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**Dynamic Optical Breast Imaging in Breast Cancer Detection**

*To be Submitted to Radiology*

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## **ABSTRACT**

### **Background:**

Considering mammography misses at least 10% of the breast cancers in Canadian women, having a more sensitive, specific, yet inexpensive, quick, and easy-to-use complimentary imaging modality is essential to reducing the impact of breast cancer. This light scanning technique uses the absorption and scattering properties of tumours and blood to determine a likelihood of cancer. One very important aspect of near-infrared (NIR) imaging is that it does not depend on breast tissue density, and this is advantageous when compared to mammography. High fibroglandular tissue density, leading to a dense mammogram, represents a scenario where conventional mammography has a high incidence of failure to detect small cancers. The objective was to validate the ComfortScan™ system as a complimentary imaging modality to mammography. Our hypothesis is that by using the ComfortScan™ system as an adjunct to mammography, the clinical diagnosis will be better correlated to the biopsy results.

### **Methods:**

The ComfortScan™ system, a light scanning technique using 640 nm light to image the breast, was used to collect 128 NIR images. A ComfortScan™ dynamic imaging session was performed for all patients and compared to mammography. Mammograms were performed using two identical GE Senographe Essential mammography units. All images were analyzed by 2 experienced radiologists having more than 5 years of breast imaging experience. In those patients requiring a biopsy, as indicated by mammography, the disease state of the tissue was determined by histopathology.

### **Results:**

There was no statistically significant difference between the diagnosis provided by mammography and that of the ComfortScan™ system ( $p > 0.05$ ). A total of 33 patients had biopsies. The diagnosis from the NIR images correlated with biopsy in 25/33 patients. The diagnosis from mammography correlated with biopsy

in 19/33 of the patients. Since biopsy is the gold standard of malignancy analysis, these results are very interesting. The NIR results show 80/126 in agreement with mammography diagnosis.

**Conclusion:**

No statistically significant difference in diagnosis was found between mammography and the ComfortScan™ system ( $p > 0.05$ ). The NIR results show 80/126 in agreement with mammography diagnosis. There were 29 NIR malignant findings that disagreed with mammography but no biopsies were available for comparison. Comparing mammography and the ComfortScan™ system in the biopsy population showed that the ComfortScan™ system (specificity 83%) matched biopsy more often than mammography (specificity 13%). Therefore, by introducing the ComfortScan™ system as an adjunct to mammography there would be better agreement between diagnosis and biopsy. This study validates the potential benefits of using the ComfortScan™ system in a clinical setting to give the radiologist more information for better diagnosis of breast cancer.

***Keywords: DOBI, breast imaging, cancer, Near-infrared***

## **LIST OF ABBREVIATIONS**

AOTFs	acousto-optic tunable filters
BI-RADS	Breast Imaging-Reporting and Data System
DOBI	dynamic optical breast imaging
LED	light emitting diode
LEDs	light emitting diodes
MRI	magnetic resonance imaging
REB	research ethics board
ROI	region of interest
SOP	standard of protocol
US	ultrasound

## **FULL STUDY - DOBI**

### **3.1 INTRODUCTION**

In Canada, an estimated 23 200 women will be diagnosed with breast cancer in 2010[1]. Approximately 1 in 9 women will develop breast cancer in their lifetime[2]. In women, breast cancer ranks as the 4<sup>th</sup> leading cause of death (5% of all deaths); trailing only ischaemic heart disease (21%), stroke (9%), and lung cancer (5.4%)[2]. Men can also be affected by this disease. The frequency of breast cancer in men compared to women is significantly lower. For every man diagnosed with breast cancer there are approximately 140 women with the disease [2].

There are several different ways to image the breast to determine the likelihood of breast cancer. The most commonly used, and the accepted standard for screening, is mammography. In mammography, an image is obtained by passing ionizing radiation through the breast, and then reading the obtained imaged, called a mammogram, to obtain a measure of tissue attenuation. Since the attenuation of x-rays by dense tissue and tumourous tissue is similar, it is difficult to detect tumours in dense breasts.

Near-infrared spectroscopy (NIRS) is a well known nondestructive imaging technique with a rapid imaging time[3]. NIRS uses wavelengths between the visible range to the mid infrared region [3]. The American Society of Testing and Materials (ASTM) defines the NIR region to be 780-2526 nm, which corresponds to the wave numbers 12820-3959  $\text{cm}^{-1}$ [3].

NIRS involves the transmission and detection of near infrared light through a sample. The incident light intensity is higher than the transmitted light intensity due to absorption and scatter caused by the sample. NIR absorption bands are normally: i) broad, ii) overlapping, iii) 10-100 times weaker than the mid-IR absorption bands[3]; and thus, severely restrict sensitivity. On the other hand, the low absorption coefficient allows for better depth penetration which translates into the possibility of imaging thicker samples. Therefore, a low absorption coefficient is very useful in order to image strongly absorbing or highly scattering samples. This allows for the measurement of turbid liquids or solids, which normally is

not possible. Since the transmitted NIR signal will depend on both the absorption and scatter of the sample, both chemical and physical information can be obtained from a single measurement.

Imaging the breast to determine the likelihood of cancer is a relatively new application compared to the other uses of NIR light. With this light scanning technique, light is passed through the breast and the intensity of transmitted light attenuation relative to the initial light intensity is measured. Light in the NIR range is attenuated mainly by the hemoglobin in the blood and, therefore, more attenuation signifies more blood. Since tumours are highly vascularized, an area of higher attenuation represents an area with higher likelihood of cancer. This light scanning technique has advantages over conventional mammography, in that, it uses a much lighter compression than mammography (i.e. it is more comfortable), it does not use ionizing radiation, and the density of the tissue being examined will not affect cancer detection.

There have been many studies involving the use of NIR light for imaging [6-44]; many of which were phantom studies [12, 13, 17, 21, 24, 26-29, 36, 37, 40, 43]. The phantom studies were used to determine the viability of the NIR imaging technique and to improve the NIR image. The work presented in this paper is a clinical trial of the ComfortScan™ system that builds upon preliminary findings of an earlier study [46].

The ComfortScan™ system uses 640 nm light to image the breast in hopes of detecting breast cancer. This system also has a very novel application of pressure. In a mammogram, pressure is used to flatten the breast and hold it in a stable position for imaging. To enhance tumour detection, the ComfortScan™ system applies pressure to the breast. Pressure is applied in order to collapse the tortuous vasculature of the tumour and trap blood near the tumour [47]. In theory, this trapped blood will deoxygenate with time, causing a larger attenuation of NIR light, thus improving the image contrast. To date, publications on the ComfortScan™ system have been limited [46 (our preliminary findings), 48, 49,50]. XinAoMDT Technology Co. [XinAoMDT Technology Co.,Hebei, China] currently owns all rights to the ComfortScan™ system. It is hypothesized that by using the ComfortScan™ system as an adjunct to

mammography there will be better agreement to biopsy results resulting in less unneeded biopsies, and thus, better patient care.

## **3.2 MATERIALS AND METHODS**

### **3.2.1 Patients**

In this study, 128 NIR studies were examined. There were ambient light problems in 2 NIR images; therefore, only 126 NIR images are reported in this paper. The mean age of the patients was  $62 \pm 8$  [SD] years. DOBI (Dynamic Optical Breast Imaging) scans and mammograms were performed on all patients. Ultrasound guided biopsies were available on 33 of the patients. Only patients already returning to the Ontario Breast Screening Program (OBSP) because of a suspicious mammogram were included in this study. Part 1 of this study examines NIR breast images from the breast with a suspicious mammogram; however, for 52 patients the contralateral breast, which was found to be mammographically normal, was also imaged to obtain normal NIR images used in Part 2 of this study. Patients with recent biopsies (within 1 month of light scan) were excluded from the study because of the possibility for abnormal vasculature due to scarring. The breast images were randomly assigned numbers DOBI1-DOBI126 for anonymity and to blind the radiologists to the patients.

### **3.2.2 Ethics**

All procedures carried out for this study were approved by the Research Ethics Board for Hamilton Health Sciences and McMaster University. Informed consent was obtained from all patients participating in this study. The line of patient care was not altered due to any results obtained from the DOBI scans

### 3.2.3 Mammography

All mammograms were performed at the Chedoke Hospital (part of Hamilton Health Sciences Centre) in Hamilton, Ontario, Canada through the Ontario Breast Screening Program (OBSP). Two identical GE Senographe Essential [GE Healthcare, Mississauga, ON, Canada] mammography units were used. The mammograms were analyzed by 2 experienced radiologists having more than 5 years of breast imaging experience, using the Breast Imaging-Reporting and Data System (BI-RADS) rating[51] . The different BI-RADS classifications are described in Table 1.

**Assessment categories of the BI-RADS Classification System**

Stage	Result
0	Assessment incomplete. Need additional imaging evaluation.
1	Negative. Routine mammogram in 1 year recommended.
2	Benign Finding. Routine mammogram in 1 year recommended.
3	Probably benign finding. Short interval follow up suggested.
4	Suspicious. Biopsy should be considered.
5	Highly suggestive of malignancy. Appropriate action should be taken.

Table 1 – BI-RADS Classifications

This table shows the various classifications using the BI-RADS classification system. The higher the BI-RADS rating, the higher the probability of malignancy.

### 3.2.4 Dynamic Optical Breast Imaging

Dynamic Optical Breast Imaging was performed using the ComfortScan system (XinAoMDT Technology Co., LTD, Beijing, China). This system has been tested by another group and has shown promising results [48, 49, 50], using different methods of image analysis.

The ComfortScan system, shown in Figure 1, is a light scanning technique using 640nm red light to image the breast.

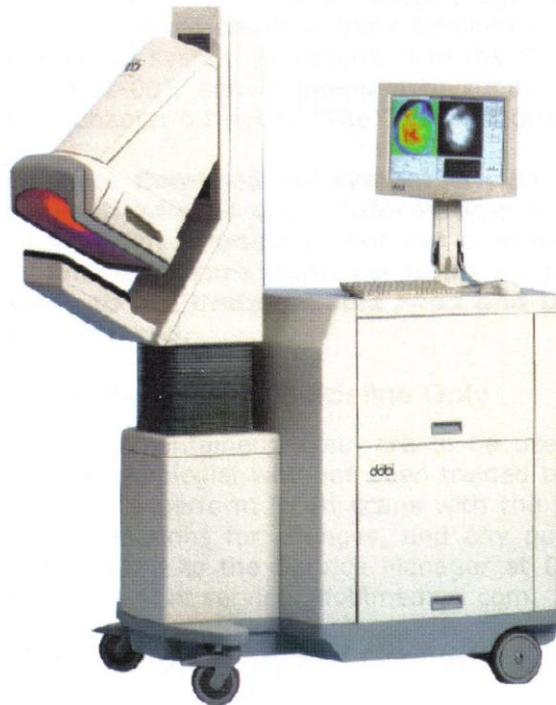


Fig. 1 – ComfortScan System

This figure shows the ComfortScan system that was used in this study. The patient is positioned on the left side and the NIR technician stands to the right in front of computer monitor.

The near-infrared (NIR) technician positioned the patient in front of the arm of the ComfortScan™ system. In order to accommodate different patient heights, the arm unit is able to independently move up and down. The technician then positioned the breast on the LED array, which is positioned in a square grid and consists of 127 LEDs on a platform angled 30 degrees from horizontal. The soft air bladder was then lowered onto the top of the breast. The Charge Coupled Device (CCD) camera, located within the soft air bladder above the breast, enables cranial-caudal imaging of the breast. At this point the patient was instructed to remain still and breathe normally. A real-time positioning image was obtained to check the position of the breast. Next, an LED check was performed using the ComfortScan™ software in order to ensure all the LEDs are functional, and ensure that the light intensity exiting the breast was within a normal

range. Errors can occur during this LED check if the breast is either too thick (not enough light is transmitted), too thin (too much light is transmitted), or improperly positioned. A suspicious Region Of Interest (ROI) marker was placed over the area of interest co-registered by a previous mammogram and, in this region, a more detailed analysis is performed. The suspicious region on the mammogram determines where the suspicious ROI marker is placed on the NIR image.

When the scan started, the soft air bladder, made of thin silicon, was inflated to apply gentle pressure (5 mmHg) during the first 15 seconds of the scan. Next, the pressure was increased to 10 mmHg and images were taken for the next 30 seconds. During the last part of the scan, the pressure was lowered back to 5 mmHg. A total of 45 images were taken during the 60 second scan, and the initial 5 images were used as a baseline. The remaining 40 images make up the dynamic part of the sequence.

A dynamic signature for every pixel was obtained using Equation 2.

$$DS(x, y, t) = \frac{I(x, y, t) - I_{ref}(x, y)}{I_{ref}(x, y)} \quad (2)$$

where  $DS(x, y, t)$  is the dynamic signature used for image production,  $I(x, y, t)$  is the intensity of transmitted light at the various positions, and  $I_{ref}(x, y)$  is the transmitted light intensity at a given position during the non-compression phase of the imaging sequence. The variables  $x$  and  $y$  represent the pixel position on the 2D NIR image, and  $t$  represents the point in time when the image was taken. This dynamic signature highlights changes in light transmission from the reference image resulting from changes in pressure of the breast. The number of LEDs used is determined by breast size and other parameters in the scanning procedure.

Through this process the variations in light transmission over the scan duration, the dynamic signature, is calculated at each pixel. These dynamic signatures can be displayed as an intensity time curve by assigning a region of interest in the image window. A false colour overlay was applied to each of the 2D images based upon these dynamic signatures. The images were then displayed by the image analysis

software as a video, which allows for easier image analysis. A green area corresponds to a relatively stable dynamic signature with time, an area of red would represent a highly increasing dynamic signature with time, and a purple area represents an area of highly decreasing dynamic signatures with time. The dynamic signature is related to the increase or decrease in light attenuation with time, which is related to the volume of blood at a given position. For example, a highly decreasing dynamic signature represents an area where the transmitted light becomes highly attenuated with time. Note that, by convention, the image analysis software (ComfortView™) displays only the compression aspect of the imaging sequence. The videos used in the image analysis show how the dynamic signatures change with respect to time; the more purple an area becomes, the higher the likelihood of malignancy. The manufacturer suggests a range of characteristics of these curves as indicators of malignancy. Based on these characteristics a rating scale provided by the manufacturer extending from DOBI 0 to DOBI 5 was given to each suspicious region in each image by the reading radiologist. Table 2 shows the manufacturers guidelines to determine these DOBI ratings.

	Benign	Probably Benign	Indeterminate	Probably Malignant	Malignant
Location (Proximity to: nipple and ROI from mammogram)	No blue near the suspicious ROI from mammogram			Blue area is located directly at ROI from mammogram	
Space (Spatial Characteristics)			Diffuse flat blue at ROI	Focal peaked blue at ROI	
Time (Temporal characteristics using ROI curve)		Strong upward trend	Wavy with amplitude 0 to -2	Downward trend with amplitude -2 to -4	Downward trend with amplitude more negative than -4
Context (Lesion Curve vs. Reference Curve)		Very similar curves that are above the x-axis (amplitudes greater than 0)	Variable curve throughout background Lesion not distinctly different	Very dissimilar pattern of curves with consistent background Diverging curves	

Table 2 – DOBI Rating system

This table shows how the DOBI images were rated. DOBI1 is benign, DOBI2 is probably benign, DOBI3 is intermediate, DOBI4 is probably malignant, and DOBI5 is malignant. A rating of DOBI 0 is given when the suspicious ROI is within 2cm of the nipple. A rating of DOBI0 is called ‘nipple blue’ and is caused by surface artifacts.

The analysis of all ComfortScan images was performed by an experienced radiologist, with at least 5 years of experience in breast imaging, who was double blinded to the study.

In order to compare the DOBI rating scheme to the BI-RADS classification, the two scales must be aligned, or normalized. To do this, an adjusted system was implemented to carefully align the two classifications. This adjusted rating system allowed for comparison of the light scan (DOBI) and mammography ranking (BIRADS) on the same scale. This conversion system is shown in Table 3, the higher the adjusted rating, the higher the probability of malignancy. A normalized rating of 1 or 2 is benign, and a rating of 3 or 4 would be malignant. Mammograms were scored using the BIRADS scale and ComfortScan™ images using the DOBI score, however, all comparisons were made using the normalized ranking.

BIRADS	meaning	DOBI Score	interpretation	Normalized
0	Incomplete	0	nipple blue or invalid image	0
1	Negative	1	benign	1
2	Benign	2	likely benign	2
3	Probably Benign	3	low malignant or probably malignant	3
4	Suspicious Abnormality	4	likely malignant	4
5	Highly Suspicious of Malignancy	5	malignant (high probability of malignancy)	4
6	Known Biopsy Proven Malignancy			

Table 3 – BIRADS/DOBI Conversion

This table shows the table used to convert both the BIRADS and DOBI systems into a normalized rating system.

### 3.2.5 Biopsy

All biopsies were performed at the Chedoke site of Hamilton Health Sciences in Hamilton, Ontario, Canada by certified radiologists. Samples were fixed in 10% formalin solution and embedded in

paraffin wax for analysis. Analysis was performed in Hamilton Health Sciences Centre by certified pathologists. The pathologist determined the histological type of tissue and characterized the sample as benign or malignant. Biopsy was used as the Gold Standard for breast cancer diagnosis.

### 3.2.6 Statistics

All statistics were performed using Minitab (Minitab Inc., release 13.20, State College, PA, U.S.A). T-tests were performed to determine if there was a significant difference between the diagnosis from mammography and that of the ComfortScan™ system. Sensitivity and specificity were calculated for all biopsy patients, and was used to produce receiver operating characteristic (ROC) curves (Figure 8-9) to evaluate the performance of mammography and the ComfortScan™ system. Figure 8 has separate ROC curves for both radiologist 1 and 2. Figure 9 has ROC curves of both mammography and the ComfortScan™ system, but a modified rating system was used. The modified rating system consisted of simply rating the suspicious ROI as malignant or benign; thus, it did not include varying degrees of malignancy, as found in Figure 8. Sensitivity and Specificity were calculated with Equations 3 and 4.

$$Sensitivity = \frac{(\#of\_true\_positives)}{(\#of\_true\_positives) + (\#of\_false\_negatives)} \quad (3)$$

$$Specificity = \frac{(\#of\_true\_negatives)}{(\#of\_true\_negatives) + (\#of\_false\_positives)} \quad (4)$$

The area under the curve (AUC) was calculated using the trapezoidal rule; thus, by looking at the average sensitivity between two points and multiplying by the corresponding difference in specificity. The trapezoidal rule is shown in Equation 5.

$$AUC = \frac{TPR_2 - TPR_1}{FPR_2 - FPR_1} \times \frac{1}{2} \quad (5)$$

where AUC is the area under the curve between point 1 and 2 on the ROC curve, TPR is the true positive rate (or sensitivity) at point 1 or 2, FPR is the false positive rate (or 1-specificity) at point 1 or 2.

### **3.3 RESULTS**

The results of the light scans were evaluated against mammography and biopsy (where available). Biopsies were only performed as required by mammographic and/or ultrasound findings, and were not based on ComfortScan™ readings. The ComfortScan™ images were analyzed and read by a radiologist who was blinded to the patient name, mammogram, and pathology results. The results are divided into 2 parts. The first part contains NIR images of patients with known suspicious mammograms visiting for follow up imaging; the second part contains NIR images of the mammographically normal contralateral breast of these patients. In this study 128 NIR images were obtained, 2 were discarded due to technical issues; there were 74 NIR images for part 1, and 52 NIR images for part 2. Three patients could not be imaged due to breast thickness; two patients had breasts too thin causing a “transmitted light intensity too high” error and one patient had breasts too thick causing a “transmitted light intensity too low” error. Below a few typical cases are illustrated before presenting the results for parts 1 and 2.

#### **3.3.1 Case 1 - carcinoma**

In Figure 2 the image of a typical carcinoma is shown. Note that the corresponding mammographic image was used to identify the suspicious ROI. The suspicious ROI is the circular region shown in purple. Both the suspicious ROI and nipple position were marked before the NIR scan commenced. The colour purple represents an area of the breast which had higher light absorption than background. When the suspicious ROI showed a colour of dark purple, the likelihood of cancer in that region increases. The dynamic signature of video sequence is shown in the bottom left corner. Notice that there is a highly decreasing dynamic signature over time.

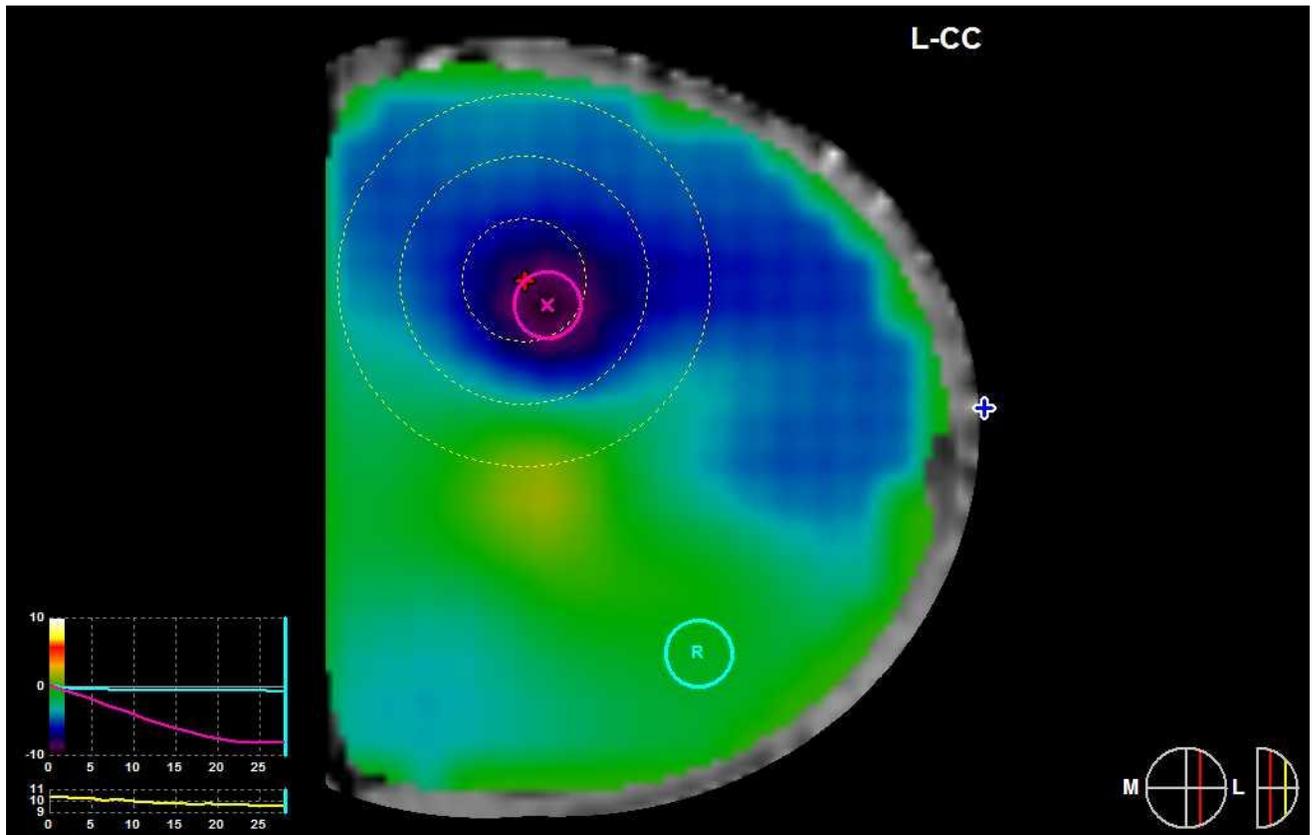


Fig. 2 – NIR Image of Carcinoma

This figure shows a typical image of a malignancy. This image is taken from a series of images which plays as a video. As time progresses the pressure on the breast is decreased, which is seen by the spectrum at the bottom left side of the above image. The other spectrum represents the dynamic signature with respect to time at two different positions in the image. The teal circle ('R') is an area with a relatively stable dynamic signature and used as reference. The purple circle ('x') has a highly decreasing dynamic signature and considered to be an area of high likelihood of malignancy.

### 3.3.2 Case 2 – Benign tumour

Next, an image with a benign finding is shown in Figure 3. The suspicious ROI in this case does not show the presence of blue or purple. The slight red colour in these images represents an area with less light absorption as compared to background. This implies that there are no regions with a higher light attenuation compared to background, and thus, no malignancies.

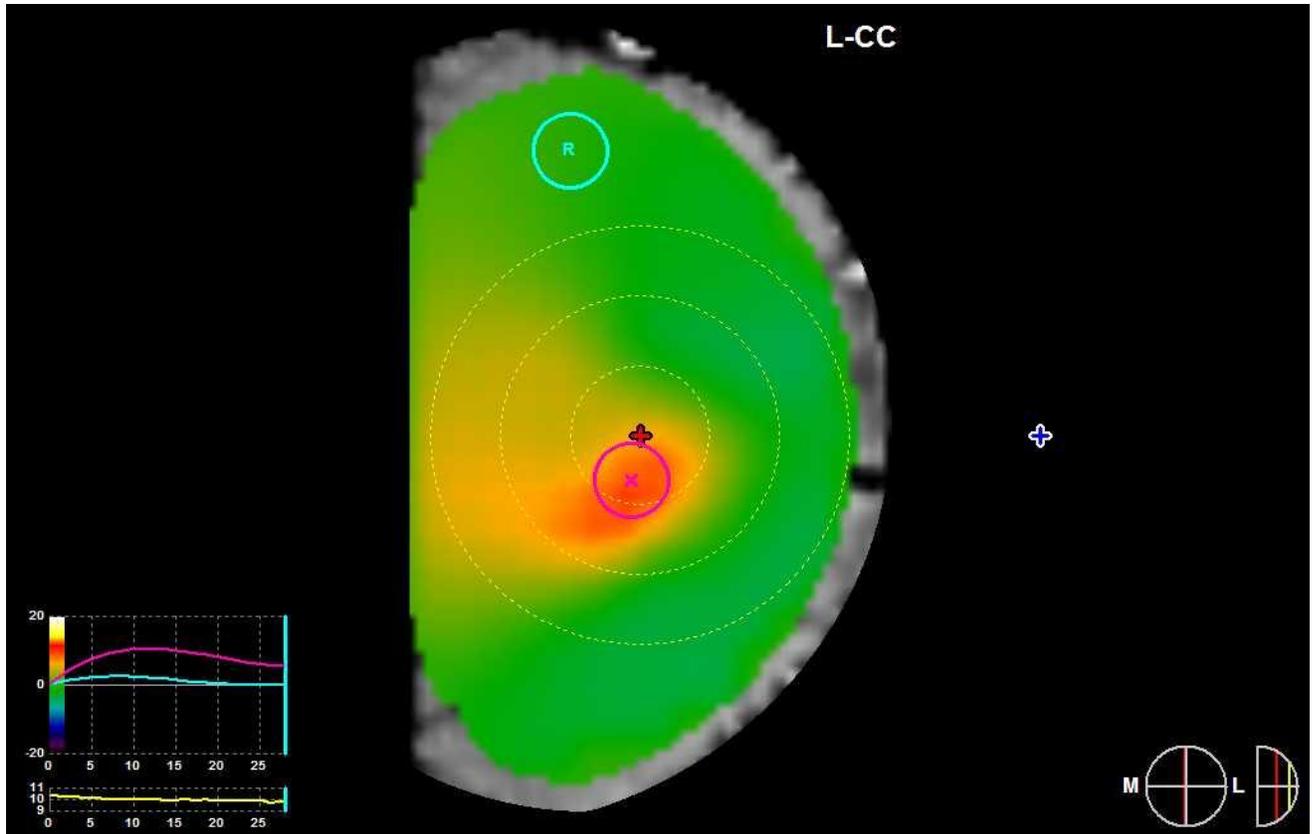


Fig. 3 – NIR Image of Benign Lesion

This figure shows no significant malignant findings. Note, there is no concentrated blue/purple ROI's near or at the anticipated suspicious ROI taken from the mammogram. The teal circle ('R') is a region of relative stable dynamic signature and used as reference. The purple circle ('X') is a suspicious region from the mammogram. Both ROI's in this image have a relatively stable dynamic signature, and thus, the diagnosis would be benign.

### 3.3.3 Case 3 – “Nipple Blue” Artifact

A sample image illustrating an invalid image and is shown in Figure 4. When the suspicious ROI is too close to the nipple surface, artifacts can be introduced. Note the concentrated region of blue/purple within 2cm to the nipple. This image is inconclusive and cannot be interpreted. This has occurred thus far in 1 out of 126 cases.

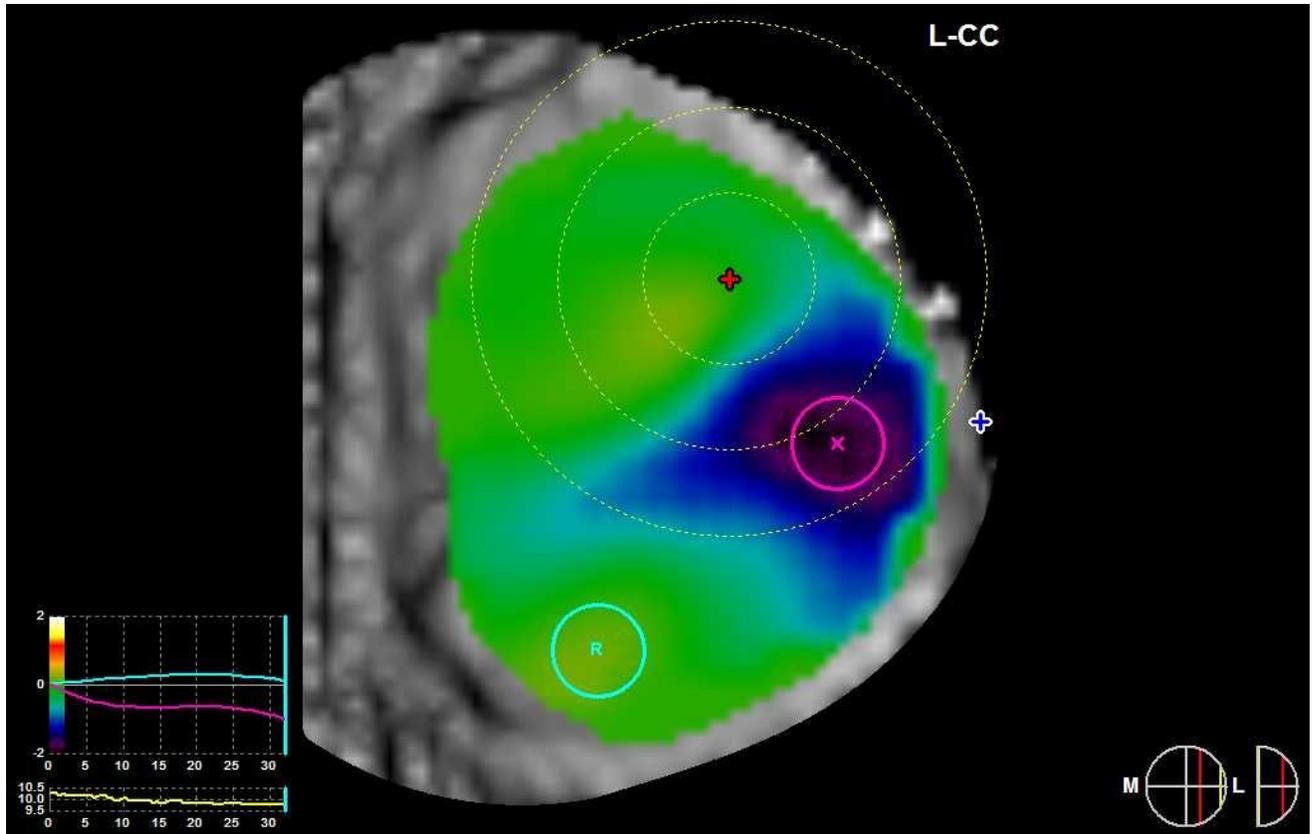


Fig. 4 – NIR Image of an Invalid Image

This figure a ‘nipple blue’ image taken by the ComfortScan™ system. The proximity (within 2cm) of the suspicious purple area to the nipple causes the DOBI rating on this image to be ‘nipple blue’. In other words, the purple area is thought to be an image artifact.

### 3.3.4 Case 4 – “Blue Bloom” Artifact

Figure 5 shows a typical “blue bloom” image. This ‘blue bloom’ image was seen in 17 of the 74 ComfortScan™ images from patients with suspicious mammograms, and 20 of the 52 ComfortScan™ images from patients with normal mammograms. The name ‘blue bloom’ was coined by one of the radiologists reading the ComfortScan™ images. The blue colour is normally associated with malignancy. The difference between a ‘blue bloom’ and a malignant finding is that ‘blue bloom’ images have significant blue throughout the entire image; however, malignant images have a well defined peaked area of blue in the image. This study suggests that such an image is the result of a pixel with a transmitted light intensity vastly

different than the rest of the image; this outlier, when its intensity is too high, would cause the rest of the image to be a relatively homogenous blue colour. The above mentioned theory is described in detail later in this chapter. In short, it is believed that a “blue bloom” image (rated as DOBI 0) is indeterminate, and instead, the dynamic signature should be comprehensively evaluated to determine the likelihood of malignancy. The dynamic signature is evaluated using the time and context characteristics that are described in Table 2.

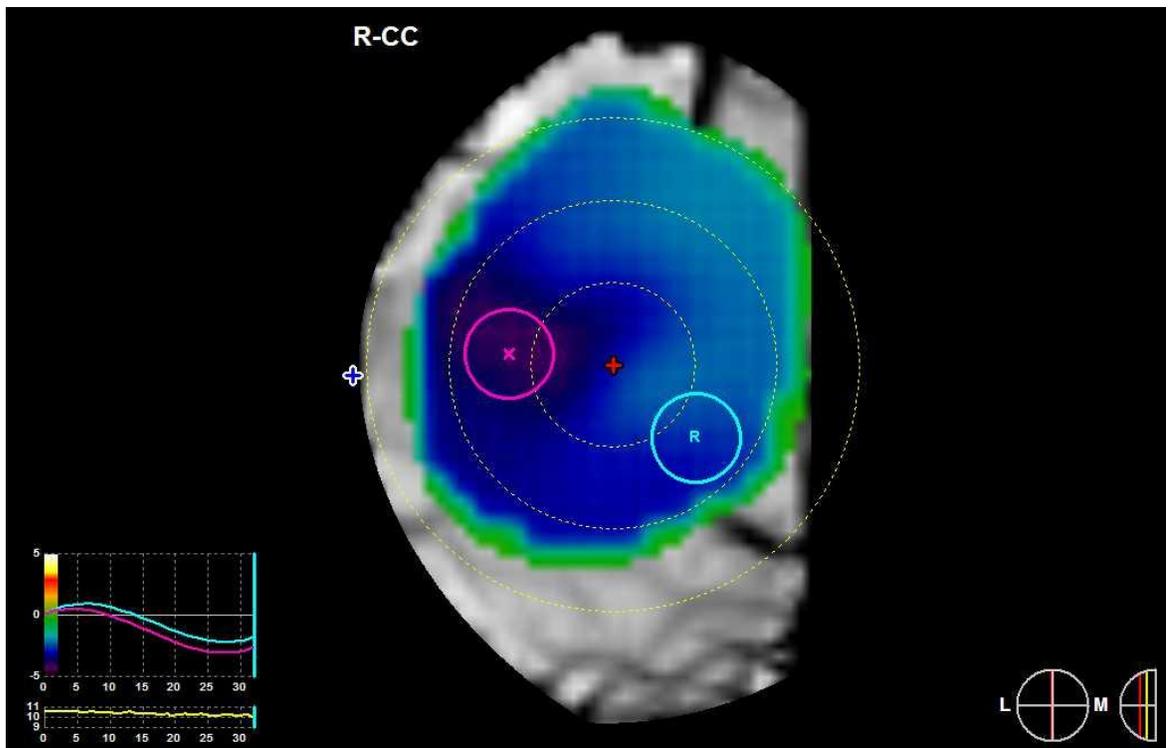


Fig. 5 – NIR of a ‘Blue Bloom’ Image

A ‘blue bloom’ image taken by the ComfortScan™ system. There is significant blue colour in the entire image. It is interesting to notice that in this case, the dynamic signatures are relatively constant throughout the image. This suggests that it is indicative of a normal breast since there is no area of highly varying dynamic signature.

### 3.3.5 Part 1 – Breasts with suspicious mammogram

Below in Figure 6 and Tables 4-6, the DOBI results from the 74 images from Part 1 are compared with the mammography classification. Please note that the numbers given are from the normalized rating system. Figure 6 indicates the number of patients with each score.

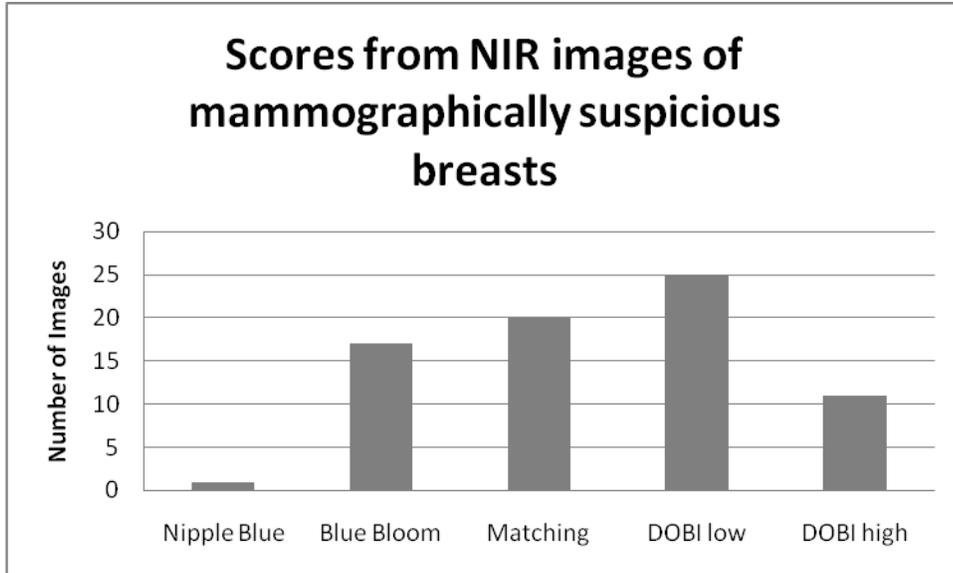


Fig. 6 – Scores from NIR images of mammographically suspicious breasts.

This figure shows the number of NIR images that are in each of the different categories. Nipple blue is an invalid image, ‘blue bloom’ is believed to be a contrast image introduced in mainly benign lesions.

One patient (out of 126) was reported as an invalid image due to a ‘nipple blue’ result. It should be noted that the adjusted BIRADS of 2 (normalized score) was associated with a suspicious region that was within 2cm of the nipple. In this NIR image, this suggests that perhaps the nipple blue image was actually correctly identifying a suspicious region. The 17 ‘blue bloom’ images showed significant blue colour throughout the entire image. Based upon the static image presentation, the diagnosis of these patients is indeterminate. However the dynamic characteristics can be used in all 17 cases to assess the disease state of the tissue as indicated in the third and fourth row of table 2. In the final analysis, these “blue bloom”

artifact cases will be categorized as either matching, DOBI low, or DOBI high, based upon their dynamic signature. The 20 ‘matching’ images are those for which the normalized rating for the DOBI and the mammogram were identical. The 25 ‘DOBI low’ images were those where the normalized DOBI rating was lower than the normalized mammography rating; hence, the ComfortScan™ system determined the breast to be less suspicious of abnormality than the mammogram. The 11 ‘DOBI high’ images were those where the normalized DOBI rating was higher than the normalized mammography rating; hence, the ComfortScan™ system determined the breast to be more suspicious than the mammogram.

Clearly, it can be seen by examining Figure 6 that the ComfortScan™ system’s results are in disagreement with mammography for some patients. In those mammograms that were suspicious, biopsies were taken and sent to pathology for analysis. Patients with normal mammograms were not asked to undergo a biopsy; therefore, it is impossible to use biopsy for validation for all patients in this study.

In Tables 4 to 6 the normalized DOBI scores and normalized mammography scores are shown, as well as their agreement with pathology (i.e. malignant or benign). Table 5 shows data for patients with normalized DOBI scores lower than normalized mammography scores. In other words, for these suspicious regions, the DOBI generated a more benign finding than mammography. Similarly, Table 6 lists the patients where the DOBI had a higher normalized rating as compared to mammography, indicating that DOBI identified the suspicious region as having a greater likelihood of malignancy as compared to mammography. The last two columns of these tables give a comparison of the DOBI and mammography rating to biopsy. These figures indicate that the ComfortScan™ system’s findings were in agreement with the available histological analysis. When compared to histological findings the ComfortScan™ system had an accuracy of 76% and mammography had an accuracy of 58%.

Image #	DOBI Score	Mammogram Score	DOBI correct?	Mammo Correct?
DOBI126	1	1	n/a	n/a
DOBI107	1	1	n/a	n/a
DOBI114	1	1	n/a	n/a
DOBI116	1	1	n/a	n/a
DOBI13	1	1	n/a	n/a
DOBI15	1	1	n/a	n/a
DOBI19	1	1	n/a	n/a
DOBI62	1	1	n/a	n/a
DOBI63	1	1	n/a	n/a
DOBI64	1	1	n/a	n/a
DOBI92	1	1	n/a	n/a
DOBI97	1	1	n/a	n/a
DOBI96	2	2	n/a	n/a
DOBI113	3	3	yes	yes
DOBI18	3	3	n/a	n/a
DOBI32	3	3	n/a	n/a
DOBI47	3	3	yes	yes
DOBI71	3	3	yes	yes
DOBI3	3	3	no	no
DOBI109	4	4	yes	yes
DOBI16	4	4	yes	yes
DOBI20	4	4	no	no
DOBI34	4	4	no	no
DOBI36	4	4	Yes	yes
DOBI43	4	4	Yes	yes
DOBI67	4	4	n/a	n/a
DOBI87	4	4	Yes	yes

Table 4 – Matching Patients

This table shows the results when comparing the rating from the ComfortScan™ system (DOBI rating) and the BIRADS rating to biopsy results. These results are for the patients with normalized (or adjusted) DOBI ratings identical to the normalized BIRADS. Note, n/a means no biopsy information was available because biopsy was not taken. (using the adjusted scoring system)

Image #	DOBI Score	Mammogram Score	DOBI correct?	Mammo Correct?
DOBI55	1	2	n/a	n/a
DOBI57	1	2	n/a	n/a
DOBI74	1	2	n/a	n/a
DOBI79	1	2	yes	yes
DOBI85	1	2	n/a	n/a
DOBI99	1	2	n/a	n/a
DOBI14	1	2	n/a	n/a
DOBI110	1	3	no	yes
DOBI120	1	3	n/a	n/a
DOBI22	1	3	n/a	n/a
DOBI58	1	3	yes	no
DOBI68	1	3	n/a	n/a
DOBI69	1	3	n/a	n/a
DOBI75	1	3	yes	no
DOBI77	1	3	yes	no
DOBI86	1	3	yes	no
DOBI101	1	3	yes	no
DOBI17	1	4	yes	no
DOBI23	1	4	yes	no
DOBI49	1	4	no	yes
DOBI2	2	4	Yes	no
DOBI105	3	4	yes	yes
DOBI38	3	4	yes	yes
DOBI7	3	4	n/a	n/a
DOBI82	3	4	n/a	n/a
DOBI9	3	4	Yes	yes
DOBI4	3	4	Yes	Yes
DOBI8	3	4	Yes	Yes
DOBI6	3	4	Yes	Yes

Table 5 – ComfortScan™ System lower than Mammography

This table shows the results when comparing the rating from the ComfortScan™ system (DOBI rating) and the BIRADS rating to biopsy results. These results are for the patients with normalized (or adjusted) DOBI ratings lower than normalized BIRADS. Note, n/a means no biopsy information was available because biopsy was not taken. (using the adjusted scoring system)

Image #	DOBI Score	Mammogram Score	DOBI correct?	Mammo Correct?
DOBI122	4	1	n/a	n/a
DOBI27	4	2	n/a	n/a
DOBI103	4	3	yes	yes
DOBI10	4	3	no	no
DOBI29	4	3	no	no
DOBI60	4	3	no	no
DOBI12	4	3	no	no
DOBI11	3	1	n/a	n/a
DOBI31	3	1	n/a	n/a
DOBI65	3	1	n/a	n/a
DOBI53	3	2	n/a	n/a
DOBI1	3	2	n/a	n/a
DOBI46	3	1	n/a	n/a
DOBI40	2	1	yes	yes
DOBI124	2	1	n/a	n/a
DOBI45	1	0	n/a	n/a
DOBI118	1	0	no	no

Table 6 – ComfortScan™ System higher than Mammography

This table shows the results when comparing the rating from the ComfortScan™ system (DOBI rating) and the BIRADS rating to biopsy results. These results are for the patients with normalized (or adjusted) DOBI ratings higher than normalized BIRADS. Note, n/a means no biopsy information was available because biopsy was not taken. (using the adjusted scoring system)

In Figure 2, a cancerous finding is shown. As the colour of the suspicious ROI becomes a darker purple with a highly decreasing dynamic signature, the likelihood of cancer increases. The DOBI rating system, shown in Table 2, is then used to determine if the breast is healthy, has a benign tumour, or has a malignant tumour.

In Figure 3 a benign finding is shown. There is no blue or purple area within the ROI shown on the image. The ROI shown on the image is obtained by examining the suspicious areas of the mammogram.

In Figure 4 a typical invalid image is shown.

In Figure 5 a typical “blue bloom” image is shown; this name was coined by one of the radiologists reading the NIR images. One theory is that these images showed significant blue (increased attenuation) throughout because of a contrast issue. The ComfortScan™ system uses an automatic contrast adjustment which identifies the range of pixel intensities and sets the colour scheme accordingly. If there are pixels with very similar intensities, but some pixels that are outliers with higher intensities, this could cause a large number of pixels to seem to exhibit significant attenuation. Also, the colour scheme is applied to all the pixel intensities for a given image; therefore, the colour blue from NIR image to NIR image may not represent the same absolute light attenuation. The colour scheme is a relative measure of light attenuation throughout a given image; this means that the same colour blue in two different NIR images may not in fact represent the same amount of transmitted signal intensity. Having both, some pixels with a higher signal intensity and a small pixel intensity range, could cause the “blue bloom” artifact and in fact represent a NIR image of a normal breast. More work needs to be done in studying this ‘blue bloom’ artifact and a larger scale clinical trial on mammographically normal breasts should be performed to see the incidence of the ‘blue bloom’ artifact in this patient population. This theory of ‘blue bloom’ images representing normal breasts is validated when examining the dynamic signature. The dynamic signatures in two different areas of the image in Figure 5 are very similar. They are both sinusoidal in shape and not highly decreasing. The ComfortScan™ image analysis determines an area has a higher likelihood of malignancy if there is both an area of higher attenuation and a highly decreasing dynamic signature. Therefore, Figure 5 would be deemed as benign through use of the dynamic signature. The dynamic signature should be a larger determinant of malignancy, rather than simply the presence of the colour blue on the image. By examining the dynamic signatures of all ‘blue bloom’ images, 11 were found to be malignant and 26 were found to be normal. These results were used to determine if the ‘blue bloom’ images matched, were higher, or were lower than mammography. In Figure 6 the results from part 1 of this study are presented.

Table 4 shows the 27 out of 74 patients where the ComfortScan™ system matched the mammogram; representing 36% of the NIR images taken from the population with initial suspicious mammograms.

The more interesting data is represented in Tables 5 and 6; these are the NIR images which either graded the breast lower than mammography (Table 5), or higher than mammography (Table 6). It was found that 39% of the time the ComfortScan™ graded the breast lower than mammography. When compared to biopsy the light scanning technique was wrong 7% (2/29) of the time, where as mammography was wrong 28% (8/29) of the time. Examining Table 6 shows that the ComfortScan™ system graded the breast higher (i.e. more likely malignant), when compared to mammography, 23% of the time. The light scanning technique, mammography and biopsy all report the same result 17% (3/18) of the time. The light scanning technique and mammography agreed, but disagreed with biopsy 28% (5/18) of the time. It is difficult to obtain numbers and truly evaluate the ComfortScan™ system's performance for NIR images from Table 6 because there is not much biopsy information for these patients. It is impressive that the ComfortScan™ system (accuracy of 76%) had a higher correlation with biopsy as compared to mammography (accuracy of 58%). Mammography showed more false positives. Unfortunately, since biopsy was only performed if the mammogram showed significant risk of malignancy, biopsy results weren't available for all patients. It would be interesting to have biopsy results from patients that show significant risk of malignancy through the ComfortScan™ system but show no risk with mammography. At the time of this study ethics was only granted with the caveat that patient care was not changed. Follow up mammograms were analyzed for the patients in Table 6; still there was no suspicious regions and therefore no biopsies ordered. These patients will be followed over the next few years to see if any abnormalities are seen.

### 3.3.6 Part 2 – Breasts with normal mammogram

In Figure 7, the DOBI and mammography classifications for the 52 NIR images are represented. All 52 patients had no suspicious regions on their mammogram. The REB approval would not allow for the line of patient care to be altered due to NIR images; thus, no biopsy results are available for these patients. Please note that the numbers given are from the normalized rating system. The 31 ‘agree’ images represent when ComfortScan™ system agreed with the mammographically normal finding. The 21 ‘disagree’ images represent when the ComfortScan™ system disagreed with a mammographically normal finding.

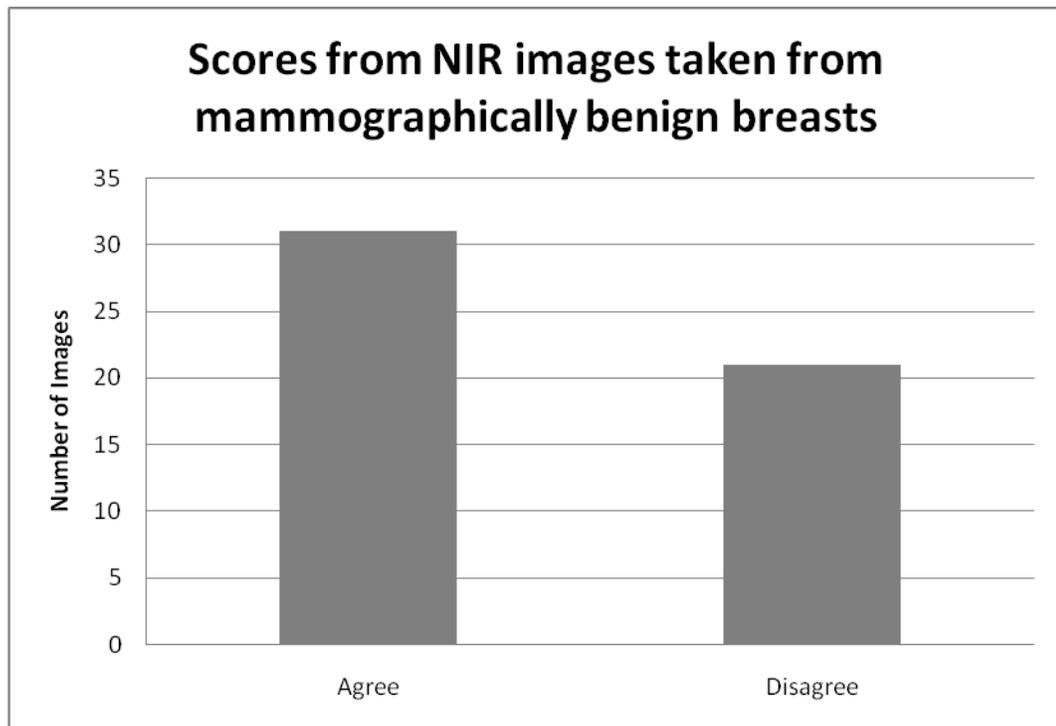


Fig. 7 – NIR images of benign breasts

This figure shows the ratings of the 52 NIR images which had mammographically benign breasts.

There were 20 ‘blue bloom’ images in Part 2. The dynamic signature was evaluated for all 20 and results showed that 15 NIR images were normal and 5 were malignant.

When examining the dynamic signature of all 37 'blue bloom' images (combining those in Part 1 and 2), it was found that 26 were classified as normal and 11 as malignant, by consideration of the dynamic signature. Of the 11 malignancies, as determined by the ComfortScan™ system, 3 were confirmed by biopsy, the rest were not sent to biopsy because all biopsies were ordered based on mammographic findings. Of the 26 normal ComfortScan™ system images, 5 were confirmed through biopsy to be benign, the rest were not sent for biopsy because of normal mammograms.

### **3.3.7 Reproducibility**

The intra-rater reproducibility was examined by re-analyzing 19 patients after all patients were analyzed; the radiologist was blinded throughout this process. To obtain the required sample size of 19, a 1-sample t test was performed using a p value of 0.01, target power of 0.9 and difference of 1. It was found that 15 out of the 19 had identical DOBI ratings. There were 4 ComfortScan™ images that were first found to be malignant and subsequently found to be benign through use of the ComfortScan™ image rating system. In these 4 images, there was no question that there was an area of higher attenuation and decreasing dynamic signature, which could be considered malignant; the reason they were found to be benign in the second analysis was because the ROI that exhibited the area of greater attenuation was found to be too far away from the suspicious ROI marker to cause a malignant rating using the ComfortScan™ image interpretation. One of the image interpretation parameters is to examine the distance of the suspicious ROI from the marker placed in the image by the imaging technologist. If the suspicious ROI on the ComfortScan™ image is further from the marker, the probability of malignancy decreases. In the 4 differing analyses: i) 3 were found to be now consistent with mammography, but no biopsy information was available for comparison, ii) 1 was now inconsistent with a malignant biopsy finding. From this information it was found that it is crucial to not only look at the suspicious ROI marker placed on the NIR image by the technologist; but also, look for any other

incidental malignant findings on the NIR image. It is believed that the suspicious ROI marker may not always be an accurate measure of suspected tumour position. The technologist approximates the tumour position from the suspicious mammogram and places a marker on the NIR image using the ComfortScan™ imaging software. The compression of the ComfortScan™ system and mammography are very different and therefore the position of the marker may be an accurate measure of tumour location.

### **3.4 DISCUSSION**

Using the ComfortScan™ system, the breast can be imaged and the likelihood of cancer can be determined. The ComfortScan™ system uses the differences in optical properties and vascularization of malignant, benign, and healthy breast tissue to obtain image contrast. More importantly, since the images are independent of breast tissue density, it has the potential to be used as an adjunct modality particularly in patients with dense breast parenchyma.

There have been previous studies [46, 48-50] investigating the potential use of the ComfortScan™ system for breast imaging; all were pilot studies, and showed encouraging results. Anthanasiou *et al.* [48] showed that dynamic optical breast imaging could be a promising tool, when used in conjunction with other imaging modalities, in determining the likelihood of breast cancer. Anthanasiou *et al.* [48] examined 5 positive breast cancers, found using MRI, and mention that further studies with larger patient population are needed to validate this technique. The next study by Anthanasiou *et al.* [50] examined 72 patients with BIRADS rating 4-5 that were scheduled for biopsy. A sensitivity and specificity for the ComfortScan™ system was reported to be 73% and 38%, respectively. These two studies by Anthanasiou *et al.* [48, 50] used a numeric level of suspicion score, which was related to the colour and maximum transmitted intensity in the ROI, rather than the dynamic signature as described in this paper. Fournier *et al.* [49] performed the most recent study by the Anthanasiou *et al.* group using the dynamic optical breast imaging system. In the

study by Fournier et al., 47 patients were used in the analysis of this novel light imaging technique. A comparison between mammography and dynamic optical breast imaging was used to determine the validity of the technique. Fournier et al. showed that there is potential to use dynamic optical breast imaging as a tool to distinguish between benign and malignant breast tumours. The study by Fournier et al. used the same dynamic signature analysis as described in this paper. Wilson *et al.* [46 (our group)] performed a pilot study examining the possible use of the ComfortScan™ system as an adjunct to mammography. The encouraging preliminary findings warranted the collection of data shown in this paper.

This study uses the same dynamic optical breast imaging unit as in the above two mentioned studies, and therefore the methods are very similar. The main differences were a larger number of patients were included in this study and results from normal breasts were included (as was suggested previously by Fournier et al. [49]). Our results agree with both Anthanasiou et al. and Fournier et al.; using dynamic optical breast imaging is a promising tool in both the detection of breast cancers and distinguishing between benign and malignant lesions. There was no significant difference between the diagnosis provided by mammography and that of the ComfortScan™ system ( $p > 0.05$ ). There were 6 patients where the NIR results contradicted mammography but agreed with biopsy. Since mammography misses up to 10% of breast cancers[53], these results are very interesting. Increasing the sensitivity of mammography would be extremely beneficial in the detection of breast cancer. There were 29 NIR results with malignant findings that disagreed with mammography with no available biopsies. This was due to mammography being the determinant for biopsy requirement. These patients have been followed for 1 year and still no malignant finding on mammography has forced the need for biopsy.

In the 37 'blue bloom' images there are 3 confirmed malignancies through biopsy. The remaining patients had either normal mammograms, or negative biopsies. By examining the dynamic signatures of these images more closely it was found that 26 patients showed normal conditions and 11 showed a high probability of malignancy. The 3 confirmed biopsy results were within the 11 NIR images with high

probability of malignancy. The 5 biopsy confirmed benign results were found within the 26 patients with normal optical dynamic signatures. This suggests that it is crucial to not only look at the presence of blue (or higher attenuation) in the NIR image, but also, critically examine the dynamic signature of any potential suspicious ROI's. It would be beneficial to obtain biopsy results on the 8 patients with abnormal dynamic signatures, but at this time the REB approval forced the line of patient care to be unaltered.

Patients with positive HER2 are at high risk for breast cancer, and therefore, have regular mammographic screening at an early age. This patient population could have an increased risk of radiation induced cancers with time because of the large dose build up over time. A non-ionizing, inexpensive imaging technique for breast cancer detection could prove very useful for these patients.

The use of the ComfortScan™ system on patients with dense breasts could prove to be very beneficial. Normally, with inconclusive mammograms caused by increased breast density are imaged using MRI to examine changes in vascularization. With the cost of MRI being so high, it would be beneficial to have a low cost imaging modality that also uses vascularization to obtain its contrast.

The benefits of using the ComfortScan™ system, that is the ability to increase the sensitivity in breast cancer detection, outweighs the cost to the patient, in terms of an extra scan time of 15 minutes. Perhaps dynamic optical breast imaging will find a place in the clinical setting during routine breast cancer screening.

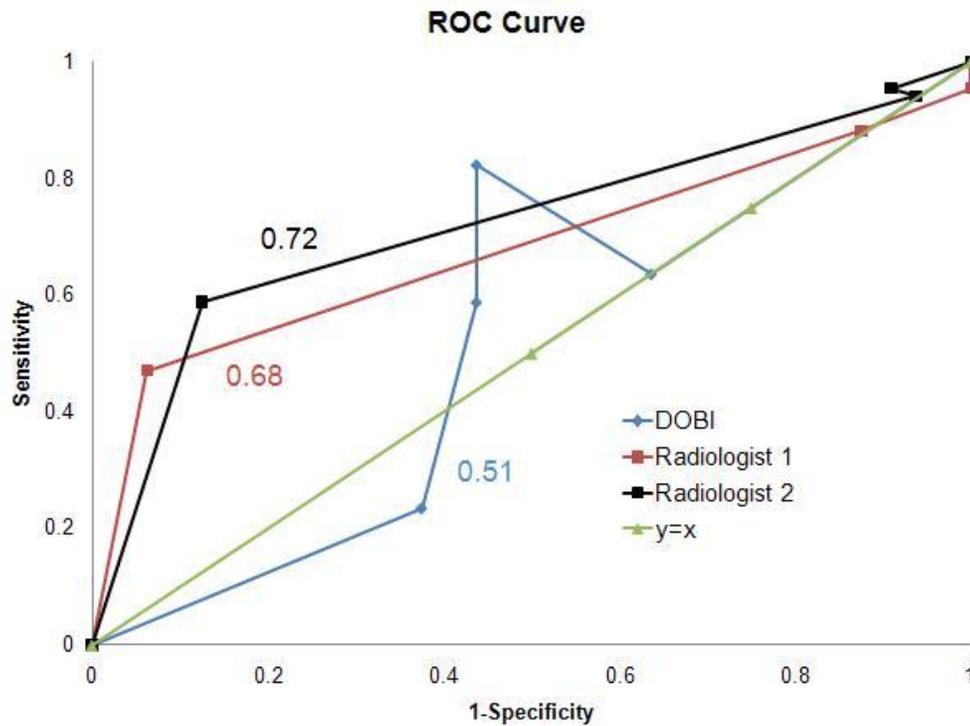


Fig. 8 – ROC Curve

This figure shows an ROC curve to compare mammography and the ComfortScan™ system. A separate ROC curve was produced for both radiologists. The area under the curve is given. The AUC was calculated using the trapezoidal rule. This shows that the ComfortScan™ system does not perform well as a screening tool.

Figure 8 shows a receiver operator characteristic (ROC) curve for mammography using the BIRADS rating system and for the ComfortScan™ system using the DOBI scoring system. This figure suggests that the ComfortScan™ system does not perform well as a screening tool for breast cancer detection. The area under the curve (AUC) for the ComfortScan™ system was 0.51, which is lower when compared to the AUC for either radiologist, 0.72 and 0.68. Therefore, mammography is better (more sensitive) than ComfortScan™ as a screening tool. However the goal here is not to evaluate the Comfortscan system's effectiveness as a screening tool, but rather to gauge its utility as an adjunct to mammography. For instance, all of the patients used to compare the Comfortscan and mammography have already been

prescreened with mammography to have a suspicious lesion. Thus patients are preselected that are mammographically positive. In order to assess the ability of the DOBI (as compared with mammography) to discriminate malignant from benign lesions, the DOBI and BIRADS rating scales were reduced effectively to either a benign or a malignant classification.

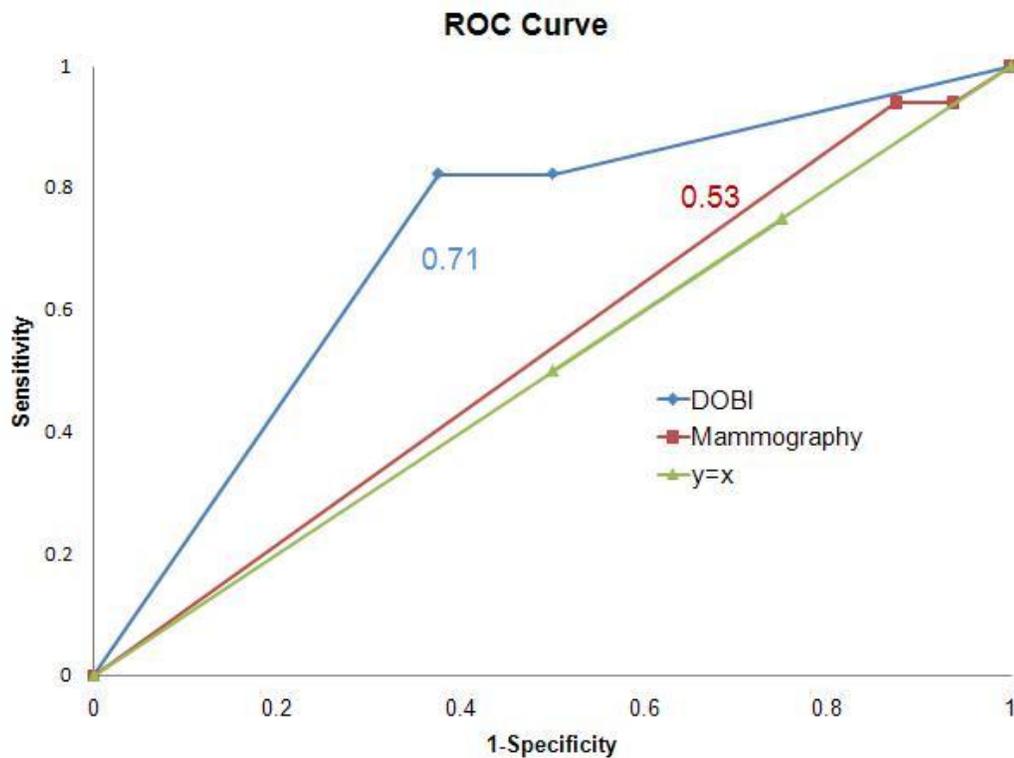


Fig. 9 – ROC Curve with Adjusted Rating System

This figure shows an ROC curve for both mammography and the ComfortScan™ system. These ROC curves, and corresponding AUCs, were obtained using an adjusted rating system. Instead of varying degrees of malignancies, as in the BIRADS rating system, a simple malignant or benign rating system was used.

Figure 9 is the corresponding ROC curve using this simplified rating system. The ComfortScan™ system is designed to be used as an adjunct to mammography not as a sole screening modality. Therefore, an ROC analysis which includes ratings of only benign or malignant is more appropriate. The AUC for the ComfortScan™ system is 0.71, whereas, for mammography is 0.53. This suggests that after identifying suspicious lesions using mammography, the ComfortScan™ system demonstrates potential in reducing the number of false positives. Therefore, may be some benefit in changing the current clinical practice to use the ComfortScan™ system to evaluate patients following a suspicious mammogram before sending for biopsy.

### **3.5 CONCLUSION**

The ComfortScan™ system has been shown to have promising results. Out of 128 NIR images in this study, there were only 2 unusable images (ambient light issue). Overall, there was statistically significant difference between the diagnosis provided by mammography and that of the ComfortScan™ system ( $p < 0.05$ ).

In Part 1, the NIR results showed: i) 1/74 ‘nipple blue’ image, ii) 27/74 matched perfectly with mammography, iii) 29/74 the DOBI rating was lower than mammography, and iv) 17/74 the DOBI was rated higher than mammography. The nipple blue image had significant blue and a decreasing dynamic signature near the nipple. This decreasing dynamic signature suggested malignancy, which was validated through biopsy; however, this image was deemed ‘nipple blue’ as per the ComfortScan™ image analysis parameter for lesion proximity to the nipple. For the images where NIR and mammography agreed, biopsy results showed that a wrong diagnosis was made 3 times, and a correct diagnosis was made 7 times, the rest of the images were not sent for biopsy. When the DOBI rating was lower than mammography biopsy results revealed: 7/29 both imaging techniques agree with biopsy, 2/29 mammography agreed but NIR disagreed with biopsy, and 8/29 mammography disagreed and NIR

agreed with biopsy. In the images where the DOBI rating was higher than mammography the biopsy results showed: 3/17 both imaging techniques agreed with biopsy, and 5/18 both imaging techniques disagreed with biopsy. There were not many cases sent for biopsy in this last category since mammography, not the ComfortScan™, decided whether or not a biopsy was needed as per REB restrictions. In the 'blue bloom' images: 4/17 were malignant through biopsy, 4/17 were benign through biopsy, and no biopsy results were available for the remaining.

In Part 2 there were: i) 31/52 NIR image agreed with mammography, and ii) 21/52 NIR image disagreed with mammography. None of the image in Part 2 went to biopsy, since the mammogram was normal. Out of the 20/52 'blue bloom' images there were 15 that were rated as normal and 5 that were rated as malignant through use of the dynamic signature.

By examining all 33 biopsy results it was found that the sensitivity and specificity for the ComfortScan™ system was 83% and 67%, respectively. The sensitivity and specificity of mammography was 94% and 13%, respectively. The sensitivity and specificity were calculated as per Equations 3 and 4. Please note that the sensitivity and specificity would be partially skewed due to mammography being the sole determinant for requirement of biopsy. Mammography determined the need for biopsy and, therefore, only patients with suspicious mammograms had a biopsy; this may cause there to be less false negatives and true negatives than the actual number for mammography. Having less false negatives and true negatives than expected would cause an increase in the sensitivity and decrease in the specificity, which could explain the high sensitivity and low specificity for mammography. It is difficult to get a true sense of the specificity of mammography because the number of true negatives cannot be confirmed. Confirming the number of true negatives through biopsy is unethical and since biopsy is the gold standard test, can only be done by waiting several decades and monitoring patient's routine mammograms.

Considering the specificity of the ComfortScan™ system is much greater than that of mammography; this study suggests that the ComfortScan™ system could be potentially used in a clinical setting as an adjunct to mammography to give the radiologist more information to provide a more definitive diagnosis.

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### **3.7 CONFLICTS OF INTEREST**

There are no conflicts of interest to declare.

### **3.8 REFERENCES**

- [1] Canadian\_Cancer\_Society. Breast Cancer Stats. 2010 [cited 2010 August 11]; Available from: [www.cancer.ca](http://www.cancer.ca)
- [2] Gaudette LAS, C.; Altmayer, C.A.; Gao, RN. Trends in Breast Cancer Incidence and Mortality. Health Reports. 1996;8(2):8.
- [3] Reich G. Near-infrared spectroscopy and imaging: Basic principles and pharmaceutical applications. Advanced Drug Delivery Reviews. 2005;57(8):1109-43.
- [4] Sibille F. Infrared Detection and Imaging. Reports on Progress in Physics. 1986;49(11):1197-242.
- [5] Reich, G. Near-infrared spectroscopy and imaging: Basic principles and pharmaceutical applications. Advanced Drug Delivery Reviews. 2005; 57 (8). 1109-1143.

- [6] Bevilacqua F, Berger AJ, Cerussi AE, Jakubowski D, Tromberg BJ. Broadband absorption spectroscopy in turbid media by combined frequency-domain and steady-state methods. *Applied optics*. 2000 Dec 1;39(34):6498-507.
- [7] Cerussi A, Hsiang D, Shah N, Mehta R, Durkin A, Butler J, et al. Predicting response to breast cancer neoadjuvant chemotherapy using diffuse optical spectroscopy. *Proceedings of the National Academy of Sciences of the United States of America*. 2007 Mar 6;104(10):4014-9.
- [8] Cerussi A, Shah N, Hsiang D, Durkin A, Butler J, Tromberg BJ. In vivo absorption, scattering, and physiologic properties of 58 malignant breast tumors determined by broadband diffuse optical spectroscopy. *Journal of biomedical optics*. 2006 Jul-Aug;11(4):044005.
- [9] Cerussi AE, Berger AJ, Bevilacqua F, Shah N, Jakubowski D, Butler J, et al. Sources of absorption and scattering contrast for near-infrared optical mammography. *Academic radiology*. 2001 Mar;8(3):211-8.
- [10] Cerussi AE, Jakubowski D, Shah N, Bevilacqua F, Lanning R, Berger AJ, et al. Spectroscopy enhances the information content of optical mammography. *Journal of biomedical optics*. 2002 Jan;7(1):60-71.
- [11] Chance B, Nioka S, Zhang J, Conant EF, Hwang E, Briest S, et al. Breast cancer detection based on incremental biochemical and physiological properties of breast cancers: a six-year, two-site study. *Academic radiology*. 2005 Aug;12(8):925-33.
- [12] Chance B, zhao Z, wen S, Chen Y. Simple ac circuit for breast cancer detection and object detection. *Rev Sci Instrum*. 2006;77:064301.
- [13] Chen NG, Guo P, Yan S, Piao D, Zhu Q. Simultaneous near-infrared diffusive light and ultrasound imaging. *Applied optics*. 2001 Dec 1;40(34):6367-80.
- [14] Chen NG, Huang M, Xia H, Piao D, Cronin E, Zhu Q. Portable near-infrared diffusive light imager for breast cancer detection. *Journal of biomedical optics*. 2004 May-Jun;9(3):504-10.

- [15] Choe R. Diffuse optical tomography and spectroscopy of breast cancer and fetal brain: University of Pennsylvania; 2005.
- [16] Durduran T, Choe R, Yu G, Zhou C, T'chou JC, Czerniecki BJ, et al. Diffuse optical measurement of blood flow in breast tumors. *Optics letters*. 2005 Nov 1;30(21):2915-7.
- [17] Guo P, Piao D, Zhu Q, Fikiet J. A combined 2-D ultrasound and NIR imaging system. *Proceedings of the IEEE 26th annual NE bioengineering conference*; 2000 april 8-9; 2000. p. 77-8.
- [18] Holboke MJ, Tromberg BJ, Li X, Shah N, Fishkin J, Kidney D, et al. Three-dimensional diffuse optical mammography with ultrasound localization in a human subject. *Journal of biomedical optics*. 2000 Apr;5(2):237-47.
- [19] Hsiang D, Shah N, Yu H, Su MY, Cerussi A, Butler J, et al. Coregistration of dynamic contrast enhanced MRI and broadband diffuse optical spectroscopy for characterizing breast cancer. *Technology in cancer research & treatment*. 2005 Oct;4(5):549-58.
- [20] Jakubowski DB, Cerussi AE, Bevilacqua F, Shah N, Hsiang D, Butler J, et al. Monitoring neoadjuvant chemotherapy in breast cancer using quantitative diffuse optical spectroscopy: a case study. *Journal of biomedical optics*. 2004 Jan-Feb;9(1):230-8.
- [21] Jayachandran B, Ge J, Regalado S, Godavarty A. Design and development of a hand-held optical probe toward fluorescence diagnostic imaging. *Journal of biomedical optics*. 2007 Sep-Oct;12(5):054014.
- [22] Lanning RT. Non-invasive characterization of breast cancer using near infrared optical spectroscopy. *UCI Undergraduate Research Journal II*. 1999;2:43-9.
- [23] Liebert A, Wabnitz H, Steinbrink J, Moller M, Macdonald R, Rinneberg H, et al. Bed-side assessment of cerebral perfusion in stroke patients based on optical monitoring of a dye bolus by time-resolved diffuse reflectance. *NeuroImage*. 2005 Jan 15;24(2):426-35.
- [24] Liu Q, Luo Q, Chance B. 2D phased array fluorescence wireless localizer in breast cancer detection 2004.

- [25] Nioka S, Chance B. NIR spectroscopic detection of breast cancer. *Technology in cancer research & treatment*. 2005 Oct;4(5):497-512.
- [26] No K, PH C. Mini-FDPM and heterodyne mini-FDPM: handheld non-invasive breast cancer detectors based on frequency-domain photon migration. *IEEE Trans Circuits Syst*. 2005;52(December 12):2672-85.
- [27] No K, Xie Q, Chou P, Kwong R, Cerussi A, Tromberg B. In vivo breast cancer measurement with a handheld laser breast scanner. *The 50th IEEE international Midwest symposium on circuits and systems (MWSCAS)*. Montreal Marriott Chateau Champlain Hotel 2007.
- [28] No K, Xie Q, Kwong R, Cerussi A, Tromberg B, Chou P. HBS: a handheld breast dyne. In *Proceedings of IEEE BioCAS*; 2006 November 29 - December 1; London: The British Library; 2006.
- [29] Sao V, Pourrezaei K, Akin A, Ayaz H. Breast tumor imaging using NIR LED based handheld continuous-wave imager. In: Reisman S FR, Mantilla B, editor. *IEEE 29th annual NE bioengineering conference*; 2003 March 22-23; 2003. p. 55-6.
- [30] Shah N, Cerussi A, Eker C, Espinoza J, Butler J, Fishkin J, et al. Noninvasive functional optical spectroscopy of human breast tissue. *Proceedings of the National Academy of Sciences of the United States of America*. 2001 Apr 10;98(8):4420-5.
- [31] Shah N, Cerussi AE, Jakubowski D, Hsiang D, Butler J, Tromberg BJ. Spatial variations in optical and physiological properties of healthy breast tissue. *Journal of biomedical optics*. 2004 May-Jun;9(3):534-40.
- [32] Shah N, Gibbs J, Wolverson D, Cerussi A, Hylton N, Tromberg BJ. Combined diffuse optical spectroscopy and contrast-enhanced magnetic resonance imaging for monitoring breast cancer neoadjuvant chemotherapy: a case study. *Journal of biomedical optics*. 2005 Sep-Oct;10(5):051503.
- [33] Sunar U, Quon H, Durduran T, Zhang J, Du J, Zhou C, et al. Noninvasive diffuse optical measurement of blood flow and blood oxygenation for monitoring radiation therapy in patients with head and neck tumors: a pilot study. *Journal of biomedical optics*. 2006 Nov-Dec;11(6):064021.

- [34] Tromberg BJ, Coquoz O, Fishkin JB, Pham T, Anderson ER, Butler J, et al. Non-invasive measurements of breast tissue optical properties using frequency-domain photon migration. *Philosophical transactions of the Royal Society of London*. 1997 Jun 29;352(1354):661-8.
- [35] Tromberg BJ, Shah N, Lanning R, Cerussi A, Espinoza J, Pham T, et al. Non-invasive in vivo characterization of breast tumors using photon migration spectroscopy. *Neoplasia (New York, NY)*. 2000 Jan-Apr;2(1-2):26-40.
- [36] Xu C, Zhu Q. Optimal probe design for dual-modality breast imaging. *SPIE-optical tomography and spectroscopy of tissue VII*; 2007 February 13; 2007. p. 64340B.
- [37] Xu R, Qiang B, Mao J. Near infrared imaging of tissue heterogeneity: probe design and sensitivity analysis. *IEEE: Eng in Med and Biol*; 2005 September 1-4; Shanghai, China; 2005.
- [38] Xu R, Qiang B, Olsen J, Povoski S, Yee L, Mao J. Localization and functional parameter reconstruction of suspicious breast lesions by near infrared/ultrasound dual modal imaging. *Conf Proc IEEE Eng Med Biol Soc*. 2005;5:4473-6.
- [39] Xu RX, Qiang B, Mao JJ, Povoski SP. Development of a handheld near-infrared imager for dynamic characterization of in vivo biological tissue systems. *Applied optics*. 2007 Oct 20;46(30):7442-51.
- [40] Zhu Q, chen N, Guo p, yan S, Piao d. Combined ultrasound and near infrared diffusive light imaging. *IEEE Symp Ultrasonics*; 2000; 2000. p. 1629-32.
- [41] Zhu Q, Chen N, Kurtzman SH. Imaging tumor angiogenesis by use of combined near-infrared diffusive light and ultrasound. *Optics letters*. 2003 Mar 1;28(5):337-9.
- [42] Zhu Q, Cronin EB, Currier AA, Vine HS, Huang M, Chen N, et al. Benign versus malignant breast masses: optical differentiation with US-guided optical imaging reconstruction. *Radiology*. 2005 Oct;237(1):57-66.
- [43] Zhu Q, Durduran T, Ntziachristos V, Holboke M, Yodh AG. Imager that combines near-infrared diffusive light and ultrasound. *Optics letters*. 1999 Aug 1;24(15):1050-2.

- [44] Zhu Q, Huang M, Chen N, Zarfos K, Jagjivan B, Kane M, et al. Ultrasound-guided optical tomographic imaging of malignant and benign breast lesions: initial clinical results of 19 cases. *Neoplasia* (New York, NY. 2003 Sep-Oct;5(5):379-88.
- [45] Zhu Q, Kurtzma SH, Hegde P, Tannenbaum S, Kane M, Huang M, et al. Utilizing optical tomography with ultrasound localization to image heterogeneous hemoglobin distribution in large breast cancers. *Neoplasia* (New York, NY. 2005 Mar;7(3):263-70.
- [46] Wilson K, Dhamanaskar K, Minuk T, Moran G. Pilot Study Investigating the Potential use of Dynamic Optical Breast Imaging in Breast Cancer Detection. Submitted to *Canadian Association of Radiologists Journal*. 2010.
- [47] Sarntinoranont M, Rooney F, Ferrari M. Interstitial Stress and Fluid Pressure Within a Growing Tumor. *Annals of Biomedical Engineering*. 2003. Vol 31. 327-335.
- [48] Athanasiou A, Vanel D, Balleyguier C, Fournier L, Mathieu MC, Delalogue S, et al. Dynamic optical breast imaging: a new technique to visualise breast vessels: comparison with breast MRI and preliminary results. *European journal of radiology*. 2005 Apr;54(1):72-9.
- [49] Fournier LS, Vanel D, Athanasiou A, Gatzemeier W, Masuykov IV, Padhani AR, et al. Dynamic optical breast imaging: a novel technique to detect and characterize tumor vessels. *European journal of radiology*. 2009 Jan;69(1):43-9.
- [50] Athanasiou A, Vanel D, Fournier L, Balleyguier C. Optical mammography: a new technique for visualizing breast lesions in women presenting non palpable BIRADS 4-5 imaging findings: preliminary results with radiologic-pathologic correlation. *Cancer Imaging*. 2007. (7): 34-40.
- [51] Liberman L, Menell JH. Breast imaging reporting and data system (BI-RADS). *Radiologic Clinics of North America*. 2002;40(3):409-+.
- [52] Koukourakis MI. Tumour angiogenesis and response to radiotherapy. *Anticancer Res*. 2001 Nov-Dec;21(6B):4285-300.

[53] Kim JG, Liu H. Variation of haemoglobin extinction coefficients can cause errors in the determination of haemoglobin concentration measured by near-infrared spectroscopy. *Physics in Medicine and Biology*. 2007;52:6295-322.

[52] IARC. *Handbooks of Cancer Prevention: Breast Cancer Screening*. B.F. Vainio H, Lyon, IARC Press.