How Reliable Are Conventional and Color-Coded Sonography of the Breast in the Differential Diagnosis of Breast Cancer?

DR. MED. CHRISTOF SOHN, ASSOCIATE PROFESSOR
DR. MED. FRANK BELDERMANN
DR. MED. MONIKA SCHIEßER
DIVISION FOR PRENATAL AND GYNECOLOGICAL ULTRASOUND IN DIAGNOSIS AND THERAPY
CLINIC OF OB-GYN, UNIVERSITY OF HEIDELBERG, HEIDELBERG, GERMANY

PROF. DR. MED. MANFRED KAUFMANN, MANAGING DIRECTOR
CLINIC OF OB-GYN, UNIVERSITY OF FRANKFURT, FRANKFURT, GERMANY

PROF. DR. DR.H.C. GUNTHER BASTERT, MANAGING DIRECTOR
CLINIC OF OB-GYN, UNIVERSITY OF HEIDELBERG, HEIDELBERG, GERMANY

Sonographic examinations of the female mammary gland within the frameworks of the diagnosis of breast cancer play a fundamental role in the early detection of benign and, in particular, of malignant growths. Sonographic blood flow determinations can be used as an auxiliary noninvasive examination method. This is based on the fact that malignomas differ from benign tumors in that they display a pathological increase in vascularization.[1,7] These changes of the circulatory conditions can be utilized in the diagnosis of the dignity of breast cancer.

The neovascularization of malignant growths is characterized by a lack of muscular coat on the vascular walls.[4] The vascular resistance is thus reduced; hence a reduction in the blood flow velocity within these minute vessels will result. Extremely slow blood flow velocities in the millimeter per second range can be depicted using the new MEM color technique (Maximum Entropy Method). This new color technique was used in this study.

The aim of our study was to determine whether or not the nature of benign and malignant breast cancer can be ascertained with greater certainty by additional blood flow measurements. One-hundred ninety-two patients with a palpable tumor or uncertain mammography findings were examined with conventional B-scan sonography on the day prior to surgical intervention. The observations were divided into benign or malignant on the grounds of the B-scan sonography and blood flow determinations. A comparison was then made between the results of the preoperative sonographic diagnosis and the histological findings.

MATERIAL AND METHODS

Technical Equipment

A high-resolution 7.5 MHz transducer was used for the examinations with the

MEM technique (Maximum Entropy Method, Acoustic Imaging Company, Dornier Medizintechnik, Phoenix).

This color technique is capable of detecting extremely slow blood flow velocities (minimum 0.1 mm/second) whereas the conventional Doppler technique can only discern a minimum blood flow velocity of about 1 to 3 cm/second.

The algorithm on which this system is founded is that developed by the U.S. Naval Forces for the use of sonar signals. These algorithms were modified to obtain an improvement in the spectral resolution and noise perception. MEM forestalls the signals from becoming imperceivable due to the noise by optimizing the separation of the flow information and the disturbing noise.

This nonlinear method of spectral assessment was first publicized by J. P. Burg in 1967.[3] The spectrum whose time series happens to appear outside the observed pattern is selected for analysis. This method enables unbiased evaluation of the subliminal spectrum by maximizing the entropy of the unknown spectra.

MEM assesses the noise distribution as a sonographic volume and thus as useful information. The noise is accurately shaped; hence MEM optimizes the separation of the actual flow information from the noise. The performance of the MEM algorithms within the surroundings of the acoustic noise is so effective that even signals which are weaker than the background noise can be detected.

Conventional color Doppler algorithms and MEM can be compared using eight key criteria as yardstick: sensitivity, penetration, resolution power, frame rate, accuracy, velocity ranges, resolution velocity, and the depiction of the flow not representable on the B-scan.

In previous examinations MEM has been shown to display the following properties:

1. It minimizes every source of noise, thus being able to detect extremely slow velocities.
2. MEM can extract the Doppler frequency deviation information from a minimum of reflected ultrasound signals in order to optimize the frame rate without a loss in resolution power or in the size of the sample volume.
3. The extracted Doppler information displays a distinctly improved noise–signal relationship with a simultaneous improvement in penetration depth.
4. The Doppler spectrum allows for a more sensitive registration in MEM despite a higher noise incidence.
5. MEM has an optimum sturdiness in the presence of noise even under conditions of minimal Doppler-signal intensity.
6. MEM depicts the flow that is not representable on the B-scan, and is furthermore better able to differentiate between Doppler signals and other signals.

In this study we evaluated the examiner's visual impression immediately and deliberately renounced the utilization of a pulsed and less sensitive Doppler, well aware of the fact that our results are based on the refined-by-experience yet nevertheless subjective interpretation of the analyst. Cosgrove successfully presented similar studies of flow characteristics.[5]

Patients

One-hundred ninety-two patients with palpable or mammographically discernible unilateral breast tumors were examined on the day prior to surgery. Patients without a sonographically discernible growth were not included in this study.

Examination Method

The sonographic examination was always carried out by the same research worker without prior inspection of the mammographic scans or knowledge of other findings. After a short case history and palpation of the breast, the tumor was depicted in a high-resolution B-mode scan and the dignity assessed as either benign or malignant.

Sonographic blood flow measurements followed—and these without taking the dignity analysis obtained with the B-scan into consideration. The sample volume protruded over 5 mm around all sides of the tumor. The sensitivity of the blood flow registration was set on maximum sensitivity and it thus only registered the slowest blood flow velocities (PRF: 210 Hz).

Classification of the Color Information

The number of color pixels was used as the basis for the determination of the blood flow within the tumor. This classification is subjective but based on many years of experience with this color technique. Experience has shown that benign tumors usually only display scattered color pixels (varying in number) when the equipment is set on maximum sensitivity, whereas malignant neoplasms display pixels and, in particular, colored surface areas. It is entirely unproblematic for the human eye to differentiate between pixels and colored areas.

We therefore classified a growth which disclosed a minimum of or even no blood flow and thus had less than five color pixels in the category of benign tumors.

The criterium for a classification as malignant was the presentation of more than five color pixels or even entire colored areas as an expression of a distinctly increased blood flow. This tumor status classification by blood flow analysis was found to be easily reproducible.

A preoperative classification of the tumor as malignant or benign was thus based on the analysis of the B-scan and the blood flow diagnosis. If there was a contradiction between the B-scan and the flow measurement, the examiner had to come to a definite decision. The sonographic results were noted immediately after the examination. The evaluation of these results followed by comparing the sonographically achieved results with the histological diagnosis.

RESULTS

We subdivided the patients (n=192) into a group with malignant growths (n=121) and into one with benign tumors (n=71) in accordance with the histopathological diagnosis. The results are summarized in Tables 1 and 2.

Group 1: Malignant Tumors (n=121) (Table 2a) (Figs. 1, 3, 4)

One-hundred twenty-one patients had a histologically ascertained carcinoma of the breast. In 116 patients, the sonographic assessment (B-scan sonography and/or flow measurement) of malignancy corresponded with the histological evidence. Blood flow diagnosis alone was unanimous with the histology as malignant in 108 cases.

The conventional B-mode scan thus enabled a correct assessment of the growth with a sensitivity of 83.5% (101:121); color presentation alone increased this sensitivity to 89.3% (108:121). A combination of both preoperative diagnostic methods enabled the correct assessment in 116 cases, corresponding with a sensitivity of 95.9% (116:121). That is, the findings were classified as malignant in 116 cases because one of the two sonographic methods or both findings were classified as malignant.

A congruence of 76.9% (n=93) was attained for the two sonographic techniques with malignant findings in both the B-scan and in the color presentation.

In 23 cases the findings of the two sonographic techniques did not agree with

one another. These were, however, classified as malignant for the following reasons. Thirteen patients (10.6%) had uncertain findings when considering the B-scan alone. Benign criteria, such as sharp margins between the growth and the surrounding tissue and bilateral narrow dorsal ultrasound shadows were found, whereas other criteria were indicative of malignancy. The color-coded presentation did, however, disclose a correspondingly high blood flow as described above, i.e., with more than five color pixels of colored areas. According to the classification, we thus correctly assumed the growth to be malignant.

A further 1.7% of the patients (n=2) had sonographic findings indicative of a benign growth; the increased blood flow was, however, a sign for malignancy. A slow blood flow—not to be expected in a malignant growth—was observed in eight patients (6.6%). Unmistakably malignant criteria in the B-scan did, however, make the diagnosis of a carcinoma undebatable.

A total of five patients from group 1 (4.1%) were incorrectly assessed as negative prior to surgical intervention (i.e., the sonographic findings in the B-scan and in the color-coded presentation were both classified as benign).

Group 2: Benign Tumors (n=71) (Table 2b) (Fig. 2)

Seventy-one patients had a histologically ascertained benign tumor. As described above, the examiner had to decide between a benign and a malignant growth in findings in which there was a discrepancy between the two ultrasound observations. This assessment was correct in 64 of the 74 benign growths. In 54 patients the tumor was only diagnosed as benign on grounds of either the B-scan or the blood flow diagnosis. The specificity of the B-scan presentation alone in benign alterations is thus just as high as the specificity with the aid of blood flow measurements alone, namely 76.1%. When utilizing both methods, the specificity increases to 90.1% (64:71).

In 45 of the above-mentioned 64 patients (63.4%), both techniques diagnosed the tumor as benign. The remaining 19 patients were only classified as benign due to the findings made in one of the two methods, as described below.

In 11.3% (n=8) color presentation was a decisive help. The uncertain findings in the B-scan could be unequivocally classified as benign due to the lack of a slow flow during the blood flow measurements. The reasons for the failure of the dignity assessment in the B-scan could have been due to the following, for example:

- normal structure of the mammary gland tissue with uncertain growth observations
- ultrasound shadows due to cicatricial tissue
- no clear assessment of the echogenity of the focal point

In two further cases (2.8%) the B-scan showed a suspectedly malignant tumor; there was, however, no increased blood flow discernible in the flow measurements, so that a benign growth was assumed.

Although 12.7% of the patients (n=9) had an increased blood flow, the tumor had to be classified as benign due to the clear-cut benignity criteria in the B-scan.

In seven patients (9.9%) the tumor was incorrectly classified as malignant by both sonographic examination methods.

Histological examination disclosed fibrocystic mastopathies and, in one case,

Table 1. Diagnosis of tumor's nature by using conventional B-scan and/or blood flow measurement with MEM technique

Sonographical Technique	Number of accurately diagnosed tumors	
	Malign tumors (n=121)	Benign tumors (n=71)
Exclusively B-scan	83.47% (n=101)	76.06% (n=54)
Exclusively color sono	89.26% (n=108)	76.06% (n=54)
Combination of B-scan and color sonography	95.87% (n=116)	90.14% (n=64)

Table 2a. Diagnosis of malignant tumors by using both techniques (B-scan and color sonography)

Combination of B-scan and color sonography	95.87%	n=116
Correctly assessed by both techniques	76.86%	n=93
Uncertain findings in B-scan but high blood flow	10.74%	n=13
B-scan indicating benign but high blood flow	1.65%	n=2
B-scan indicating malign, low blood flow	6.61%	n=8
TOTAL	95.87%	n=116

Table 2b. Diagnosis of benign tumors by using both techniques (B-scan and color sonography)

Combination of B-scan and color sonography	90.14%	n=64
Correctly assessed by both techniques	63.38%	n=45
Uncertain findings in B-scan but no blood flow	11.27%	n=8
B-scan indicating malign but no blood flow	2.82%	n=2
B-scan indicating benign but high blood flow	12.68%	n=9
TOTAL	90.14%	n=64

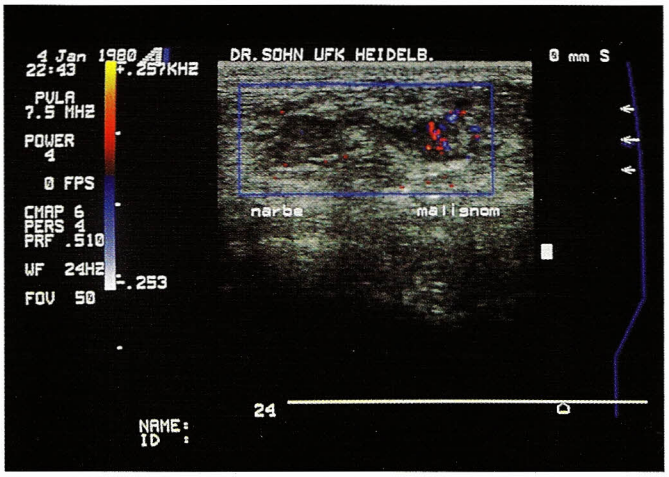

Figure 1. Malignant tumor and scar in the same section: the scar shows no blood flow; the malignant lesions, many color pixels.

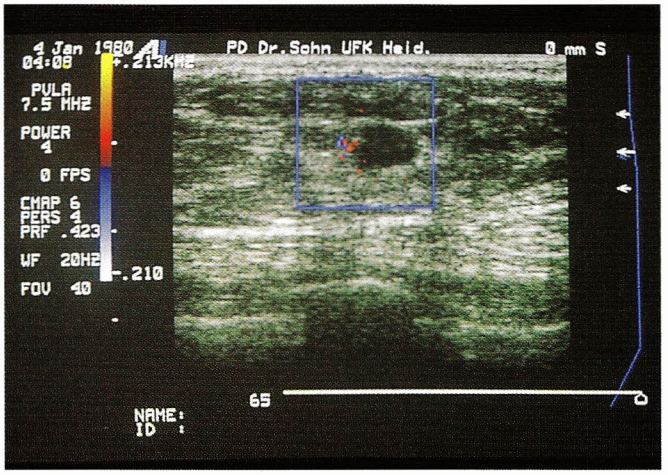

Figure 2. Benign breast lesion with fewer color pixels.

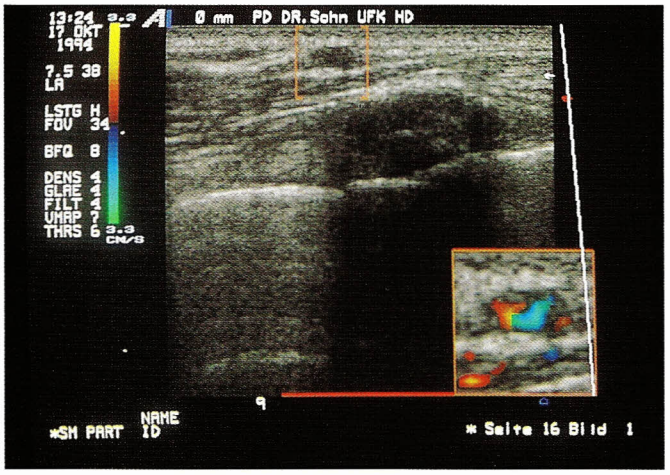

Figure 3. Very small malignant breast lesion with a high blood flow.

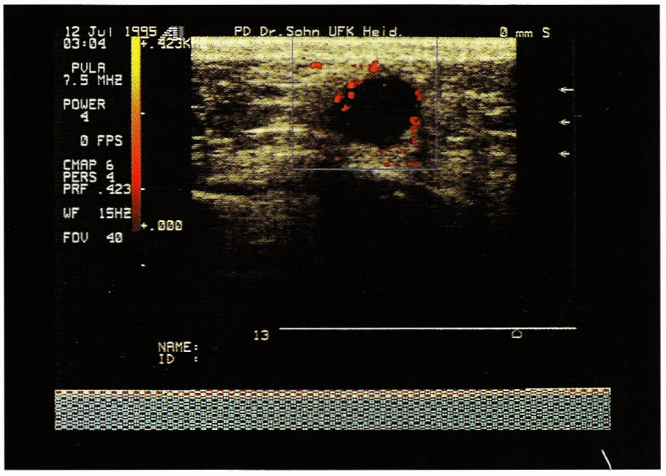

Figure 4. One-centimeter malignant breast lesion with many color pixels.

a foreign matter granuloma.

Our results show that blood flow measurements using the MEM color technique supply fundamental additional diagnostic information to the conventional B-scan. B-scan diagnosis alone has a sensitivity of 83.5%; flow measurement alone increases the sensitivity to 89.3%. The utilization of both methods increases the sensitivity to a remarkable 95.9%. A combination of both techniques results in a specificity value of 90.1%.

DISCUSSION

Our results—which are similar to those of numerous studies carried out by various authors during the past few years—clearly show that color-coded sonographic examinations for the determination of the dignity of tumors of the breast increase the certainty of the diagnosis.

Auxiliary color presentations increased the accuracy of the diagnosis of malignant breast tumors by 12.4% and that of benign growths by 14.8% when compared with the conventional B-scan alone. The specificity of exclusively B-scan sonography or color sonography alone is identical, namely, 70.1% as far as benign tumors are concerned. A combination of both methods is necessary to increase the accuracy to 90.1%.

Both methods are thus not alternative methods but rather supplement one another concerning the information they supply; together they obtain a specificity of over 90%. An extremely high sensitivity of almost 96% was also only obtained for malignant tumors by simultaneous determination of the dignity of the growth using the B-mode scan. The newer method of sonographic flaw measurement—currently a time-consuming and costly technique—does not make the evaluation of the conventional B-scan superfluous, as made evident by our separate procedures. Eight malignant tumors and nine benign growths would have been incorrectly interpreted by the analysis of the flow measurement alone.

The incorrect preoperative classification of the findings can be understood as follows: the foreign body granuloma consisted of infected tissue in the process of organization. Blood circulation can thus already be physiologically increased. Mastopathic changes, with an increased blood flow, exist in the same way.

One particular case is exemplified here: a mastopathy was tentatively diagnosed on the basis of sonographic examinations. The histological evaluation, however, disclosed a ductal invasive carcinoma primarily with intraductal components. The reason for the false allocation into the benign group is probably to be found in the fact that the largest invasive focus only had a diameter of 3 mm.

Twenty-one focal diagnoses (13 malignant, 8 benign tumors) could not be clearly classified as far as their dignity was concerned using the B-scan alone. In these cases the flow measurements using the MEM technique supplied the decisive

information for the tumor differentiation.

In four cases (two carcinomas, two benign lesions) the results of the B-scan examination were corrected by an indisputable flow measurement (i.e., apparently malignant B-scan findings were seen to be benign on the blood flow measurements and benign changes seen to be malignant; histologically these tentative diagnoses were found to be correct).

Our results correlate well with those obtained by other authors. An accuracy of 90% to 94% in the determination of the nature of breast cancer can be attained when utilizing different Doppler methods. When comparing the results obtained by various examiners, one must, however, take the different methodic techniques utilized into consideration. The MEM technique which we used—the only prototype at our disposal to date—has the advantage of being able to discern extremely slow blood flow velocities. Its disadvantage lies in its inability to quantify this blood flow. The development of an objective and automatic registration is imperative.

When utilizing the Doppler methods, different authors used entirely different parameters for the evaluation of the blood flow measurements. The similarity in the results is amazing when taking these differing parameters into consideration!

Madjar et al. suggest the utilization of the maximum systolic flow velocity, the mean tumor flow, and the sum of the flow velocities as a quantitative flow parameter for tumor differentiation.[11] They see the mere presentation of color pixels as a criterion with little expression in the search for uniform standards of examination. We cannot agree with this interpretation. Our experience has shown that the combination of the B mode scan and the presentation of slow blood flow velocities using color-coded non-Doppler sonography is the most expressive method, although both methods are based on subjective criteria. The new color-coded techniques for the detection of the slowest of blood flow velocities is the best method of detecting the blood flow in the neo-vascularized tumor tissue.

There are also no mandatory agreements for the choice of the to-be-analyzed parameters in examinations carried out with the help of the newest Duplex systems or the C.W. Doppler. White et al.[18] and Schild et al.[12] found a high diastolic flow to be a conspicuous characteristic in malignant processes. Burns et al.[4] showed that the difference in maximum systolic frequency in comparison with the contralateral breast side offers high accuracy in tumor differentiation. Madjar et al.,[9,10] on the other hand, differentiate between malignant and benign processes by an observed increase in frequency shifts, and, in agreement with Heilenkötter et al.,[8] on the basis of the number of vessels per breast side. In our opinion there is no reliable method for determining the number of vessels, as one can never be sure of not recording the same vessel a number of times.

In conclusion, one can say that the color Doppler as well as the newest non-Doppler techniques of blood flow analysis and thus the diagnosis of the nature of breast tumors have continued to improve. Flow examinations in vessels below the resolution level of sonographic techniques are now possible.[10] The Doppler principle (duplex system, C.W. Doppler) is, in particular, not capable of detecting the extremely slow flow velocity in malignant tumors for methodic reasons.[9,12,14,15]

An absolute 100% accuracy in the determination of the nature of breast findings cannot be attained despite the improved methods of diagnosis due to blood flow measurements using Doppler or non-Doppler sonography—as our results have shown. As a noninvasive method, sonographic blood flow diagnosis is exceptionally important in uncertain findings in the B-scan, in cicatricial tissue with ultrasound shadow formation, in a dense body of the breast which is difficult to evaluate on a mammographic scan and in the follow-up after breast-conserving treatment. However, when considering the implications of the diagnosis "breast cancer," no patient may renounce the histological security of the tentative diagnosis. A completely reliable preoperative assessment of a tumor of the breast is not attained even with the most modern of visual techniques.

The emphasis of our examinations has thus shifted in another direction: we could demonstrate that the degree of blood flow of a malignant tumor correlates with its biological behavior.[15,16] The sonographically discernible blood flow gives indications for the prognostic evaluation of a tumor of the breast. Perhaps one can differentiate between biologically highly malignant alterations and less aggressive changes. This has to be examined in further studies. **STI**

REFERENCES

1. Algire GB. Chalkley HW, Legallais FY, et al. Vascular reactions of normal and malignant tissue in vivo. J Natl Cancer Inst 1945;6:46-73.
2. Blohmer J. Mammasonographie. In: Sohn C, Holzgreve W. Ultraschall in gynäkologie und geburtshilfe. Thieme-Verlag; 1995.
3. Burg JP. Maximum entropy spectral analysis. 37th Annual Soc Explor Geophys International Meeting; 1967; Oklahoma City.
4. Burns PN, Halliwell M, Wells PNT, et al. Ultrasonic Doppler studies of the breast. Ultrasound Med Biol 1982;8(2):127-43.
5. Cosgrove DO, Bamber JC, Davey JB, et al. Color Doppler signals from breast tumors. Radiology 1990;176:175-80.
6. Delorme S, Anton H-W, Knopp MV, et al. Vaskularisation des mammscarcinoms: quantitative und morphologische beurteilung mittels farbcodiertier sonographie. Abstract 423 Ultraschall Klin Prax 1991;6S:219.
7. Folkmann J. How is blood vessel growth regulated in normal and neoptastic tissue? Cancer Res 1986;46:467-73.
8. Heilenkötter U, Jagella P. Farbdoppler-sonographie exstirpationsbedürftiger mammatumoren - darstellung einer untersuchungs-methode. Geburtsh u Frauenheilk 1993; 53: 247-52.
9. Madjar H, Sauerbrei W, Münch S, et al. Methodenanalyse zur Doppleruntersuchung der weiblichen brust. Ultraschall in Med 1990; 4:196-201.
10. Madjar H, Prömpeler H, Kommoss F. Ergänzt der Farbdoppler die mammadiagnostik? Radiologe 1992;32:568-75.
11. Madjar H, Prömpeler H, Wolfahrt R, et al. Farbdopplerflubdaten von mammatumoren. Ultraschall in Med 1994;15:69-76.
12. Schild R, Schroers B, Funk A, et al. Dopplersonographische untersuchungen von mammatumoren in CW. Technik Zentribl Gynäkol 1993;115:483-7.
13. Sokin C, Stolz W. Dopplersonographische durchblutungsmessung von brusttumoren. Abstract 424 Ultraschall Klin Prax 1991; 6S: 219.
14. Sohn C, Grischke EM, Wallwiener D, et al. Die sonographische durchblutungsdiagnostik gut - und bösartiger brusttumoren. Geburtsh u Frauenheilk 1992;52:397-403.
15. Sohn C, Stolz W, Grischke EM, et al. Die dopplersonographische untersuchung von mammatumoren mit hilfe der farbdopplersonographie, der Duplexsonographie und des CW-Dopplers. Zentribl Gynäkol 1992; 114: 249-53.
16. Sohn C, Grischke EM, Stolz W, et al. Untersuchungen zum Zusammenhang zwischen dem grad der durchblutung und dem biologischen verhalten von mammatumoren. Ultraschall Klin Prax 1993;8:11-4.
17. Sohn C. Analysis of the relationship between the degree of blood supply and biological characteristics of breast tumors with the MEM color system. In: Madjar H, Teubner J, Hackelöer BJ, eds. Breast ultrasound update. Basal Karger; 1994. p 313-18.
18. White DN, Cledgett PR. Breast carcinoma detection by ultrasonic doppler signals. Ultrasound Med Biol 1978;4:329-35.

Translated from the original: Sohn C, Thiel C, Baudendistel A, v Fournier D, Bastert G. Welche Sicherheit bietet die konventionelle Mammasonographie und farbcodierte Sonographie in der Diagnostik von Mammatumoren? Zentralbl Gynakol 1996:118:142-7.