

Value of Electrical Impedance Scanning (EIS) in the Evaluation of BI-RADS™ III/IV/V-Lesions

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Two hundred and fifty-six (256) patients (72% preoperative, 28% pre-Mammotome) were prospectively examined with EIS using the TS 2000 (TransScan Research and Development Center, Israel; temporarily distributed by Siemens, Erlangen) with the "LOS"-software (level of suspicion). All exams were performed with the targeted scan probe, the observer knowing all clinical and imaging facts. The area of the lesions was examined with EIS at least with 5 single scans. The evaluation included a scaling of lesions from 1 (surely benign) up to 5 (highly suggestive for malignancy) as well as the additional notification of spots. Results of EIS were based upon the automatic scaling which is provided by the software and were compared with mammography and histology. Furthermore the influence of the histology, size of lesions, and presence/absence of spots on the EIS results were analyzed.

Histology revealed benign results in 138 lesions and malignant results in 118 lesions (DCIS=61, ID-Ca=51, IL-Ca=5, mucinous Ca=1). Mammography as expected yielded high values with 91% sensitivity and 62% specificity. Overall sensitivity of EIS was 75.4%, specificity 42.03%, negative predictive value 66.7% and positive predictive value 52.7% (89 TP, 58 TN, 80 FP, 29 FN). EIS was false negative in 20 ID-Ca, 3 IL-Ca, 1 IDL-Ca, 4 DCIS, and 1 mucinous carcinoma. Sensitivity and specificity of EIS did not differ for the different histological differentiations neither for the degree of invasion. Also the additional notification of "spots" didn't show a correlation to malignancy. There were significant differences of the sensitivity of EIS regarding the tumor size. While EIS correctly diagnosed 85% of lesions <10 mm in size, only 64% of lesions >10 mm were detected. Most frequent lesion types for false positives were mastopathy (55/80 FP) and fibroadenoma (21/80 FP). Patient acceptance of EIS was perfect and there were no drop outs because of movement artifacts.

In conclusion the "LOS"-software clearly improved the clinical performance of the TS 2000 as compared to the initial software. The high sensitivity of EIS in small cancers which was found in our study may indicate an advantage of this method. However, the overall sensitivity and specificity with this setup of EIS is still far too low. Further improvements especially including the measurement of higher frequencies should be realized.

Introduction

Breast carcinoma is the most common malignant tumor of woman in the industrialized world. Nearly every 8th woman suffers from breast cancer during their lifetime with increasing incidence in many countries. Early detection is crucial in all malignant tumors and much research is done in this context. Though the major imaging modalities in breast diagnostics, such as mammography and sonography, have been strongly improved over the past decade they are still often not satisfactory as up to 15% of breast cancers are not visible with these methods. Therefore several new imaging methods, such as laser mammography, ther-

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mography, or Electrical Impedance Scanning, have been, and more or less continue to be, evaluated. Electrical Impedance Scanning is a method that goes back to 1926 when Fricke (1) published the results about “the electric capacity of tumors in the breast” in the *Journal of Cancer Research*. They found moderate variations of electrical impedance values in the normal breast and a significantly higher conductivity at 20 kHz for tumor tissue compared with normal tissue. Surowiec (2) investigated the dielectric properties of the central part of breast tumors, the tumor surrounding tissue, and the peripheral normal breast tissue at frequencies ranging from 20 kHz to 100 MHz. Significantly higher dielectric constants and conductivity values were found in tumor tissue compared with normal breast tissue, especially at low frequencies. These differences are (among other influencing mechanisms) attributed to changes of cellular water content, amount of extra cellular fluid, membrane properties, packing density, destruction of tight junctions and cell membranes, and a changed orientation of malignant cells. Of key importance is the fact that most benign lesions exhibit electrical properties similar to normal tissue and not of malignancies, thereby offering a potential of differentiation of benign and malignant lesions. However, also in the healthy breast, moderate variations in impedance values are observed, reflecting the differences among various types of breast tissue. In contrast to these observations in normal tissue, malignant tumors show substantially increased capacitance and conductivity values resulting in decreased impedance. However, there hasn't been a setup to measure those different electrical properties *in vivo* for long time.

Then during the 1980s, the Breast Center Pistoia started electrical-impedance breast imaging with the “Mammoscan” (3, 4). In recent years, this electrical-impedance imaging system has been improved. The TransScan TS 2000 device (TransScan Medical, Migdal Ha'Emek, Israel; distributed by Siemens AG) was introduced in 1999 and received FDA approval for diagnostic use on breast lesions (Fig. 1). This technique is based on the measurement of low-level electrical currents altered by tissue-specific conductivities within the breast tissue. With this set up a biocompatible low level electrical current (0.1-2.5 V, alternating current <5mA, frequency 200 Hz) flows through the patient's body, applied via a metal cylinder held in the patient's contralateral hand. To facilitate the necessary tight contact between the breast and the probe a gel similar to ultrasound gel is used while the hand held scan probe is applied to the breast. There are 2 different scan probes for a scanning examination and targeted examination mode with a 16 × 16 and 8 × 8 sensor matrix, respectively.

The probe area for the scanning/targeted examination mode is approximately 79 × 79 mm² and 47 × 47 mm², respectively. Each sensor is 3 × 3 mm² in size. The center-to-center distance is approximately 4 mm, thus leaving a gap of 1

mm between adjacent electrodes. A metallic strip of 7 mm width, termed the guard ring, which hinders electrical edge effects, surrounds the sensing area.

During the examination the patient lies recumbent. She holds the reference electrode cylinder (diameter 3.4 cm, length 12 cm) in her hand contralateral to the breast being examined (Fig. 2).

Initial Setup and Software

The initial setup consisted in two different examination steps, the scanning mode and the targeted examination mode. During the scanning examination the probe was guided in a pre-defined sequence by the operator to record 33 data sectors, which cover the entire breast. Scanning of both breasts, with the display of both conductance and capacitance of each, yielded in total four 33-sector maps. The respective central sector mapped the nipple region. Since conductivity of nipple tissue is very high (in accordance with intrinsic cell properties), the healthy nipple was always represented as a white spot. Thereafter, the region of the suspicious breast lesion was carefully scanned with the high-resolution probe in the targeted mode. A spot in EIS is consistent with an increased value of conductivity/capacitance because of decreased impedance. If a spot was obviously more luminous than the surrounding tissue and did not correspond to a skin lesion or a scar and was not caused by an artifact (*i.e.*, bone, air bubble, contact artifact) it was classified within this software version as suspicious and as a positive EIS finding. Some of these lesions showed increased signal intensity in conductivity and some in conductivity and capacity. The major limitation of this software was a very high number of false positive examinations due to cutaneous lesions.

Advanced Setup with the “LOS”-Software

Within this setup the scanning examination mode was omitted and only the high resolution smaller probe with the 8 × 8 sensor matrix was used to examine the region of the suspicious lesion. Therefore the probe was first applied to the nipple and then at least 2-3× to the area of interest. The level of suspicion (LOS)- software that was also used for this study features a post-processing function with colored indicator bar representing 5 levels of suspicion (1, 2, and 3 are read as negative; 4 and 5 are positive), comparable to the BI-RADS classification for mammography. This algorithm takes into account data across 7 frequencies, including the critical frequency at 5000 Hz, the nipple recording, presence or absence of a high-conductivity focal spot, and the patient's age. The algorithm was derived empirically and statistically. First 1057 cases (170 cancer, 256 screening, 531 benign cases) were measured at 100, 200, 1000 and 2000 Hz and additionally 25% of the cases also at 3000, 4000 and 5000 Hz.

Afterwards the algorithm was tested on a different set of 87 carcinoma cases, 153 benign cases and 356 recordings from asymptomatic women (screening cases). The algorithm uses a set of “predictors” – variables that predict the likelihood of carcinoma. For each predictor, thresholds were found that optimally differentiated between malignant, benign and normal cases. With this setup at the end of the examination the investigator gets a definite scoring of the lesion and only has to take into account the presence or absence of spots.

Materials and Methods

256 preoperative/pre-Mammotome patients with BI-RADS III/IV/V-lesions (52% preoperative, 48% pre-Mammotome) were prospectively examined with EIS using the TS 2000 (TransScan Research and Development Co., Israel; temporarily distributed by Siemens, Erlangen) with the “LOS”-software (level of suspicion). The examinations were done after the patients read a short brochure about the additional examination and gave informed consent. The mammographic and sonographic results were classified according to the BI-RADS™ classification. Lesions with a score of 3-5 were included in the study. Investigation of EIS was performed close to mammographical imaging. The lesion localization was carefully analyzed reading the cc and ml-projections and multiple measurements were done at the region of interest in order to exclude false negatives. An additional ultrasound localization procedure was not done. According to the used software all exams were performed with the targeted scan probe. At the beginning of each EIS examination, the skin of the suspicious area was carefully inspected to detect and document skin surface lesions because of potential false positive measurements. The investigator had to decide the reason for and character of the spots. After the measurement was finished the software provided an automatic scaling of lesions from 1 (surely benign) up to 5 (highly suggestive for malignancy). All cases with questionable correlation of EIS and the lesion, lesions only visible with ultrasound and also the rare cases with artifacts caused by skin alterations were not included in the study. The results of the automatic EIS scaling for each lesion were compared with mammography and histology. Furthermore, the influence of the histology, size of lesions and presence/absence of spots on the EIS results were analyzed.

Results

Summarizing mammographic and sonographic findings, 96 lesions were scored as BI-RADS III, 112 cases as BI-RADS IV and 48 cases as BI-RADS V. 72% of the patients were postmenopausal and 28% premenopausal. Histology revealed benign results in 138 lesions and malignant results in 118 lesions (DCIS=62, ID-Ca=51, IL-Ca=5, mucinous Ca=1). Mammography yielded high values with 91% sensi-

tivity and 62% specificity. Comparing EIS with the gold standard of histology there were 89 true positive, 58 true negative, 80 false positive and 29 false negative EIS results, resulting in an overall sensitivity of EIS of 75.4%, specificity 42.03%, negative predictive value 66.7% and positive predictive value 52.7%. Sensitivity and specificity of EIS didn't differ for the different histological differentiations or for the degree of invasion. Looking for the presence or absence of “spots”, no significant differences were found regarding sensitivity and specificity. In a further evaluation step the sensitivity and specificity of EIS was analyzed for the different histological differentiations. No significant differences were found either for the histological subtypes (invasive ductal vs. lobular carcinoma) or for the degree of invasion (*in situ* vs. invasive carcinoma) or the degree of calcification. As a last step of evaluation the influence of the lesion size was checked and strong differences were found. While EIS correctly diagnosed 85% of lesions <10 mm in size, only 64% of lesions >10 mm were detected. EIS was false negative in 20 ID-Ca, 3 IL-Ca, 1 IDL-Ca, 4 DCIS, and 1 mucinous carcinoma. The most frequent lesion types for false positives were nodular mastopathy (55/80 FP) and fibroadenoma (21/80 FP). Patient acceptance of EIS was 100% and there were no dropouts because of movement artifacts.

Discussion

To the best of our knowledge there has been only one publication about EIS using the same setup and software as in our study. Glickman (5) reported results of an independent test group with 87 carcinomas, 153 benign and 356 asymptomatic cases. Histology was only available in symptomatic cases. The sensitivity in this publication was 84% with a specificity of 52%. Fuchsjäger (6) reported, in an oral presentation, the preliminary results of the European multicenter trial (Vienna, Jena, Stockholm and Frankfurt) with the LOS-software at the RSNA 2001. The early results (130 lesions) of this study, which we also participated in, were a sensitivity of 88.4% and specificity of 50.6%. At the RSNA 2002 again Fuchsjäger (7) summarized the results of another multi-institutional study on 260 lesions with a sensitivity of 89% and a specificity of 62%. In this study Fuchsjäger found the same increased sensitivities for smaller cancers as we did in our study (79% ≥ 10 mm vs. 100% ≤ 10 mm). Also there were no differences in specificity for small and large lesions. However, the overall level of values is much higher in both studies than in our study. This may be caused by a high percentage of lesions in our patient group, which were located at a greater depth, which is known to be a negative factor for EIS. This was nicely demonstrated by Malich (8) in his phantom experiments and his further *in vivo* study (9-11). Moreover we did not include lesions only visible sonographically in our study and we did not use sonography to localize the lesion before the EIS examination but did multiple measurements in the



Figure 1: TransScan machine TS 2000.

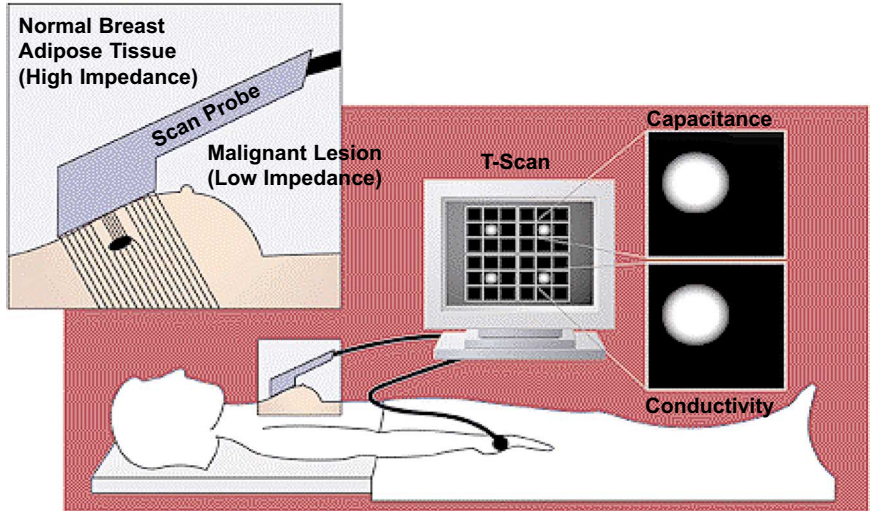


Figure 2: Schematic TransScan examination (Initial software).



Figure 3: Clinical TransScan examination.

suspect area. The low specificity is a result of the high number of false positives (Score 4-5) that we had in our study.

There have been many more publications about EIS using the initial setup and software. Wersebe (12) reported, in her pub-

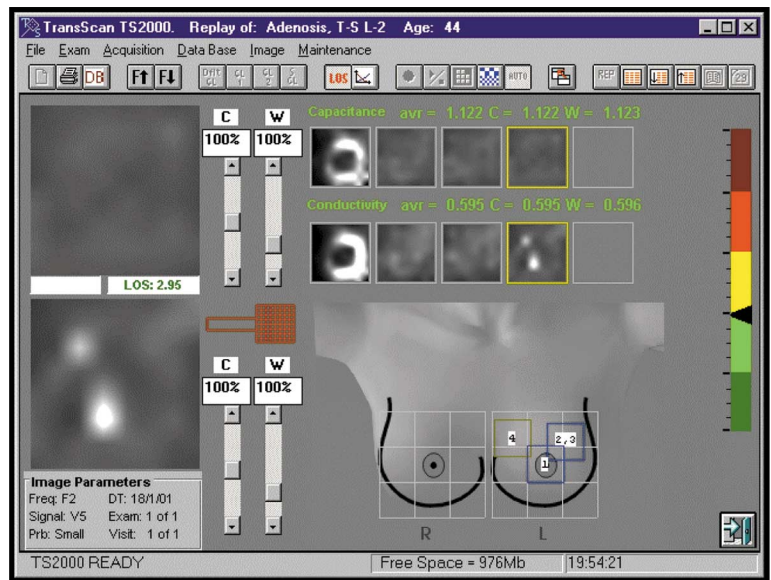


Figure 4: TransScan examination window (LOS-Software).

lication about 129 histologically proven lesions, the lowest values for EIS with an overall sensitivity of 62% and a specificity of 69%. Again a correlation was found in this study between the tumor size and sensitivity of EIS with a sensitivity of 48% for lesions ≥ 48 mm and 71% for 11-20 mm, respectively. However, the authors also report a higher specificity of EIS for lesions ≥ 20 mm, which does not correspond to our results. In an earlier report Fuchsjäger (13) also published his results about the initial EIS setup with 95 histological proven lesions and found a sensitivity of 77.3% and a specificity of 82.3%. Malich (8) examined 387 lesions with the initial setup and found an overall sensitivity of 79% and a specificity of 64%. The sensitivity without knowledge of depth and size was 64.6%, with knowledge of size 76.2% and with knowledge of both 85.9%. The specificity was not significantly influenced.

Conclusion

Relative to the results of EIS with the initial setup (10-12) the LOS-software represents a real improvement of this method. The sensitivity of EIS with this advanced setup, however, still is far too low for routine clinical use or even a screening setup. The increased sensitivity for small malignant lesions could indicate a potential of this method and in this context a combined ultrasound or even an x-ray system with an EIS probe may have a higher clinical impact.

Furthermore, the technical considerations of Scholz (14, 15) regarding hardware changes, which allow EIS measurements at much higher frequencies, may increase the sensitivity and specificity of this promising method.

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