CTLM as an Adjunct to Mammography in the Diagnosis of Patients with Dense Breasts*

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ABSTRACT

PURPOSE: The objective of this study was to evaluate the utility of CTLM (computed tomographic laser mammography) as an adjunct examination to mammography in women with dense breast tissue (Breast Imaging Reporting and Data System [BI-RADS] density category 3 or 4).

Materials and Methods: The study involved 155 women scheduled for biopsy or surgery from September 2007 to February 2008. The breasts' density were first evaluated with mammography, parenchyma patterns of "heterogeneously dense" (BI-RADS3: 51 to 75% fibroglandular) and "extremely dense" (BI-RADS4: 75% fibroglandular) were used to classify breasts as dense. CTLM examination was performed subsequently with mammography on patients with dense breasts. We retrospectively compared the finding of mammography alone, CTLM alone, adjunct CTLM to mammography (mammography +CTLM) with pathology. Sensitivity, specificity, positive predictive values were calculated by using standard methods. Between-group differences were evaluated with the χ^2 test for categorical variables.

Result: 155 women underwent mammography were classified into 74 heterogeneously dense breast (BI-RADS3) and 81 extremely dense breast (BI-RADS4). Pathologic analysis revealed 79 malignant and 76 benign breast lesions. Positive lesions were observed significantly more often in malignant than in benign lesions (72.15% VS. 31.57% χ^2=25.558 P = 0.000) Among extremely dense breasts: the sensitivity of mammography alone, CTLM alone, mammography+CTLM were, respectively, 34.40%, 74.40%, 81.57%, the sensitivity of mammography VS mammography + CTLM were 34.4% VS. 81.57% (χ^2=13.071 p=0.000). The specificity of mammography alone, CTLM alone, mammography+CTLM were 90.48%, 71.00%, 72.22%, the specificity of mammography VS mammography +CTLM were 90.48% VS 72.22% (χ^2=4.386 p=0.072) Among heterogeneously dense breasts: the sensitivity of mammography alone, CTLM alone, mammography+CTLM were 68.29%, 85.00%, 95.34%, the sensitivity of mammography vs. mammography+CTLM were 68.29% VS 95.34% (χ^2=11.131 p=0.001). The specificity of mammography alone, CTLM alone, mammography+CTLM were 85.00%, 61.00%, 55.26%, the specificity of mammography VS mammography+CTLM were 85.00% VS 55.26% (χ^2=8.288 p=0.004). The sensitivity of CTLM in heterogeneously dense breasts vs.

extremely dense breasts were 74.40% VS 85.00% (χ^2=0.446 p=0.504), the specificity in them were 71.00% VS 61.00% (χ^2=0.000 p=1.000).

Conclusion: Our data indicate that the diagnosis of CTLM was not affected by tissue density in breasts and could provide information about angiogenesis in most malignant and a few of benign breast lesions. CTLM could successfully distinguish malignant from benign lesions of dense breasts. When CTLM was used as an adjunct to mammography in heterogeneously dense breasts and extremely dense breasts, the sensitivity increased significantly. This study suggests that in clinical practice, adding CTLM in dense breasts may be useful.

Key words: Computed tomographic laser mammography, laser technique, tomography, optical imaging, mammography, breast cancer

INTRODUCTION

Early detection and effective treatment of women with a diagnosis of breast cancer are major factors contributing to the decline in the mortality rate. Radiology examination can help in early detection and diagnosis. Current methods of diagnosing breast disease include mammography, ultrasound (high frequency probe and ultrasonic elastographic) and computed tomography (CT), magnetic resonance imaging (MRI), near and far infrared, PET-CT[1]. Mammography is the most widely used; however, conventional screen-film mammography has limited sensitivity for detection of breast cancer, especially in breasts with dense tissue. Digital mammography was developed to address some of the limitations of screen-film mammography; however, the value of digital mammography is not substantially different from that of screen-film mammography. Radiology physicians are in need of more functional information.

Tumor "angiogenesis" is known to be critical for the autonomous growth and spread of breast cancers. Tumor angiogenesis is a complex process that involves both the incorporation of existing host blood vessels into the tumor and the creation of tumor microvessels[2]. If these vessels could be found, the functional information can be used by physicians.

The basic principle underlying the new device—CTLM (computed tomographic laser mammography) imaging is the "angiogenesis." In the last several years, optical tomography on breast imaging has gained interest all over the world. Light has been investigated since the late 1920s as a diagnostic tool for breast cancer by transillumination; however, it had low spatial resolution and afforded little in spectral quantification of lesions. Hence, it did not attain sufficient sensitivity and specificity to be used clinically. In recent years, optical mammography developed. Optical introscopy of laboratory animals is extensively developed for studies of DNA and pharmacological preparations. Optical mammography is either projection or tomographic apparatuses. Optical tomographic mammographs are available. CTLM (Imaging Diagnostic Systems Inc., USA) used in our study is now being clinically tested in several countries; the other apparatuses such as Philips OMPS transmission mammography (Optical Mammo Prototype System, Netherlands), SoftScan Optical

projection mammography (Advanced Research Technologies Inc., Canada), ComfortScan mammography (DOBI Medical International, Inc. USA) are in research [3-5].

This study was to evaluate the utility of computed CTLM (computed tomographic laser mammography) as an adjunct examination to mammography in women with heterogeneously dense and extremely dense breast tissue (Breast Imaging Reporting and Data System [BI-RADS] 3 and 4).

Materials and Methods

Patients

From September 2007 to February 2008, 155 women (23–74 years of age; median age: 41 years) in Tianjin Medical University Cancer Hospital were scheduled for biopsy or surgery within 30 days. None of the patients had undergone current chemotherapy or irradiation of the breast and were not biopsied up to 30 days before the examination. All the patients had undergone mammography and CTLM examination before surgery.

According to Breast Imaging Reporting and Data System [BI-RADS], all women who had undergone mammography were classified into heterogeneously dense breast (BI-RADS3) or extremely dense breast (BI-RADS4) .

Mammography

Bilateral 2-view mammography (Senography 2000D, GE Medical Systems), was performed in the craniocaudal and mediolateral projections. Spot compression and additional views were obtained where appropriate. Two mammographies independently analyzed the data for this purpose. The physicians classified all patients into two groups: heterogeneously dense breast group (BI-RADS3) and extremely dense breast group (BI-RADS4)

CTLM

Computed tomographic laser mammography (CTLM 1020, Imaging Diagnostic Systems, USA) was performed on one side with lesions. The patient lay in the prone position on the examination table with one breast pendant in a scanning chamber, where the breast is surrounded by the laser source detector. The scan ring must properly fit the size of the patient's breasts. In general, a 2mm-slice thickness would be set to most patients. When the breast is too small or too large, a 1mm- or a 4mm- slice thickness should be used, respectively. Before scanning, the breast was moved to the middle of the scanning ring. The detector system consists of two rings each with 84 photo-detectors (picture 1). The unit rotates 360 degrees around the breast and takes 17 seconds. After each rotation, the ring descends, creating a slice at each step. The scanning platform alternates direction to avoid twisting the cables. The whole breast scan would be made of 10-40 slices. While one slice is being scanned, the proprietary software is reconstructing the previous slices. The scan is ready to be read immediately after completion. The device produces striking three-dimensional views, which can be rotated, in real time, along any axis. CTLM also produces sagittal axial and coronal views.

Exclusion criteria included ulcers or wounds on the breast, various forms of porphyria, current biopsy within 30 days, or chemotherapy or irradiation of the breast.

CTLM Image Interpretation

The CTLM device uses a laser wavelength (808nm) in the NIR spectrum that matches the crossover point of absorption of both oxygenated and deoxygenated hemoglobin. The hurdle that has to be overcome is the difference in the way photons transverse the tissue. Light travels in tissue in a random fashion because of scatter. The average path of light can be predicted despite the scattering and absorption of light in tissue. CTLM uses a large number of source and detector positions in each slice, taking into account the diffusion approximation of light propagation in tissue and showing the location of the increased vascularity in the breast.

The device produces striking three-dimensional views, which can be rotated along any axis in real time. It also produced sagittal, axial, and coronal views. An inversion factor is introduced into the reconstruction algorithm so that areas of high absorption (high hemoglobin concentration) are visualized in white. Avascular areas show as green or black. The available tools allow us to focus on any area by removing overlying obscure areas. Image quality can be improved with window and level controls. Images are usually viewed in a Maximal Intensity Projection (MIP) and then in a Front to Back Reconstruction (FTB), also known as a Surface Rendering Mode. The two modes are used to evaluate the vascularization patterns to determine whether the images represent normal or abnormal vascularization.

CTLM imaging was read by trained radiology physicians, blind to any imaging and clinical information. To guarantee the accuracy of the data, the difficult cases were reviewed by Eric Milne, MD (USA).

CTLM interpretive data: 1 stands for benign lesions; 2 stands for malignant lesions, 0 stands for the lesions that were not ascertained.

Mammography imaging interpretation

Mammography interpretive data: 1 stands for benign lesions record; 2 stands for malignant lesions; 0 stands for the lesions which were not ascertained.

Mammography+ CTLM Image Interpretation

Combined, the results of mammography and CTLM are accepted as malignant when any one was malignant and accepted as benign or malignant when the results were the same. If one of them is not ascertained, the records were dependent on the other result, as shown in Table 1.

Table 1 CTLM + mammography Image Interpretation

	Interpretation								
Measurement	benign			malignant			not ascertained		
Mammography	1	1	1	2	2	2	0	0	0
CTLM	1	2	0	1	2	0	1	2	0
Mammography+CTLM	1	2	1	2	2	2	1	2	0

1 = benign 2 = malignant 0 = not ascertained

Statistics

The result of mammography, CTLM, and mammography+ CTLM is analyzed to identify true-positive, true-negative, false-positive, and false-negative examination, according to pathology. On the basis of these classifications,
sensitivity (true-positive/ [true-positive+false-negative]),
specificity (true-negative/ [false-positive+true-negative]),
positive predictive value (true-positive/ [true-positive+false-positive]).
Statistical analysis was performed with the SPSS statistical package. A χ^2 test was used to compare group differences.

Result

Mammography

Two radiology physicians classified all patients into two groups: 74 in the heterogeneously dense-breast group and 81 in the extremely dense-breast group. The results of impression of mammography were 48 benign lesions, 15 malignant lesions, and 11 ascertain lesions in extremely dense breast. There were 41 benign lesions, 15 malignant lesions, and 6 ascertain lesions in the heterogeneously dense-breast group, as shown in Table 2.

CTLM

Radiology physicians recorded CTLM impression: There were 35 benign lesions, 34 malignant lesions, and 5 ascertain lesions in extremely dense breast. There were 33 benign lesions, 43 malignant lesions, and 5 ascertain lesions in the heterogeneously dense-breast group, as shown in Table 2.

Mammography+CTLM

There were 32 benign lesions, 40 malignant lesions, and 2 ascertain lesions in extremely dense breast. There were 23 benign lesions, 57 malignant lesions, and 1 ascertain lesion in the heterogeneously dense- breast group, as shown in Table 2.

Table 2 Findings in Three Examinations

Breast Density	Mammography			CTLM			Mammography+CTLM		
	1	2	0	1	2	0	1	2	0
Extremely n=74	48	15	11	35	34	5	32	40	2
Heterogeneously n=81	41	34	6	33	43	5	23	57	1

Pathologic Diagnosis

In 155 lesions, 150 underwent surgery, 3 were biopsied, 2 were needle biopsied. In the 155 breast lesions studied, 76 were malignant and 79 were benign at pathologic analysis. The tumor stages of the 155 breast cancers are listed in Table 3.

Table 3 Pathologic Findings in 155 Lesions

Pathologic Findings	Breast Density	
	Extremely Dense	Heterogeneously Dense
Benign	**n=37**	**n=39**
Hyperplasia	16	9
Inflammation	2	7
Intraductal Papilloma	4	9
Fibroadenomas or adenofibromas	9	11
Adenosis	3	0
Simple cyst	1	0
Adiponecrosis	1	0
Normal tissue	1	3
Malignant	**n=37**	**n=42**
DCIS	4	5
Invasive ductal cancer	28	45
Neuroendnocrine carcinoma	0	1
Mucoid adenocarcinoma	0	1
Apocrine gland carcinoma	1	0
Phyllodes tumor	2	0
Glycogen-rich clear cell carcinoma	1	0
Interstitial sarcoma	1	0

From our results, CTLM positive predictive is 72.41% (63/63+24). They supported that CTLM successfully shows the angiogenesis of malignant lesion in the breast. In our study, 72.15% (57/79) malignant lesions showed angiogenesis; however, 57% (24/76) benign lesions also showed angiogenesis. Among these cases, there are 8 fibrocystic changes, 6 inflammation, 4 ductal disease, 2 adenosis, 1 fibroadenoma, and

1 adiponecrosis. Increased absorption was observed significantly more often in malignant than in benign lesions (72.15% [57/79] vs. 31.57% [24/76] χ^2=25.558 p=0.000), as shown in Table 4.

Table 4 CTLM findings in benign and malignant lesions

Pathology	+*	-*	
Benign	24	52	χ^2=25.558
Malignant	57	22	p=0.000

+* angiogenesis was showed in CTLM -**angiogenesis was not showed

Among extremely dense breast, sensitivity of mammography alone□CTLM alone, and mammography+CTLM were, respectively, 34.40%, 74.40%, and 81.57%. The sensitivity of mammography vs. mammography+CTLM were 34.4% vs. 81.57% (χ^2=13.071 p=0.000). The specificity of mammography alone, CTLM alone, and mammography+CTLM were 90.48%, 71.00%, and 78.13%. The specificity of mammography vs. mammography+CTLM was 90.48% vs. 72.22% (χ^2=4.386 p=0.072). Among heterogeneously dense breast, sensitivity of mammography alone, CTLM alone, mammography+CTLM was 68.29%, 85.00%, 95.34%; the sensitivity of mammography vs. mammography+CTLM was 68.29% vs. 95.34% (χ^2=11.131 p=0.001). Specificity of mammography alone, CTLM alone, and mammography+CTLM was 85.00%, 61.00%, 55.26%. The specificity of mammography vs. mammography+CTLM was 85.00% vs. 55.26% (χ^2=8.288 p=0.004). The details are shown in Table 5 and Table 6.

Table 5 Imaging findings according to pathology

breast density	**mammography**				**CTLM**				**mammography+CTLM**			
	TP	FN	TN	FP	TP	FN	TN	FP	TP	FN	TN	FP
Extremely	11	21	38	4	29	10	25	10	31	7	26	10
Heterogeneously	28	13	34	6	34	11	22	14	41	2	21	17

Table 6 Statistical Data

breast density	**mammography**		**CTLM**		**mammography+CTLM**	
	sens	spec	sens	spec	sens	spec
Extremely	34.40%	90.48%	74.4%	71.00%	81.57%	72.22%
Heterogeneously	68.29%	85.00%	85.00%	61.00%	95.34%	55.26%

Sensitivity of CTLM in heterogeneously dense breast vs. extremely dense breast was 74.40% vs. 85.00% (χ^2=0.446 p=0.504); specificity in them was 71.00% vs. 61.00% (χ^2=0.0001 p=1.0)

Discussion

Mammography is the golden standard of breast imaging diagnosis. It has high sensitivity in fatty breast with sharp contrast[6]. Screening mammography, as well as

digital mammography, is of limited value in dense breasts. In extremely dense and heterogeneously dense breasts, mammography sensitivity is decreased. Mammography sensitivity was 45% to 70%[7]. In our study, the sensitivity of digital mammography in extreme dense breast is 34.4%, lower than reported; in heterogeneously dense breast, mammographic sensitivity was 68.29%, according to reports. In our study, the specificity declined from 90.48% to 85%. Relevance research is indicated. The risk of cancer is increased from 2.5 to 5 times with the density ascending. So it is important for the malignant lesions to be detected early in dense breast[8]. Because of the limit of mammography, radiology physicians turn to ultrasonography. For a simple cyst, the accuracy of ultrasound is 96% to 100%. However, ultrasound imaging is used for the differentiation of hyperplasia from solid lesions that mammography could not distinguish. It is not as high a result as that of the overlapping characteristics of solid benign and malignant lesions [9, 10, 11]. In the last several years, functional imaging, such as MRI and PET-CT. MRI, has gained interest and has received more attention. Functional imaging can provide important information in function with high sensitivity in detecting invasive ductal cancer and ductal carcinoma.[12] A new field of research is laser-light-based breast imaging. Initial attempts to use laser light for "transillumination" and to detect the angiogenesis of the breast have been developed. In the early 21st century, a computed tomographic laser-light-based scanner for the breast, called CTLM (computed tomography–laser mammography), is now being used clinically and has gained some initial acceptance.

Our study showed that the sensitivity was significantly increased by using CTLM adjusted to mammography, from 34.4% to 81.57% (χ^2=13.071p=0.000), and in heterogeneously dense breast, from 68.29% to 95.34%□χ^2=11.131□p=0.001).

In 1971, Folkman [13] first proposed that tumor cells were capable of stimulating endothelial cell proliferation by means of a soluble "tumor angiogenesis factor." Angiogenesis is defined as the formation of new blood vessels through the sprouting of capillaries from preexisting microvessels[14]. This process serves as the fundamental method by which neovascularization occurs in the human body. In most mature tissues, the rate of endothelial cell turnover is extremely slow, in the order of years. A markedly increased rate of angiogenesis takes place during the normal physiologic processes of embryogenesis, uterine maturation, placental development, corpus luteum formation, and wound healing. In each of these instances, the angiogenic process is strictly regulated and is terminated following completion of its intended function. Research has shown, however, that regulated or unregulated angiogenic activity plays a role in a number of different diseases. Examples include diabetic retinopathy, in which associated ocular angiogenesis, in developed countries, is the leading cause of blindness. A possible role of angiogenesis in the development of atherosclerosis is the focus of ongoing study. In the most extreme case, angiogenesis has been shown to play an important role in the pathogenesis of tumor growth and metastasis [15-18]. Tumor cells control neovascularization through secretion of angiogenic factors, which attract endothelial cells that proliferate and invade the stroma toward the tumor mass. Then "angiogenesis" could be found. Tumors are unable to grow larger than circa 1 mm3

without developing a new, hypoxia-triggered blood supply.[19]

Based on this theory, The CTLM device uses a laser wave length (808nm), in the NIR spectrum that matches the crossover point of absorption of both oxygenated and deoxygenated hemoglobin. This wave length also minimizes the effects of both fat and water[20]. Laser used by CTLM can easily penetrate the breast tissue that is not affected by the density. Our study supported that the CTLM sensitivity of heterogeneously dense breast vs. extremely dense breast was similar (74.40%VS.85.00% p=0.504). Specificity was also similar (71.00%VS61.00% p=1.000). The results were not varied from heterogeneously dense breast to extremely dense breast. It has been shown that CTLM was not affected by tissue density on the angiogenesis. CTLM has the potential to be used as an adjunct tool to mammography in both heterogeneously dense breast and extremely dense breast.

We are, therefore, looking at the absorption pattern of hemoglobin in vessels. In tumor angiogenesis, the vessels are concentrated and are structurally and functionally abnormal. This gives a greater volume of hemoglobin that can be visualized by CTLM in a confined area. In the analysis based on this principle, CT features of malignant angiogenesis as follows: 1 abnormal shape: CTLM showed both forms of normal and abnormal desoxyhemoglobin and hemoglobin. It is important for physicians to distinguish normal vein from abnormal "angiogenesis." On coronal views, abnormal "angiogenesis" showed round and ovoid areas of high absorption, high hemoglobin concentration, visualized in white, and distinguished from triangular and cone-shaped areas (picture 2). On the 3D-MIP view, the irregular shape of "angiogenesis" showed oblate spheres, dumbbell shapes, diverticulum, and circles, distinguished from the clear "tunnels", (picture 3). 2 Isolated areas of high absorption: the normal vessels are shown as "ribbons" running through the breast from chest wall to nipple in MIP-3D view. The branches of vessels shown as star-shaped and branch-shaped could always be found, (picture 4). The depressed globose areas of high absorption could be found in the nipple area. This is the normal vessel at areolar which differs from the "angiogenesis" (picture 5). However, "angiogenesis" of malignant tumors always showed high isolated absorption, which may not have any relation to veins. 3 "Angiogenesis" of malignant tumors located deep in the breast: in the normal vessels of the breast, always on the surface of the breast tissue, deep vein was uncommonly found. There were six cases which showed deep veins in this study. However, "angiogenesis" of malignant lesions were almost found in deep tissue. The surface and deep imaging could be shown and distinguished better by comparative analysis 3D-MIP and 3D-FTB, (picture 6). Beginning lesions located on the surface, such as adiponecrosis or mastitis, could be distinguished from deep malignant lesions according to this feature. These findings of CTLM aid breast imaging diagnosis.

From our results, CTLM positive predictive, 72.41% (63/63+24), supports that CTLM successfully shows the angiogenesis of malignant lesions in breasts. However, some beginning lesions also showed angiogenesis. Although there is some overlap between benign and malignant findings, increased absorption was observed

significantly more often in malignant than in benign lesions, 72.15% VS 31.57% χ^2=25.558 p=0.000. To this hypothesis, a CTLM scanner was used to characterize benign and malignant breast lesions. We can conclude that CTLM could distinguish malignant from benign lesions. Some literature [21, 22] reported that these findings can be visualized by CTLM. A variety of benign lesions also showed increased vessels as malignant lesions. Determination of confirmative, histologic parameters of breast lesions, such as microvessel counts, would be able to provide additional information about lesion biology. So we conclude that CTLM is able to characterize benign and malignant breast lesions by showing the angiogenesis.

Our data indicate that the diagnosis of CTLM was not affected by tissue density in breasts and could provide information about angiogenesis in most malignant and in a few benign breast lesions. CTLM could successfully distinguish malignant from benign lesions of dense breast. When CTLM was used as an adjunct to mammography in heterogeneously dense breast and extremely dense breast, the sensitivity increased significantly. This study suggests that in clinical practice, adding CTLM in dense breasts may be useful.

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