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Electrical impedance scanning as a new imaging modality in breast cancer detection—a short review of clinical value on breast application, limitations and perspectives

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Abstract

Objective. Cancer cells exhibit altered local dielectric properties compared to normal cells, measurable as different electrical conductance and capacitance using electrical impedance scanning (EIS). Therefore, active biocompatible current is applied to the patient for calculation of both parameters taking into account frequency, voltage and current flow.

Subjects and methods. 240 women with 280 sonographically and/or mammographically suspicious findings were examined using EIS. All lesions were histologically proven. A lesion was scored as positive, when a focal increased conductance and/or capacitance was measurable using EIS. The lesion was visible as a bright area in a 256 grey-scale computer output. Due to system limitations patients having a pacemaker or pregnant had to be excluded from the study.

Results. 91/113 malignant and 108/167 benign lesions were correctly identified using EIS (80.5% sensitivity, 64.7% specificity). NPV and PPV of 83.1% and 60.7% were observed, respectively. Accuracy was 0.73.

A wide range of factors can induce false positive results, although by an experienced observer a number of these findings can be detected such as scars, skin alterations, contact artefacts, air bubbles and naevi, hairs and interfering bone. Based upon visibility on ultrasound (194 lesions visible, 86 not visible) significant differences in the detection rate occurred. Histology-dependent detectability rate varied significantly with lowest rate in CIS-cases (50%). Specificity values varied histology-depending, too; probably depending on the rate of proliferation between 75% (inflammatory lesions) and papillomata (50%). Best detectability was observed in malignant lesions with a size between 20 and 30 mm.

Further possible applications will be discussed regarding the currently available literature (lymph nodes, salivary glands, mathematical and animal based models).

Conclusion. EIS appears to be a promising new additional technology providing a rather high sensitivity for the verification of suspicious breast lesions. Further investigations on histomorphological characteristics of false negative as well as false positive lesions are essential to gain further knowledge about the bioelectricity of breast lesions. Currently high false positive rate and observer-dependence limit clinical usage.

Keywords: Breast cancer; Electrical impedance; Conductance; Mammography; Breast ultrasound; Adjunctive technology

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1. Introduction

Fricke and Morse first described altered capacitance values of breast cancer tissue versus normal breast tissue in 1926 [1]. Continuing from that first description, the principle that electrical impedance properties of tissues can offer interesting and potentially valuable information—quantifiable as the parameters of electrical conductance and electrical capacitance kept under investigation over decades. In the normal breast, moderate variations of these values are observed, reflecting the differences among various types of breast tissue [2]. In contrast to these observations in normal tissue, malignant tumours show substantially increased capacitance and conductance values resulting in a decreased impedance [2–4]. In vitro studies have shown 20–40-fold higher values for both parameters in malignant as compared to normal tissue [2]. These differences are attributed to changes of cellular water content, amount of extracellular fluid, membrane properties, packing density, destruction of tight junctions and cell membranes and changed orientation of malignant cells [5,6]. Most benign lesions exhibit the electrical properties of normal tissue, and not of malignancies, thereby offering the potential to differentiate benign and malignant [3,7]. Mainly in the early 1990s the BIOFIELD-technology for measurement of passive skin-surface electropotentials has been investigated [6]. However, EIS differs significantly from this approach in that EIS measures active-applied, alternating current as opposed to inherent, biological electricity (DC versus AC).

Early EIS results were published in 1990 by Piperno et al. [8]. During the last decade, the technical equipment and application mode has undergone significant refinement. The current EIS system, TransScan TS2000 (TransScan Medical, Ltd., Israel; distributed by Siemens-Elema, Stockholm, Sweden) is a real-time, non-invasive method by which the increased conductance and capacitance of a malignant tumour is measured on the skin surface of the breast. To date, only limited clinical experience and initial results of electrical impedance scanning in the detection of malignancies have been published [9,10]. In 1999, TS2000 was approved for use by the American Food and Drug Administration (FDA) as an adjunct to mammography for the evaluation of equivocal breast lesions [11].

The primary goal of this study was to evaluate the association of EIS-detectability rates and size of the lesions. In addition, it was the aim to clarify whether detectability rate of EIS depends on sonographical visibility. Finally a short overview about currently available applications, limitations and perspectives of EIS is given.

2. Patients and methods

Beginning in April 1999 to March 2001, 240 consecutive eligible patients (mean age 57 years, SD 13 years) presenting 280 suspicious lesions were included in this prospective study performed at our institution. Eligibility was determined by the patient having a finding in mammography and/or ultrasound, not being pregnant, and not having a pacemaker. Each patient received information about this technique; all voluntarily accepted the examination.

The mammographic and sonographic results were classified by different experienced radiologists according to the level of suspicion (LOS) categorisation method.

Lesions of LOS 2-5 for which pathology results would be available were involved in the study. The EIS examination was performed with full knowledge of the results of mammography and ultrasound.

The principle measuring procedure is described in the following way:

A low-level, biocompatible, active electrical current (0.1 mA) is applied using different frequencies (100–5000 Hz currently available) using a voltage of 0.5 V (range from 0.1 to 0.5 V available) via a metal-cylinder (base electrode) held in the recumbent patient's hand. This current flows through the patient's body. Good contact of the metal-cylinder to the patient's skin is achieved by applying ultrasound gel to the metal-cylinder. The scan probe held by the examiner is applied to the breast at the region of interest. Good contact is facilitated with the use of ultrasound gel on the

scanner-field, too. The array of sensors (8×8 matrix) on the scan probe measures electrical current. Measuring area is approximately 3.5×3.5 cm in size, inflexible and quadrant. From the measured current, voltage and frequency the computer calculates tissue-related resistivity and finally extrapolates conductance and capacitance. The display of both the conductance and the capacitance values are separately visible real time on a 256-grey scale on the monitor. An increased conductance only or conductance and capacitance value is visible as a "bright white spot". Although a range of frequencies are used and stored, according to the FDA-approval currently used reading frequency is 200 Hz when used on humans. Recordings were taken at the region of interest. The skin surface at the scanned location was carefully inspected, as artefacts caused by skin lesions, scars, moles, contact artefacts, bone, or air bubbles can represent high conductance or capacitance and therefore also create spots [12]. The impedance images were interpreted in accordance with established criteria [9,12] and as described below. One examination was performed in approximately 5 min. The nipple always shows as a bright signal, and should be bilaterally comparable (size, intensity) within the same healthy patient. However, any inconsistency between the nipple signal of left and right breast was not registered as a positive finding, due to the fact that the observed nipple signals, even in healthy patients, differ in their appearance. Only if there was a separable focal spot in the nipple area (indicative of retroareolar malignancy), the spot was classified as a positive finding in EIS.

The clinical values as characterised by the resulting sensitivity, specificity, false positive rate, false negative rate, positive predictive value, negative predictive value and accuracy were evaluated with respect to the suspicious lesion. In addition, size, location, depth and distance from skin level were measured for lesions which were visible in ultrasound.

Finally all lesions were biopsy-proven. Selection of technique was based upon the lesion and patient: ultrasound-guided puncture of liquid tissue with cytology, ultrasound-guided core needle-biopsy (each with at least 3 cylinders of tissue), minimally-invasive breast biopsy (each with at least 12 cylinders of tissue), local surgical excision of the lesion, quadrant resection, or mastectomy. For all proven malignancies, the elected treatment method was either local surgical excision of the lesion, quadrant resection, or mastectomy, followed by other appropriate therapy measures.

3. Results

3.1. Radiological and pathological results

The following histopathological findings and mean sizes of the suspicious findings were observed. As depicted in Table 1, 16 of the examined lesions were ductal carcinoma in situ. 8/16 DCIS-cases were correctly detected by EIS, whereas eight were falsely detected as negative (sensitivity 50%).

Taking into account only invasive malignancies, EIS detected 83/97 lesions correctly as positive, yielding to a sensitivity of 85.6%. These data are presented in Table 2.

Table 1
Histopathological findings

Histopathological finding	Number of lesions	Percentage
Invasive ductal carcinoma	61	54.0
Invasive lobular carcinoma	22	19.5
Invasive tubular carcinoma	6	5.2
DCIS	16	14.2
Other malignancies	8	7.1
Malignancies total	113	100
Hyperplasia/metaplasia	36	21.6
Fibroadenoma	33	19.8
Cystic tissue	29	17.3
Fibrotic tissue	29	17.3
Adenosis/adenoma	20	12.0
Papilloma	8	4.8
Other histologies (necrosis, lipoma, etc.)	12	7.2
Total benign lesions	167	100
Total of all lesions	280	—

Table 2
EIS parameter in CIS and in invasive cancers

	CIS	Invasive malignancies
Total no. of cases	16	97
TP	8	83
FN	8	14
Detection rate	50.0	85.6

In total 91/113 histologically proven invasive malignant lesions were correctly detected using EIS (sensitivity 80.5%), whereas 108/167 benign lesions showed no spot using EIS (specificity 64.7%), leading to a value of NPV 83.1% and PPV 60.7%, respectively. Accuracy was 72.6%.

In correlation to histological findings, detection rate of malignancies was: 54/61 invasive ductal cancers (88.5%), 17/22 invasive lobular cancers (77.3%), 6/6 invasive tubular cancers (100%) and 6/8 other malignant invasive findings.

Specificity values varied histology-dependent significantly: inflammatory-reactive findings were correctly negative in EIS in 9/12 cases (75%), fibroadenomata in 23/33 (69.7%), cysts in 20/29 cases (68.9%), fibrosis 19/29 (65.5%) adenosis 12/20 (60.0%), hyperplasia 21/36 (58.3%) and papilloma in 4/8cases(50%).

In addition, the association of EIS results and lesion sizes was investigated: accuracy of lesions <10 mm in size was 69.5%, and 70.7% in lesions less than 2 cm in longest diameter. Best accuracy was achieved in lesions between 20 and 30 mm in longest diameter (80.6%), whereas accuracy decreased for larger lesions to 72.7%.

The majority of our malignant findings was sonographically visible. However, tumour detection rate of EIS differed dependent on sonographical visibility: 86/102 malignant lesions sonographically visible were correctly detected by EIS, whereas only 5/11 sonographically not visible lesions showed correctly positive signal in EIS. Detection rate varied between 84.3% and 45.5% (highly significant).

Specificity values of the two subgroups were almost similar: 58/92 sonographically visible lesions of benign nature were correctly negative in EIS and 50/75 sonographically not visible lesions showed a correctly negative EIS-result (63.0% versus 66.7%; not significant).

3.2. Technical results

Contact problems occurred mainly due to the inflexible scanner size in small breasts and on peripheral lesions. False positive results occurred in prominent findings of the breast as well as on (known) skin alterations. Lesions were difficult to interpret especially when located close to the chest wall (due to contact problems) and close to the nipple (due to the bright signal of the nipple itself). When interpreting not only 200 Hz results but the range of frequencies, it occurred that bright spots switched into black areas in higher frequencies. Even in very superficially located cysts no visualisable change of conductance/capacitance occurred. EIS was interpreted as positive, when at least conductance showed a focal increased value. In 65/113 cases of a malignant finding, capacitance did not reveal such a result. The absolute values of conductance and capacitance depend critically on the pressure between breast and scanner and vary, consequently, investigator dependent. However, an interpretation of the absolute values is not possible using the currently available equipment.

4. Discussion

Initial results using electrical impedance scanning as an additional diagnostic tool were first described by Fields [13] and published by Malich [9] with promising values of true positive results.

Both studies found slightly higher values of sensitivity than in the actual study: 86% and 93% [9,13]. Nissan and co-workers described a sensitivity of 86% for EIS, although slightly different study protocol conditions were used (EIS-findings scored in a range of 1–5, rather than positive/negative) [14].

Within the last 2 years some important new results of clinical as well as theoretical studies were published.

It is documented in several studies that due to the currently high false positive rate of the

available EIS-system, its usage should be limited to adjunctive examinations [10,13,14].

It was proven that the FP-rate of EIS shows significant association to the hormonal status and state of the cycle of women [15].

Using an animal based model (VX2-tumours implanted in the lower leg of White New Zealand rabbits) minimal spatial resolution in vivo was found to be depth dependent [16]. Smallest detected tumour in this study set-up was 9 mm^3 in size approximately.

Using κ-factor analysis it could be shown on 100 histologically proven, mammographically suspicious or dubious cases, that this value is 0.62 for US and EIS (some individual) and 0.82 (individual) for EIS and MRM. Consequently, additional usage of EIS to US seems to be useful in those cases, where MRM is not available or contraindicated [17].

Mathematical simulations by Scholz and Anderson demonstrated and proved limitations of the current system, especially regarding the depth and spatial resolution [18].

In this study it could be demonstrated that not only depth, but also size of the lesion has an influence on the detection rate. In addition, the exact knowledge of the localisation of the lesion (using ultrasound) increases the tumour detection rate significantly. When using ultrasound and EIS, patient is recumbent, whereas the position is standing having X-ray. Thus, the difficulties finding the exact localisation of the mamographically suspicious, sonographically not visible lesions might explain, the lower sensitivity of this subgroup.

The following factors are important to address because they may influence both, sensitivity and specificity of the EIS-examination:

- Skin artefacts, bones, moles, contact artefacts and scars can induce false positive results.
- Sharpness and brightness of spots depend on the depth of the lesion and, consequently are highest in superficially located structures. The currently measured false negative rate may be associated to physical limitations as discussed by Scholz and Anderson using mathematical simulations. In this study theoretical limitations of the technique, mainly induced by interferences of the current flow depending on the depth are proven [18]. Due to limited discrimination of the conductance values for lesions located 3 cm or deeper, the interfering non-malignant tissue between the lesion and surface acts as a buffer in assimilating the electrical parameters of both tissues. This would explain why the focal increased values failed to register conductance high enough to induce a focal spot.
- Inframammary ridge as well as nipple surrounding may induce falsely positive signals as well as prominent lesions. Freshly biopsied and surgically treated lesions regularly induce a spot due to the injury of the skin (in biopsies dependent on needle thickness).

Summarizing of the aforementioned facts, the clinical value of EIS depends critically on the experience of the user. This might explain the differing values of sensitivity of several groups having different levels of experience as presented on European Congress of Radiology 2001 [19–21]. A new software version implementing a range of frequencies, the nipple signal as well as the relative changes of conductance and capacitance of the whole scanning field presents the results of EIS examination in a five level output given by the system, observer independent according to the BIRADS-classification. This software advance increases the objectivity of the examination [22].

Cysts usually do not cause a focal increase of conductance, probably because the cystic membrane isolates the liquid from the surrounding (sometimes visible as a slightly darker area in EIS). However, some cancer-induced tissues are also surrounded by membranes or capsules (e.g. the ovarian metastasis of the present study), which may be the source for the false negative cases. On the other hand isolated, superficially located cysts should induce a focally decreased conductance / capacitance potentially visible as a "dark spot". This phenomenon never occurred in our examinations, the reason for this absence remain unclear.

In addition, it is unclear why the FP-value differs for various histological findings between 18.8% and 50.0%. Potentially the higher proliferation

rate of papillomata and hyper/metaplasia in contrast to cysts and fibroadenomas may induce a focal increased conductance.

Reasons for the changes in conductance of malignant tissue are still under investigation. This property of tissue seems to be associated with changes typical for invasive cancers: destroyed tight junctions and cell membranes, increased pathological perfusion, and amount of extracellular fluid, etc. [5]. This might explain why the detection rate of carcinoma in situ is significantly lower than that of invasive cancers, as suggested by Rigaud and coworkers [5].

It remains in parts unclear, why a remarkable number of malignant lesions did not induce a focal increased value of capacitance. The observed discrepancy of focal increased conductance and homogeneous (not focally increased) capacitance should be addressed regarding histopathological findings in future studies.

Few studies are published using EIS on other locations outside the breast. Up to now it seems to be possible to use EIS in order to achieve a clarification of suspicious lymph nodes of various locations (best: cervically, inguinally located) [23]. In addition, EIS might be of value in the differentiation of sonographically suspicious findings of parotid and submandibular gland [24]. The usage for melanoma-metastases revealed only in parts promising results [25], however, a new probe is available to investigate and clarify naevi and melanomas itself.

Technical developments should focus on an increased scanner flexibility, on an impedance based biopsy set-up as well as an application set-up of EIS which is performed in breast-positions similar to those of mammography.

Further studies in close co-operation with pathologists are essential to increase the knowledge of electrophysiological and electropathological changes and characteristics in various lesions and tissue-types in vivo.

5. Summary

We conclude that EIS is a promising additional technique for the detection of cancer-induced breast lesions. In addition, this new technology might be of interest in regions other than breast. However, currently low specificity and observer-dependency limit its clinical application.

Our institution continues to actively pursue this new technology on account of the promising results to date.

References

[1] H. Fricke, S. Morse, J. Cancer Res. 16 (1926) 340.
[2] A. Surowiec, S. Stuchly, R. Barr, A. Swarup, IEEE Trans.Biomed. Eng. 35 (1988) 257.
[3] J. Jossinet, Physiol Meas. 19 (1998) 61.
[4] N. Mitsuyama, T. Morimoto, Y. Kinouchi, et al., Nippon Ganka Gakkai Zasshi 89 (1988) 251.
[5] B. Rigaud, J.P. Morucci, N. Chauveau, Clin. Rev. Biomed. Eng. 24 (1996) 257.
[6] J. Cuzick, R. Holland, V. Barth, R. Davies, M. Faupel, I. Fentiman, H.J. Frischbier, J.L. LaMarque, M. Merson, V. Sacchini, D. Vanel, U. Veronesi, Lancet 352(9125) (1998) 359.
[7] J. Jossinet, Med. Biol. Eng. Comput. 34 (1996) 346.
[8] G. Piperno, E.H. Frei, M. Moshitzky, Front. Med. Biol. Eng. 2 (1990) 111.
[9] A. Malich, T. Fritsch, M.G. Freesmeyer, M. Fleck, A. Anderson, W.A. Kaiser, Eur. Radiol. 10 (2000) 1555.
[10] A. Malich, M. Facius, C. Marx, et al., Eur. Radiol. 10 (2000) F51.
[11] FDA Premarket Approval database, http://www.fda.gov/cdrh/pma/pmaapr99.html. P970033, 4/16/99.
[12] TransScan TS 2000 User Manual.
[13] S.I. Fields, M. Rossman, E. Phillips, et al., Radiology 209 (Suppl. 1) (1998) 272.
[14] A. Nissan, R.M. Spira, H.R. Freund, S. Fields, Eur. J. Surg. Oncol. 28 (Suppl. 1) (2000) 282.
[15] C. Perlet, M. Kessler, S. Lenington, H. Sittek, M. Reiser, Eur. Radiol. 10 (2000) 1550.
[16] A. Malich, T. Böhme, M. Facius, M. Fleck, W.A. Kaiser, Eur. Radiol. 11/2 (Suppl. 1) (2001) 260.
[17] A. Malich, T. Boehm, M. Facius, M. Freesmeyer, M. Fleck, R. Anderson, K.A. Kaiser, Clin Radiol. 56 (2001) 278.
[18] B. Scholz, R. Anderson, Electromedica 68 (2000) 35.
[19] M.H. Fuchsjäger, H. Ringl, T.H. Helbich, M. Funovics, M. Rudas, G. Wolf, Eur. Radiol. 11/2 (Suppl. 1) (2001) 266.
[20] A. Wersebe, K.C. Siegmann, N. Fersis, U. Vogel, C.D. Claussen, M. Müller-Schimpfle, Eur. Radiol. 11/2 (Suppl. 1) (2001) 266.
[21] A. Malich, T. Böhm, M. Facius, M.G. Freesmeyer, M. Fleck, W.A. Kaiser, R. Anderson, Eur. Radiol. 11/2 (Suppl. 1) (2001) 266.

[22] J.A. Glickman, et al., Novel EIS postprocessing algorithm for breast cancer diagnosis, IEEE Trans. Med. Imaging 21 (2002) 710–712.
[23] A. Malich, T. Fritsch, C. Mauch, T. Boehm, M. Freesmeyer, M. Fleck, R. Anderson, W.A. Kaiser, Br. J. Radiol. 74 (2001) 42.
[24] M. Facius, A. Malich, R. Anderson, M. Fleck, W.A. Kaiser, Eur. Radiol. 11/2 (Suppl. 1) (2001) 306.
[25] M. Facius, A. Malich, A. Anderson, M. Fleck, W.A. Kaiser, Eur. Radiol. 11/2 (Suppl. 1) (2001) 191.