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An assessment of computed tomography laser mammography in breast cancer diagnosis

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ABSTRACT

Introduction: Computed tomography laser mammography (CTLM) is a type of opticaltomography imaging. The main advantage of optical methods is the absence of ionizing radiation. Therefore, it can be used regardless of the age or pregnancy condition of the patient. Moreover, CTLM does not require breast compression.

Aim: The aim of the study is to evaluate the accuracy of CTLM for detecting breast cancer and therefore to asses the suitability to place this new technique in the diagnostic chain of procedures.

Material and methods: A group of 175 white European women were enrolled in the study (age 25–79, average 55 years old). All of the subjects had a CTLM performed in 2006 at the Department of Radiodiagnostics in the Maria Sklodowska-Curie Memorial Cancer Centre.

Results and discussion: Based on the histopathology, breast cancer was found in 70 (40%) cases; in 105 (60%) cases malignancy was not found. When comparing CTLM results to the golden standard of histopathology, a differentiation between benign and malignant foci was found, obtaining the following values for the sensitivity of 71%, specificity of 72%, PPV 63,2% and NPV 79,1%).

Conclusions: The obtained levels of sensitivity and specificity in this study exclude CTLM as a stand-alone diagnostic method and it is assessed as unable to compete with current state-of-the-art approaches.

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1. INTRODUCTION

Breast cancer is the most common malignant tumor found in women. Efficient disease prevention is very difficult, almost impossible. However, breast cancer detection in its early and clinically limited stage gives women a chance for full recovery. The basic method for breast cancer detection is X-ray mammography. However, this examination has two major limitations. The first is ionizing radiation and the second is an insufficient level of sensitivity in breast cancer detection, especially in dense breasts. These limitations provide the motivation for searching new methods that would be more efficient in early cancer stage detection. One of these methods is computed tomography laser mammography (CTLM), which is a type of optical tomography imaging.

The first attempts of breast imaging with optical methods using 600–1000 nm wavelength date back to the 1930's. However, technical issues concerning low sensitivity and specificity for many years precluded this method from clinical practice.[1] The return of optical imaging was in the last decade of the 20th century.[2] The main advantage of optical methods is the absence of ionizing radiation. Therefore, it can be used regardless of the age or pregnancy condition of the patient. Moreover, laser mammography does not require breast compression and a dense breast is not as problematic as in radio-mammography.[3] The laser light used in a CTLM scanner has a wavelength of 808 nm and it is strongly absorbed by the haemoglobin, but it penetrates other tissues of the breast with ease.[4,5]

2. AIM

The aim of this study is to evaluate the accuracy of laser mammography in breast cancer detection and also to create reference images of breast cancer with CTLM and therefore to asses the suitability to placing this new technique in the diagnostic chain of procedures.

3. MATERIAL AND METHODS

The study included a group of 175 white European women, age range 25–79 (average 55 years old). This patient sample was selected by requiring a positive result with RTG mammography (MMG) and/or with an ultrasound (US) examination.

Afterwards, in each case a CTLM acquisition and histopathological (HP) verification was performed. All examinations were performed in 2006, at the Department of Radiology, Maria Curie-Skłodowska Memorial Cancer Centre and at the Institute of Oncology, Gliwice Branch. None of the patients included in the study had multiple lesions in the breasts. Therefore, the analysis was conducted on 175 pathological lesions.

The study was performed using CTLM scanner Model 1020 (Imaging Diagnostics Systems, FL, USA). The system's wavelength was 808 nm. The result of a CTLM examination was determined positive, if there were regions of a pathological increment of light absorption found. This result was considered to be cancer positive. The negative CTLM result was determined, if there were no pathological light absorption regions found. This result excluded the presence of cancer. It was established that the region of high light absorption corresponds to foci visible in the MMG/USG, if it was found in the same quadrant. Regions of high light absorption (CTLM+) were analyzed in the second step using Matlab (Mathworks, MA, USA) software.

Two factors were calculated using MATLAB:

1. Anisotropy factor (AF). An ellipsoid was fitted to each region. A ratio between the standard deviation and the root mean square of ellipsoid's radiuses was calculated. This way the anisotropy factor was independent from spatial orientation and it ranged from 0 in the case of a sphere to 1 for an ellipsoid.
2. Signal-to-noise (SNR). It was calculated as a ratio between the median of values in the region of interest and the median value of the surrounding area.

The findings of CTLM were compared with the HP results to examine sensitivity and specificity of the method in breast cancer. Images of breast cancer described as CTLM+ or CTLM– were compared with:

- morphology in mammography (size less and more than 2 cm),
- HP type (preinvasive, infiltrating cancer), malignancy level (G).

The null hypothesis of no correlation between CTLM and other breast cancer properties was tested with 2 Pearson's test with Yate's correction for a small group. The correlation between CTLM and the malignancy level was verified with a Mann-Whitney's test.

Prior to analysis used patients' records were anonymized and de-identified for this study in accordance to Polish law. The approval of Local Bioethics Commission, Data Protection Agency and participants was not required.

4. RESULTS

The analysis consisted of 175 findings. In 70 cases it was cancer and in 105 cases it was benign. This classification was confirmed by microscopic examinations and 12 months of follow-up. The most commonly found was infiltrating ductal cancer (65%). In a subgroup of benign lesions, the most occurring was dysplasia (78%). In 79 cases out of a total of 175 (45%), a strong light absorption was found and in the remaining 96 cases the CTLM result was negative. The CTLM+ result was true positive in 63% of the cases and CTLM– was a true negative in 79%.

Increased light absorption CTLM+ was found significantly more often in cases of a malignant cancer (50/70 = 71%) than in the benign (29/105 = 28%) ones ($P < 0.001$).

In evaluating if the CTLM is beneficial as a predictive factor distinguishing malignant and benign types of lesions, a sensitivity of 71% and specificity of 72% were found. The positive predictive value was 63.2% and the negative predictive value was 79.1%.[6]

SNR was calculated for each of 79 CTLM+ cases. The obtained values ranged from 1.08 up to 1.8. The SNR for most of the lesions was lower than 1.3; therefore, to enhance detectability, a 3D data representation and contrast enhancing colour scales were used (Figure 1). Only with these tools, the delineation of low contrast changes was possible.

Unfortunately like AF, the SNR was not useful to discriminate between benign and malignant cases. The statistically significant differences were not found. A positive result of CTLM was found in 32 of 45 (71%) total cases of cancer with a size smaller than 2 cm. Similarly, in cases of cancer with a size greater than 2 cm, a positive CTLM was found in 18 of total of 25 (72%) (Table 1).

The HP result was not clear in 8 cases (Table 2). Therefore, only 62 cases could be included in this part of the analysis. According to the HP results, the material was divided into the subgroups: infiltrating cancers (54 cases) and pre-invasive cancers (8 cases). In the first group of cancers 40 cases of CTLM+ were found and in the latter only 5 cases.

Although the statistical tests showed no relation between the CTLM result and the cancer growth type, it may be blurred by the low and unbalanced number of cases in the second subgroup.

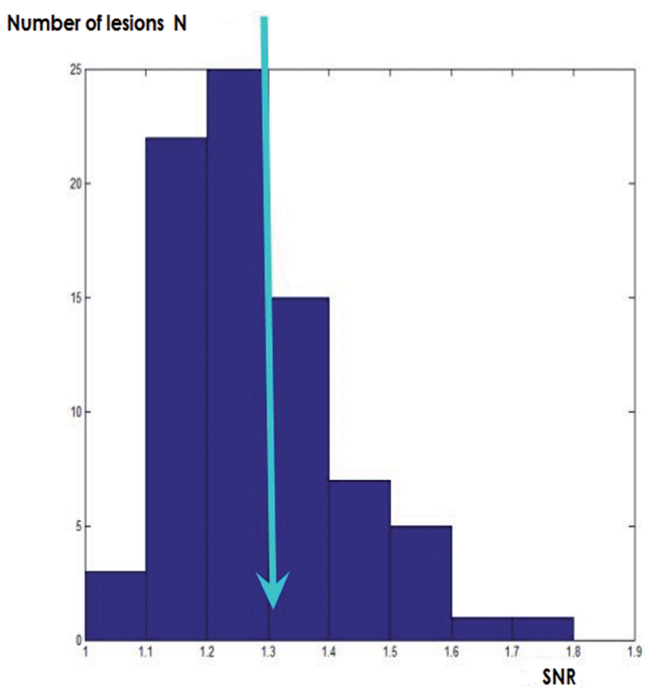

Figure 1. SNR value in CTLM+ lesions.

Table 1. Dependence of CTLM results and line diameter of a tumor (cancer), correlation between CTLM results and HP properties.

	Line diameter of a tumour less than 2 cm	Line diameter of a tumour more than 2 cm
CTML+ CTML–	32 13	18 7
Pearson's test with Yate's correction	X	P
	0.01 0.04	0.937 0.843

The connection between CTLM results and malignancy level (G) was analysed in a subgroup of 56 cases (Table 3). However, no statistically significant difference was found.

A comparison between results of CTLM and HP of breast lesions was shown in Table 4. The low number of

Table 2. Correlation of histologic type of breast cancer with CTLM image.

	Invasive cancers	Preinvasive cancers
CTML+ CTML–	40 14	5 3
Pearson's test with Yate's correction	X	P
	0.469015 0.067726	0.4934408 0.7946774

Table 3. Correlation of grade of malignancy with CTLM image.

Grade of malignancy	Number of lesions	CTLM+	CTLM–
G1	12	10/12; 83%	2/12; 17%
G2	32	23/32; 72%	9/32; 28%
G3	12	8/12; 66%	4/12; 34%

Table 4. Comparison of CTLM and HP results in breast lesions.

HP result	No. of lesions	CTML+ n(%)	CTLM– n(%)	False negative	False positive
Ductal carcinoma in situ (DCIS) percent from the line	8	5 (65%)	3 (37%)	3/8; 37%	
Invasive ductal cancer percent from the line	45	34 (76%)	11 (24%)	11/45; 24%	
Infiltrating lobular cancer percent from the line	7	6 (86%)	1 (14%)	1/7; 14%	
Undefined cancers, mucoid, papillary percent from the line	10	5 (50%)	5 (50%)	5/10; 50%	
Fibroadenoma percent from the line	9	5 (55%)	4 (45%)		5/9; 55%
Benign dysplasia percent from the line	83	17 (20%)	66 (80%)		17/83; 20%
Atypical ductal hyperplasia percent from the line	8	6 (75%)	2 (25%)		6/8; 75%
Papilloma percent from the line	3	1 (33%)	2 (67%)		1/3; 33%
Tubular adenoma percent from the line	1	_	1 (100%)		0/1; 0%
Radial scar percent from the line	1	_	1 (100%)		0/1; 0%
Sum	175	79	96	20/70; 29%	29/105; 28%

cases in subgroups made the interpretation of results very difficult. The regions of high light absorption were significantly more often found in cases of atypical ductal hyperplasia, than in benign dysplasia ($P < 0.01$). No connections between CTLM results and the linear size or cancer growth type or malignancy level were found.

5. DISCUSSION

In the group of 175 cases included in the study, in 70 cases, a cancer was found and in 105 cases, the foci were benign. A positive CTLM result was significantly found more often in malignant cases (71%) than in benign cases (28%) with $P < 0.001$. Such a significantly more frequent positive CTLM result in a group of cancers can be explained by the presence of a dense vascular network and a higher concentration of haemoglobin than found in normal breast tissue.[4,5]

Obtained results are in an agreement with those presented by Floery.[7] He used a similar CTLM scanner with 808-nm wavelength and found a positive CTLM result in 70% of invasive cancer cases. Assuming the positive CTLM result as diagnostic criteria, the sensitivity was found at the level of 71% and specificity at the level of 72%. The false-positive (29%) and false-negative (28%) number of cases found in this material is at a similar level found in the literature (Floery 30%, Athanasiou 27%).[1,7]

The sensitivity and specificity of CTLM was lower than conventional X-ray mammography. Intriguing questions arose from the data analysis: Why some of the cancers do not attenuate laser light and why do benign lesions in some cases show increased haemoglobin deposition?

In a group of 70 cancers (62 invasive and 8 DCIS) 20 lesions did not show increased light attenuation. Preinvasive cancers appeared more often CTLM– than the invasive ones. However, these differences were not statistically significant and a low number of DCIS cases could influence the result.

The opinions regarding neoangiogenesis in ductal cancer in situ are not coherent.[8] DCIS is limited by the basement membrane. It does not infiltrate the stroma and it does not present the ability of angiogenesis.[9] However, there are reports[10–12] that state the ductal cancer (DCIS) may present hypervascularization. In spite of changes, the DCIS does not grow beyond the basement membrane, but the vessel's density (MVD) in stroma between ducts affected by DCIS may be higher than that of a normal tissue.[10,11] This fact may explain positive CTLM results in 5/8 cancers in the subgroup.

The situation in atypical ductal hyperplasia cases is similar. This may justify the concept that the angiogenesis is not necessarily a typical feature of invasive cancers, but it may occur in preneoplastic lesions.[11–13] In the analysed group, a positive CTLM result was found in 29/105 (28%) benign lesions. Most of the ADH tumours (6/8) presented elevated laser light absorption (CTLM+), but even 1 in 5 cases of benign dysplasia was CTLM+.

Similarly, Floery[7] found in group of 53 benign lesions 34% of CTLM+ results. The features of hypervascularization in benign lesions were found by Bobek-Billewicz as well.[5] The level of vascularization in fibroadenomas varies and depends on the proportion of cellular and fibrous elements[14] – the more cellular components, the higher the level of vascularization.[15] The HP image of atypical ductal hyperplasia is close to the one of DCIS. DCIS is an atypical epithelial hyperplasia affecting at least two ducts or covering an area of 2–3 mm. If such hyperplasia is not accompanied by high grade atypical and necrotic foci, a smaller lesion is considered to be an atypical ductal hyperplasia.[16]

For the facts mentioned above, in 2003 the WHO proposed a common name for atypical ductal hyperplasia and DCIS – intraductal neoplasia.[1] In both the lesions there is an increased vascularization in stroma between affected ducts.[10] If within the performed examinations 8 cases of the atypical ductal hyperplasia were in the same group as DCIS, the specificity would rise from 72% to 76%.

The Anisotropy factor was analysed in order to find differences between malignant and benign lesions with high laser light absorption. The spherical lesions were found with similar frequency in both subgroups (41% vs. 52%). This concurs in agreement with Floery,[7] stating that the shape of the lesion is not a diagnostic parameter. No correlation between light attenuation and malignancy level G was found. The highest number of false negative results was found in group G3. It can be explained by a more frequent presence of necrosis, which does not absorb laser light.

Different results were presented by Floery,[7] who was the only one analysing the correlation between CTLM and the malignancy level. Floery found that the false-negative results are found more frequently in G1 group. These findings may seem contradictory with those here presented. The cancers with the highest malignancy level have a different vascularisation density, but also necrosis regions are found more often. Therefore, the obtained sensitivity in G3 groups can depend on the ratio between the number of cancers with and without necrotic regions. Moreover, the ratio between the volume of necrosis and tumour tissue can influence the results.

A very important restriction of this optical method is the low spatial resolution and low SNR.[17] In this study, more than half of the lesions had SNR lower than 1.3.

The detectability of this level is limited for the human eye. Therefore, an additional 3D image augmentation and colour scales had to be used to enhance contrast of the cancer lesions.

Laser light penetrates tissues of the breast easy but 5% light is totally absorbed by every centimetre of tissue. If breast is big the laser light may be totally absorbed before it reaches the detector. This fact may explain difference our results and presented for Chinese women were sensitivity of mammography CTLM+ even was 95.34% in heterogeneously dense breast.[18]

6. CONCLUSIONS

CTLM cannot be considered as an independent diagnostic tool for breast cancer. CTLM NPV should be compared with MMG and ultrasound; therefore, this excludes CTLM as a method for screening a group of young women with a high risk of breast cancer.

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