity of selected parameters.

Parameter	Cut-off value	Sensitivity	Specificity
$T_{90\%,l}$	≤ 20 sec	64%	92%
T_{max}	≤ 28 sec	67%	91%
$T_{max} \times B_{max} / (B_{max} - B_{(0)})$	≤ 28.4 sec	73%	92%
$(T_{90\%,l} - T_{10\%,l}) / (T_{10\%,r} - T_{90\%,r})$	≤ 0.23 sec	68%	75%

Discussion

Based on the fact that microbubble echo-enhancers are blood-pool agents, they can be used as intravascular tracers to study the dynamic blood flow in tumors. The real-time property of ultrasound makes the combination of ultrasound investigation and contrast agents particularly suitable for functional kinetic measurements of transit times and other indices.

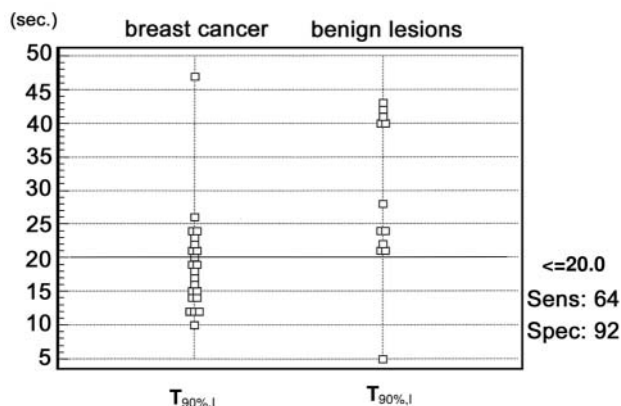


Figure 5. Sensitivity and specificity of the parameter $T_{90\%,l}$.

While Doppler sonography examinations have been used for several years (1, 3, 11, 13, 16, 18-21), it has not been possible to achieve a 100% differentiation between benign and malignant tumors on the basis of blood flow. For instance, Dixon *et al.* (11) examined 53 patients by color Doppler and obtained 25 positive scans of 32 carcinomas, for a sensitivity of 78% (specificity of 100%) for breast cancer. Kedar *et al.* (13) attempted to quantify color Doppler in a group of 74 patients and were able to prove that the peak and mean velocities were significantly higher for cancers than for benign lesions. Similarly, Blohmer *et al.* (1) carried out an examination of 74 patients by means of color and pulsed-wave Doppler and determined a significantly higher systolic velocity for malignant lesions as compared to the contralateral breast.

In addition to the question of whether there are significant differences in the blood flow in benign and malignant lesions, the vascularization of tumors should be considered. In Madjar *et al.*'s study (20), it was surprising that, in all the 471 patients investigated, all the lesions showed a blood flow (in contrast with other studies in which up to 30% of the patients did not show a blood flow – see below). However, neither the Resistance Index (RI) nor the AB ratio allowed for reliable discrimination between malignant and benign lesions. There was a high variability of flow velocities in malignancies. This contrasts with the results of Adler *et al.* (5) who, however, determined a clear vascularization in only 53% of carcinomas. The difficulting is evaluating the RI can be seen from the contradictory results obtained by different researchers. Sohn *et al.* (22) found significantly lower RI values in cancer tumors than in benign lesions, whereas Madjar *et al.* (20) determined that malignant tumors had significantly higher RI values than benign tumors.

Prospective resistance measurements were carried out on large patient collectives (n=142) with the result of a cut-off at 0.8. Hollerweger *et al.* (23) showed that a resistive index (RI) < 0.8 is typical for benign lesions and an RI > 0.8 is

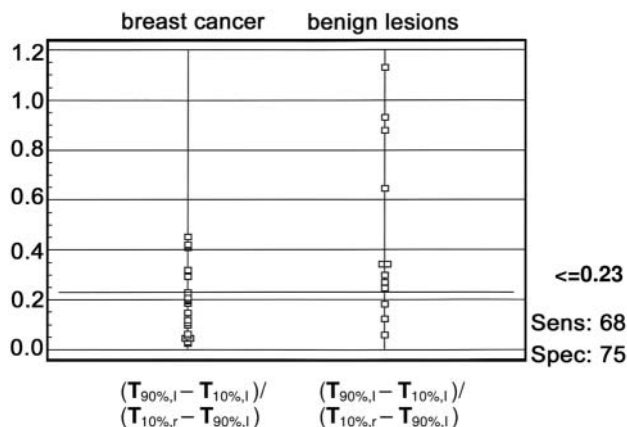


Figure 6. Sensitivity and specificity of the wash-in wash-out parameter.

significant for malignant lesions, with a sensitivity of 55% and a specificity of 96%. These authors also defined a malignancy indicator for an RI > 0.8 and RI differences > 0.2. Additional results with regard to the RI were obtained by Rettenbacher *et al.* (24), who showed that the RI underwent significant changes depending upon the menopausal status of the women. In 200 pre- and postmenopausal women a significant difference ($p=0.0001$) was measured, with the postmenopausal women having the higher RI values. The authors concluded that reduced metabolic activity in postmenopausal women is behind these differences. A different explanation for a higher vessel resistance might be the increase in arteriosclerosis in older people, with a corresponding age-dependent increase in systemic diseases, such as diabetes and hypertension, which might also lead to changes in resistance in the breast. It is an open question whether such changes increase the risk of developing breast cancer.

There is still no standardization of the RI. In general, there is a tendency to find increased RI in carcinomas (7, 25, 26), but with much overlap into the benign range. These extremely vague results are also true for other measurable blood vessel parameters (*e.g.*, PI, V_{max} , systolic Doppler frequency, end diastolic peak Doppler frequency) (27, 28).

When it is possible to obtain images of vessels the following questions arise: How many vessels or arborizations of these vessels can be seen in a ROI and are they located peripherally and/or centrally? Since all these categories are subjective, they are difficult to evaluate. On the one hand, smaller malignant tumors show a lower blood flow than larger malignant tumors. Significantly more vessels can be imaged in malignant tumors (25), but it is still unclear whether an increased vascularization (29, 30) is to be found at the periphery (31) or in the center of the tumor (28). In a comparison with angiography (32), color signals were obtained more frequently in carcinomas (89%) than in benign lesions (56%), thus the color Doppler and angiography results are in agreement.

In summary, it can be said that more Doppler signals, a higher flow-rate and a greater concentration of vessels can be seen in breast carcinomas than in benign lesions (4), but the specificities and sensitivities diverge too much between studies for a reliable standard to be defined.

Here, it was shown that benign and malignant lesions had a different enhancement (Figures 3 and 4). Malignant lesions showed a significantly quicker wash-in and wash-out of the contrast agent as compared with benign lesions, as seen in the images of contrast agent enhancement in a patient with a T3 breast carcinoma (Figures 1a-c). Despite the lack of clarity regarding blood circulation in tumor vessels, it can be hypothesized that, due to an increased number of vessels, collaterals and shunts, the blood circulation is increased significantly in tumors, enabling a more rapid wash-in and wash-out of the contrast agent.

As in our study, Huber *et al.* (14, 33) used the contrast agent Levovist®. Fifty-seven patients were examined with the aim of objectively evaluating the effects of a microbubble contrast agent on color Doppler imaging. It was first shown that the peak of the color pixel density was clearly higher for carcinomas (14.3%) than for benign lesions (9.3%). Secondly, the time to peak enhancement was shorter in carcinomas (38 sec) than in benign tumors (71 sec). More recent studies as well all show an increase in the accuracy of the differential diagnosis for breast lesions. Schröder *et al.* (34) were able to obtain a significant ($p=0.01$) improvement of the specificity/sensitivity to approximately 100% using the contrast agent Levovist®. For non-palpable lesions, Moon *et al.* (35) reported that the difference in distinguishing between malignant and benign tumors was also significant ($p=0.01$) when was used (Levovist®). Stuhmann *et al.* (36-38) also obtained equally good results, encouraging others to use a contrast agent to distinguish between scar tissue and a relapse.

Various parameters were defined in this study, for which both the method and the measurements are reproducible and which deliver significant results. One disadvantage, however, was the Levovist® dose. Each patient received the same bolus of the contrast agent, regardless of body weight. In heavier patients this might have affected the brightness of the image because of dilution due to the body mass and intravascular fluid. An additional methodological problem was the ROI which, at the time of the measurement, could not be adjusted for technical reasons to fit the course of the vessel and it was always rectangular.

Unfortunately, the size of the patient collective was too small for valid conclusions to be drawn, especially the benign group which was also inhomogeneous. The low sensitivity in a small collective means that standard use of the contrast agent cannot be justified at present.

The first results of the use the contrast agent Levovist® for the evaluation of breast lesions are promising. To

confirm the results obtained in the current study, a larger patient population should be investigated.

The use of Doppler ultrasound with a contrast agent as a routine method for determination of vascularization in breast lesions is a relatively inexpensive procedure in comparison with CT and MRI. Currently, however, it does not offer 100% reliability in distinguishing between benign and malignant lesions so that it is not possible to dispense with pre-operative surgery (punch biopsy). In a comparison of different single methods, Blohmer *et al.* (28) showed that Doppler is not the best method. However, a combination of diagnostic procedures may be more effective than employment of a single diagnostic method. Perhaps 3D/4D in combination with a contrast agent will offer a better diagnostic predictability than current methods (39, 40).

Employment of the new second generation of sulphur hexafluoride contrast agents is trend-setting, e.g., Sonovue (Bracco/ALTANA, Konstanz), which permits the representation of the smallest blood vessels with the slowest possible flow. Indications for there use, however, are restricted to the infiltration of the pectorals muscle, the differentiation between scar and relapse, as well as the description of the tumor vascularisation by primary chemotherapy. In no way may these procedures be regarded upon as established in the field (41, 42).

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