

REVIEW ARTICLE

Combined multimodality imaging and optical techniques: a futuristic approach for breast cancer

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Abstract

More than 1,000,000 women were diagnosed with breast cancer in the last decade worldwide. The prognosis for this disease improves greatly when it is detected early. Detecting the efficacy of treatments *in-vivo* can not only expedite the development of drugs but also enable treatments to be more individually tailored. Drugs can induce cell apoptosis and can be a biomarker for monitoring the effectiveness of, for example, chemotherapy. It is preferable to undertake this detection using non-invasive techniques and with non-ionising radiation when possible to minimize discomfort and risks to the patient.

Techniques currently used to diagnose or monitor lesions in the breast often require ionising radiation (e.g. x-ray mammography) or are expensive and time-consuming (e.g. MRI). A number of non-ionising imaging techniques have been investigated for the imaging of the breasts including: near-infrared spectroscopy, electrical impedance spectro scopy and tomography, microwave imaging spectroscopy and photoacoustic and thermo acoustic imaging. Optical imaging can detect suspicious lesions and cell apoptosis, and in some cases can be used as an alternative to imaging using ionising radiation. Optical signals in tissues can however be dependent on a number of factors including vascularity, cellularity, oxygen consumption, water concentration, lipid content, oedema, fibrosis and remodelling.

A key challenge to detecting cancer utilizing light has been the ability to differentiate between absorption and scattering. The breast has a high level of scattering and absorption to optical wavelengths. Most of the important physiological information is contained in the absorption processes. However, scattering processes tend to dominate in breast tissue to the extent that signal requiring propagation over more than just a few millimetres will be dominated by diffusely scattered light.

This article reviews recent advances in optical techniques as well as combinations with an advanced molecular imaging method for the early detection of breast cancer and assessing the efficacy of response to therapeutic regime(s).

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Introduction

The use of the near infra-red for breast examination

One of the key challenges in detecting cancer with light has been the ability to differentiate between absorption and scattering [1]. The attenuation of light in tissues depends on the medium's absorption, scattering and the propagation distance between the source and the detector. These dependencies can be non-linear. The breast has a high level of scattering and absorption to optical wavelengths. Most of the important physiological information is contained in the absorption processes; however, scattering processes tend to dominate in breast tissue, to the extent that signal requiring propagation over more than just a few millimetres will be dominated by diffusely scattered light. This is unfortunate as photons scattered a small number of times carry more spatial information than those scattered many times (i.e. diffuse light). This dominance of scattering causes the reconstruction of the detected signals into an image to be highly challenging, as all of the detected signals cannot be assumed to be from light transmitted on the line-of-sight to the source, as is found in CT imaging, but instead it represents an integral over the entire tissue volume [2].

Fortunately, there exists an optical window in the near infra-red (NIR) in which optical measurements can be taken as shown in Figure 1. NIR techniques use a therapeutic window which lies approximately between 700 and 900 nm (estimates of this window size vary). This window exists because haemoglobin (the greatest absorber of light in the visible wavelength region) and lipids (the highest absorber in the IR region of the spectrum) both have a coincident low absorption coefficient in the NIR. It is also a region where tissue autofluorescence is low if one chooses to use a fluorescent agent to image [3]. Even in this spectral region the typical scattering length in breast tissue is 1 mm [2].

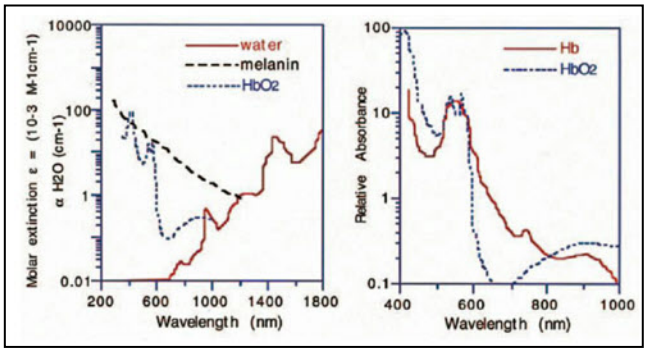

Figure 1 *Spectral dependence of tissue chromophore absorption. A tissue optical window exists in the red/NIR between 600 and 1300 nm [1]*

Optical techniques

Various aspects of the use of optical techniques for understanding breast lesions have been studied by a number of groups, which include monitoring tumour response to neoadjuvant chemotherapy [6-12], tumour detection [13-14] and healthy breast tissue [15].

There are different ways in which one can examine breast lesions using optical techniques. In order to be of use in imaging, the normal and diseased tissue must have distinguishable optical properties. One can either use the endogenous contrast of the tissue in the body itself to provide information [14], or alternatively introduce a different material, for example, a fluorescent material, which can identify specific processes or properties of the tissue in the body that can be excited and then observed as it decays [16-17]. In the former case, in order to image deeper tissue, one must identify a region of the electromagnetic spectrum in which absorption is low but scattering is sufficiently high to provide contrast. The contrast can be due to, for example, high absorption due to angiogenesis or haemoglobin absorbance. The optical properties of tissues can depend on a number of factors including vascularisation, cellularity, oxygen consumption, oedema, fibrosis and remodelling [13].

Performance of optical techniques for breast lesion detection and monitoring is not limited by mammographic density [18], and therefore these techniques may be particularly beneficial for young women, women taking hormone replacement therapy or high-risk subjects who may not benefit from conventional imaging. Optical methods can be used to examine 'tissue functional changes associated with the appearance, progression, and treatment of breast cancer' [18]. Overall wavelengths in the NIR region of interest, tumours absorb significantly (i.e. up to 3 times) more than normal tissue as a result of the increased blood supply to the tumour and the higher concentration of haemoglobin [1].

There are two kinds of optical technique without fluorescence agents, which include diffuse optical tomography (DOT) and diffuse optical spectroscopy (DOS). Optical spectroscopy and DOT are both non-invasive techniques. Spectroscopy, although does not provide imaging information, can be used to probe both compositional and functional characteristics [19].

Diffuse optical tomography

Diffuse optical imaging (DOI) is used to reconstruct images of inside the patient's breast by utilizing data from a large number of different sources and detector locations. This technique can be used to localise different subsurface structures. It uses a small number of different wavelengths (typically up to 6) in the NIR region and a low temporal bandwidth. Tomography is used to describe techniques which can produce three dimensional images. In this case, the tomography uses the diffusely scattered light in the tissue.

Optical imaging can be done in a number of different geometries. The use of a planar geometry is beneficial because of its simplicity and ease of implementation. However, it has been proven to have a low penetration depth, is hard to quantify and struggles to provide depth and size information. In contrast, optical tomography has the ability to provide some depth and size information. It uses photon propagation models to reconstruct from a number of images, the true 3D image at a higher resolution, greater penetration depth and improved quantification performance over the planar technique.

In NIR optical tomography, different moda lities may be employed to acquire images [14]. One can use continuous wave imaging, frequency domain imaging or time domain imaging. In continuous wave (CW) or time independent imaging, a continuous light source is used to illuminate the tissue (Figure 2).

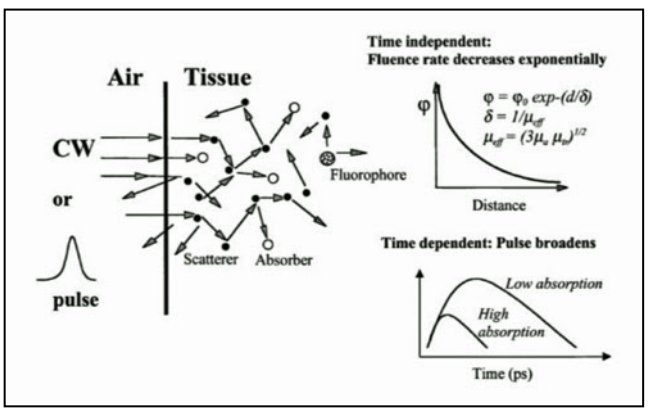

Figure 2 *Demonstration of the effect of using continuous wave compared to time domain optical techniques. In continuous wave experiments one only observes the light intensity to decay with distance but it is not possible to retrieve timing information about the propagated light. In time domain techniques a very short pulse is sent into the tissue, which is broadened, scattered and absorbed into the tissue. This extra timing information yields more information about the tissue through which it traverses [1]*

The subsequently scattered time invariant light intensity is measured in different positions on the tissue surface. In time domain photon migration (TDPM) imaging, a short impulse of light is sent into the patient, which is broadened and attenuated as it traverses and interacts with the tissue. The broadening provides an indication of the distribution of times-of-flight of photons through the tissue.

In frequency domain photon migration (FDPM) imaging, light with a sinusoidally modulated intensity is incident on the tissue. This intensity wave propagates through the tissue and is both attenuated and phase-shifted before being detected elsewhere on the tissue surface. An example of the relative amplitude and phase of the incident and detected waves in FDPM is shown in Figure 3.

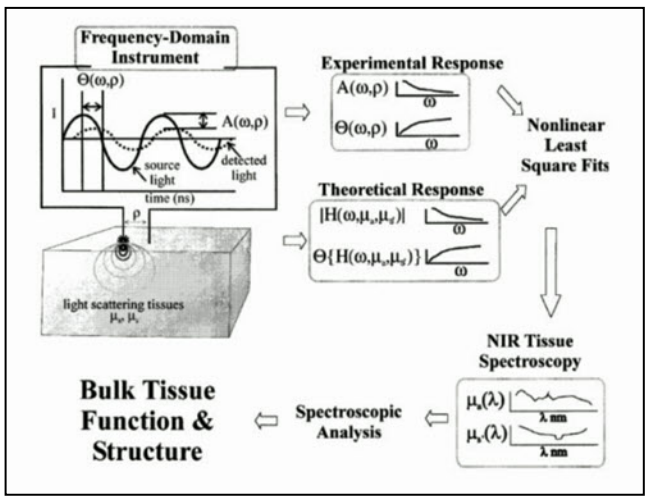

Figure 3 *Frequency dependent photon migration. NIR intensity modulated light is launched into tissue and is measured after propagation [1]. The data acquired is fitted to a model which determines the calculated values for absorption and reduced scattering at each optical wavelength measured. Where applicable, the absorption spectra are used to calculate the concentration of the principle tissue chromophores*

The resolution of NIR techniques is low due to light scattering. Continuous wave transmission imaging cannot provide depth information whereas time and frequency domain imaging can do. Using multiple wavelengths, benign and malignant lesions can be differentiated by considering the deoxy-haemoglobin concen tration. NIR diffuse optical tomography can differentiate between cysts and solid masses [13].

Diffuse Optical Spectroscopy

Diffuse optical spectroscopy (DOS) tends to use data over a broad range of wavelengths from a small number of source and detector positions to reconstruct the entire spectrum over the wavelength range-of-interest. This in turn can provide functional information or biochemical composition of the breast. Tissue scattering at a single wavelength provides little functional information of breast tissue; however, scattering as a function of wavelength over an extended range is highly useful to determine breast composition and physiology [20].

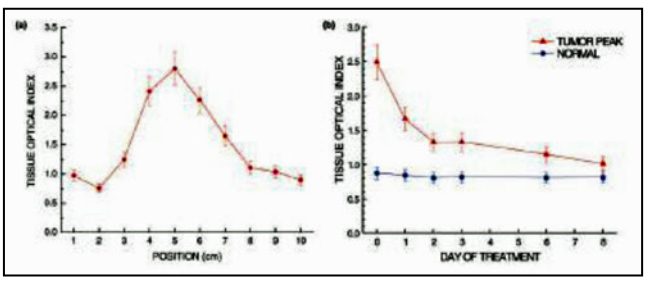

Figure 4 *Comparison of TOI [18]*

Tissue found in tumours tends to scatter more readily than the normal tissue. Scattering in tissue results from inhomogeneities in the tissue structure, which causes discontinuities in the material refractive index, i.e. the tumour tissue tends to contain smaller scattering particles than the surrounding normal tissue [1]. Tromberg *et al.* [1] and Cerussi *et al.* [20] have shown that using this information one can derive a quantity known as the Tissue Optical Index (TOI); [TOI = (ctHHb *ctH2O)/(% lipid), where ctHHB is the concentration of deoxygenated haemoglobin and ctH2O is the concentration of water in the tissue], which demonstrates that the tumour tissue has a higher contrast than normal tissue. A higher TOI indicates an increased metabolic activity and malignancy as shown in Figure 4, which shows that DOS using the tissue optical index can be used effectively to localise tumours and monitor the response of patients to neoadjuvant chemotherapy rapidly after the commencement of treatment (i.e. in the timescale of days). These early changes can indicate whether a patient is responding to the treatment or not, and allow more information to be provided to the individual in charge of their treatment regime.

Kukreti *et al.* [19] have used double differential spectroscopic techniques to find breast cancer markers in the NIR. By using this double differential technique, they were able to remove patient-specific variations, which are uncorrelated with the presence of cancer in their measurements. The technique examined the presence and concentration of lipids in cancerous tissue, which is notably markedly different to that in the normal tissue. In this method, the spectra of the four basic components of the breast are calculated (which in Cerussi's paper [20] are defined as concentrations of de-oxy and oxy-haemo globin, water and lipids in the breast), and an average spectrum of the normal breast is calculated. The results of this calculation are compared to the measured values, and a fit of these basis components to the measured spectra is made. This fit will indicate the relative presence of the four basic components in the region measured. Any difference in the spectra that the fit cannot account for are considered residual spectra and are considered to be the specific tumour component.

Diffuse optical spectroscopy and imaging (DOSI) uses 'broadband technology, both in near-infrared spectral and temporal signal domains in order to separate absorption from scattering and quantify uptake of multiple molecular probes based on absorption or fluorescence contrast' [7]. It has been developed with the aim to improve both breast cancer detection and its management. By using both broad temporal and spectral signals, it can separate absorption from scattering and establish quantitatively the uptake of multiple probe materials, which can provide either fluorescence or absorption contrast. When this technique has been combined with x-ray mammography (which can give structural information) or MRI (which can give vascular flow information), more information can be gleaned. DOSI is affected by 'intrinsic and extrinsic contrast mecha nisms, quantitation of biochemical compo nents, image formation/visualization, and multimodality co-registration' [7].

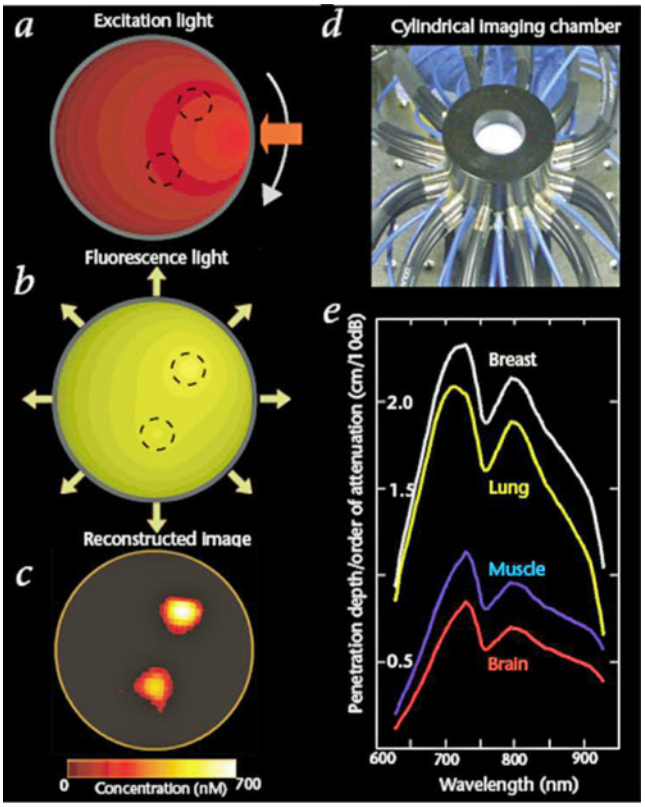

Figure 5 *Fluorescence molecular tomo graphy [3]. (a) A single point source illuminates the tissue. This wavefront propagates through the tissue to excite the fluorochromes. (b) Each excited fluorochrome acts as a secondary source of light at a higher wavelength (lower frequency), with an intensity that is a function of the position of the light source. (c) The measurements of the emissions from the fluorochromes are tomographically combined to give a 3D image. (d) An example of cylindrical FMT system that has been used for mouse imaging. For small animals the resolution achievable is ~1mm. (e) Modelled data of the penetration depth of NIR light through different tissues*

Fluorescence Molecular Tomography

Three-dimensional fluorescence molecular tomography (FMT) tests have been carried out using fluorescent agents injected intravenously in mice to be carried by the blood in order to image the vascular volume fraction (VVF) and how this changes with

antiangiogenic chemotherapy [21, 22]. FMT uses target specific molecular fluorescent reporters that can reconstruct volumetrically the light from the probes (Figure 5).

By using annexin V labelled with a fluorescent chromophore, one can probe cell apoptosis in the NIR. One example of where this has been successfully done *in-vivo* by Petrovsky [23] used a Cy-annexin (where Cy is Cy5.5 fluorophore) that bounds to apoptotic Jurkat T-cells to study how the treatment of a variant of Lewis lung carcinoma reacted to cyclo phosphamide treatment.

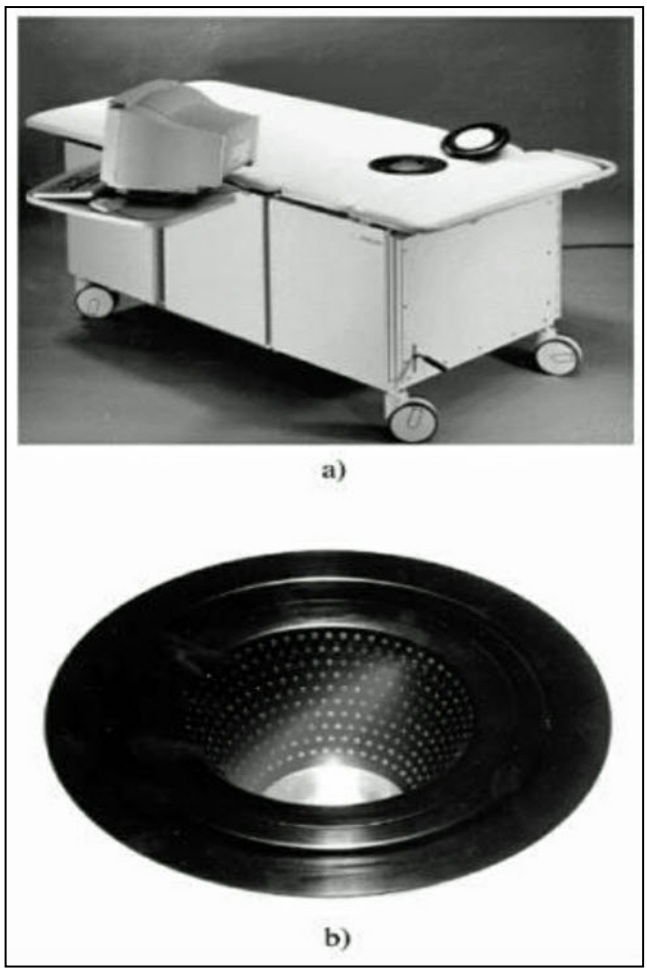

Figure 6 *(a) The Philips Optical Mammo Prototype system. (b) A close up of the cup area of the unit. This system acquires data at a rate of 2 minutes per wavelength. The patient lies on the system and the pendulant breast hangs in the cup which is filled with optically matched fluid [14]*

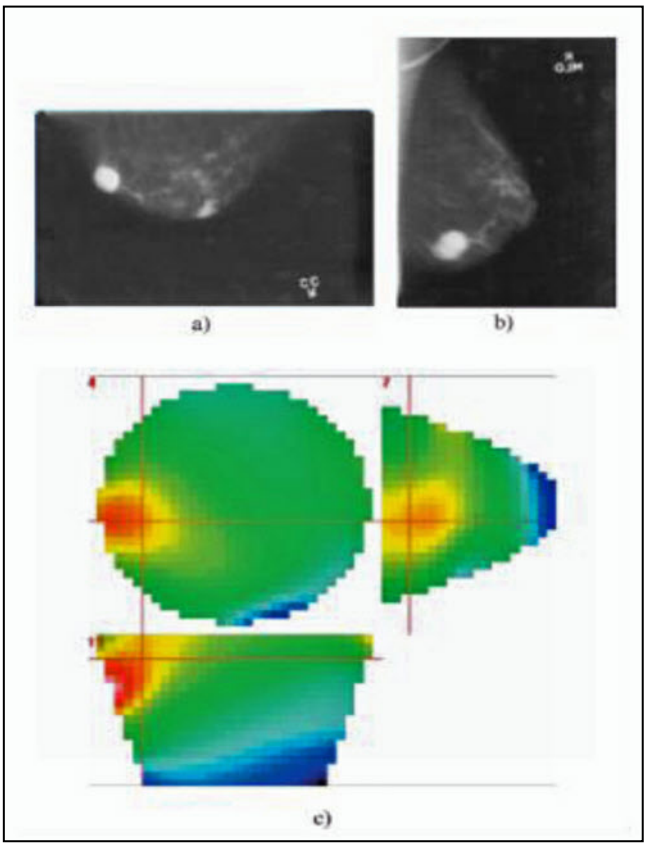

Figure 7 *Examples of optical images collected from a patient with a 1-2 cm breast mass using the Philips system (a) craniocaudal x-ray mammogram (b) mediolateral view of x-ray mammogram, (c) optical reconstruction of the cranio caudal, mediolateral and coronal view of same patient. In the optical images, which have been reconstructed from CW data, the mass is shown by a high attenuation (red) [14]*

Phillips medical system

One example of an optical breast probe made by Philips Medical is shown in Figure 6 [14]. This system has 256 optical fibers arranged in a conical holder. The pendulant breast sits inside the cone and is surrounded in a scattering medium, which simulates the optical properties of the breast. Each fiber is used in turn as a transmission fiber and sequentially emits the light from 3 different laser diodes. In the data shown in below, it has taken data using a CW transmission. The remaining fibers detect the subsequent transmitted light.

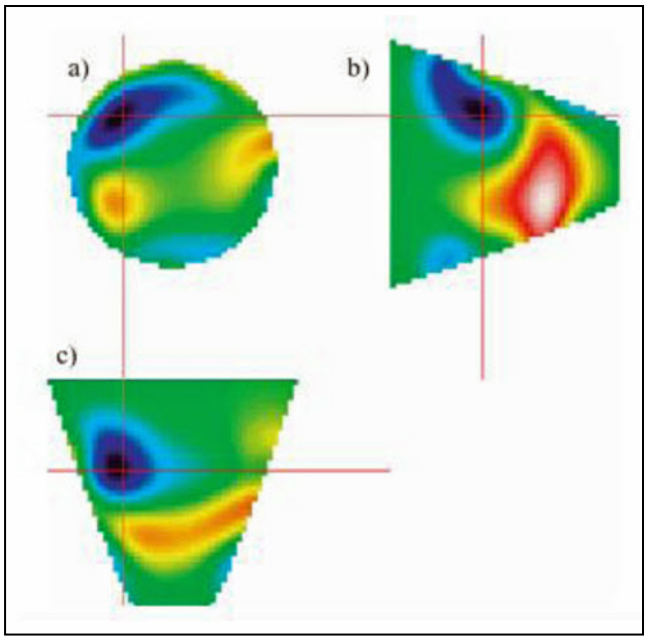

Figure 8 *Example of data for a fluid filled cyst using the Phillips optical mammography system reconstructed from CW data. The cyst has a low attenuation (blue) [14]*

All of the data are then used to reconstruct the image using back-projection. This system acquired the images shown in Figure 7 (which shows a breast mass), and Figure 8, which shows a fluid filled cyst.

Laser breast scanner

A different probe for undertaking studies to monitor neoadjuvant chemotherapy is shown in Figure 9. This system is called the laser breast scanner and is a bedside system, which may be used to monitor the patient's response to neoadjuvant chemotherapy. This system combines frequency domains measurements with broadband continuous wave tissue spectroscopy to measure the complete broadband absorption and reduced scattering spectra in the NIR. This scanner is a low cost system, which has been used to measure tumours that are typically near to the surface and large [7].

Another example is given by Francescini *et al.* [24], where they use a dual wavelength (690 nm and 810 nm) frequency domain (110 MHz)

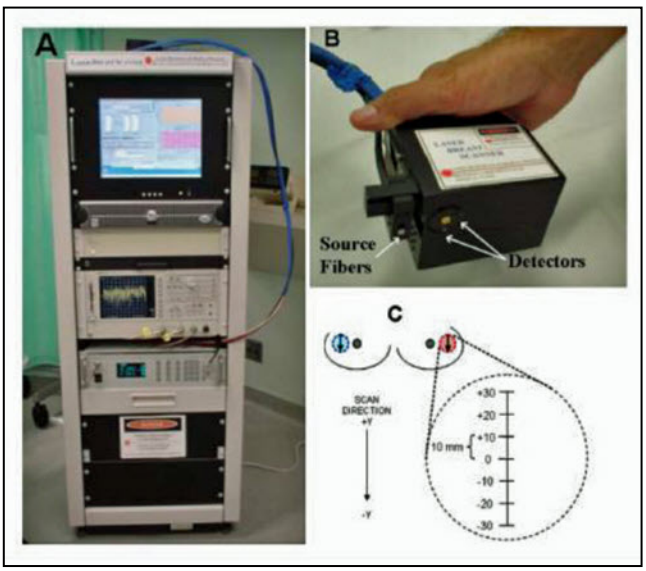

Figure 9 *Laser breast scanner [7] showing: (A) the system electronics and console, and (B) the light source fibers and detectors. The procedure for undertaking measurements in the tumour region and in the contralateral breast is shown in (C). The probe is moved in 1 cm increments so that optical properties both of the tumour and normal region may be measured*

optical scanner to undertake a trans illumination raster scan of a female breast in 3 min (Figure 10). The breast undergoes light compression between 2 parallel glass plates. On one side of the plate is the laser source and on the opposite side of the other plate is the detection fiber, which is coupled to the detection equipment. Images can be obtained in real time using a transmission laser beam of 2 mm diameter and a detection fiber with a 5 mm diameter. Through the use of a time or frequency domain technique, it is possible to retrieve both amplitude and phase information from the collected data thereby allowing the separation of absorption and scattering coefficients. The disadvantage of using a technique involving compression is that the compression causes a reduction in blood volume, which, although improving transmission, reduces contrast, as blood is a principle contrast medium in the tissues, and provides the best means of identifying between tumour and healthy tissue [2].

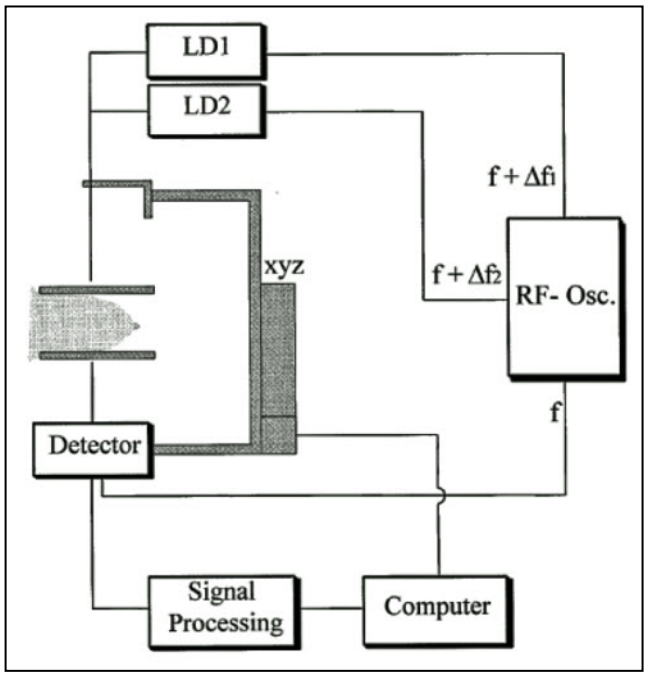

Figure 10 *Schematic diagram of a frequency domain optical system. An RF oscillator sinusoidally modulates 2 laser diodes at similar frequencies (f = 110 MHz, Δf1 = 1kHz, Δf2 = 0.8Hz). The oscillator also provides a timing signal to the detector. An edge correction computer algorithm triggers the detection electronics [24]*

Measurement of healthy breast tissue

Measurements of healthy breast tissue have been undertaken by Srinivasan *et al.* [15]. They found that body mass index correlated inversely with total haemoglobin and water fractions in the breast. Scatter power on average was indicative of radiographic breast density composition, and scattering amplitude varied inversely with breast diameter. Similarly, Shah *et al.* [25] found that menopausal state caused differences in intrinsic tissue absorption and scattering parameters (Figures 12 & 13) where the former is higher and the latter greater for premenopausal patients as compared to postmenopausal patients. Women using HRT had intermediate values to the other two populations. These tests were done on 14 subjects using photo migration using a hand-held probe. Tissue concentrations of the four materials shown in Figure 12 was calculated using wavelength dependent absorption at 674, 803, 849, and 956 nm.

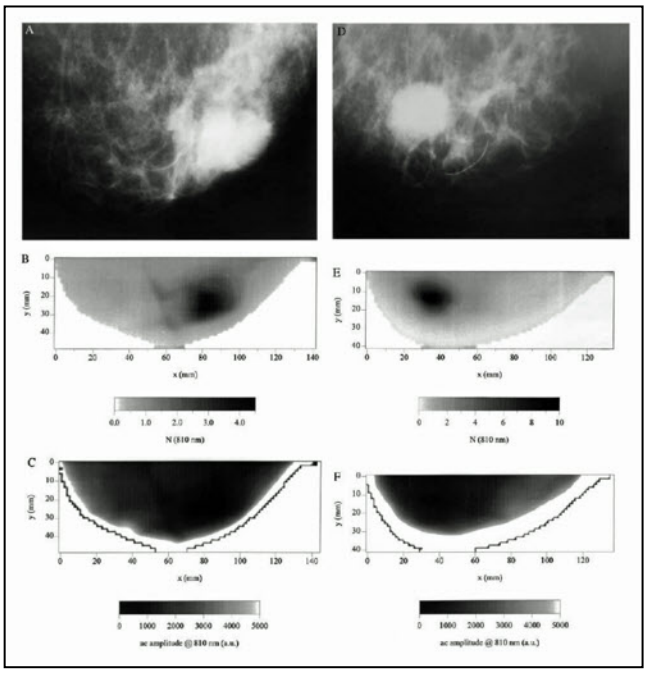

Figure 11 *(A) and (D) are x-ray mammograms, (B) and (F) are optical mammograms using the frequency domain technique, and (C) and (F) are the optical mammograms of the patient using CW light intensity data [24]*

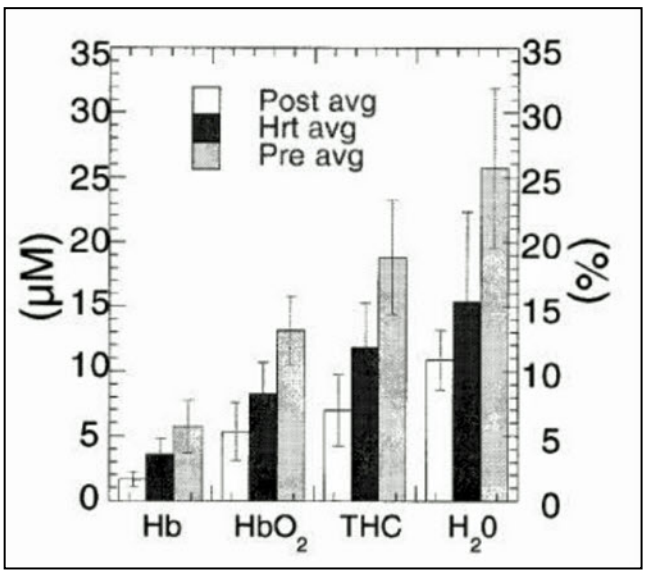

Figure 12 *Mean concentrations (left axis, μM) of haemoglobin (Hb), oxy haemoglobin (HbO2), total haemoglobin (THC) and water relative to pure water (right axis %) for each subject group of pre menopausal, post menopausal and patients taking HRT. Error bars give the normalised standard deviation to the mean [25]*

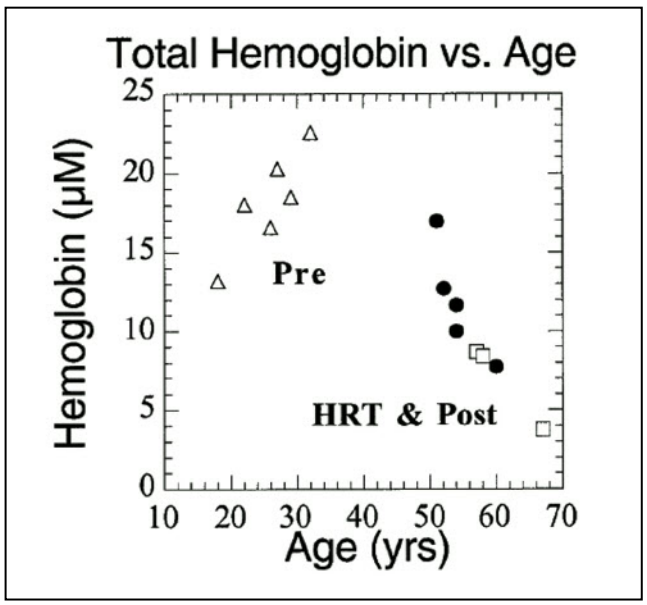

Figure 13 *Total haemoglobin (Hb) concentration with age for all subjects, indicating whether they are pre-menopausal, post-menopausal or taking HRT [25]*

Combinations of optical methods with other techniques

A number of groups have attempted to combine optical imaging with other diagnostic imaging techniques [2]. Usually the other modality is used to provide information to assist the optical image reconstruction. This should allow the physiological information detected with the optical technique to be combined with the far superior spatial resolution offered by the other modality, which may be MRI, ultrasound or x-ray mammography.

MRI and optical tomography

Ntziachristos *et al*. [22] have undertaken to do a concurrent combination technique of diffuse optical tomography (DOT) and MRI on suspicious breast lesions. The DOT incorporated the use of a contrast enhancer (indocyanine green (ICG)), and the MRI used gadolinium for the same purpose (Figure 14).The DOT was able to give 'localization and quantification of exogenous tissue chromophore concentrations'.

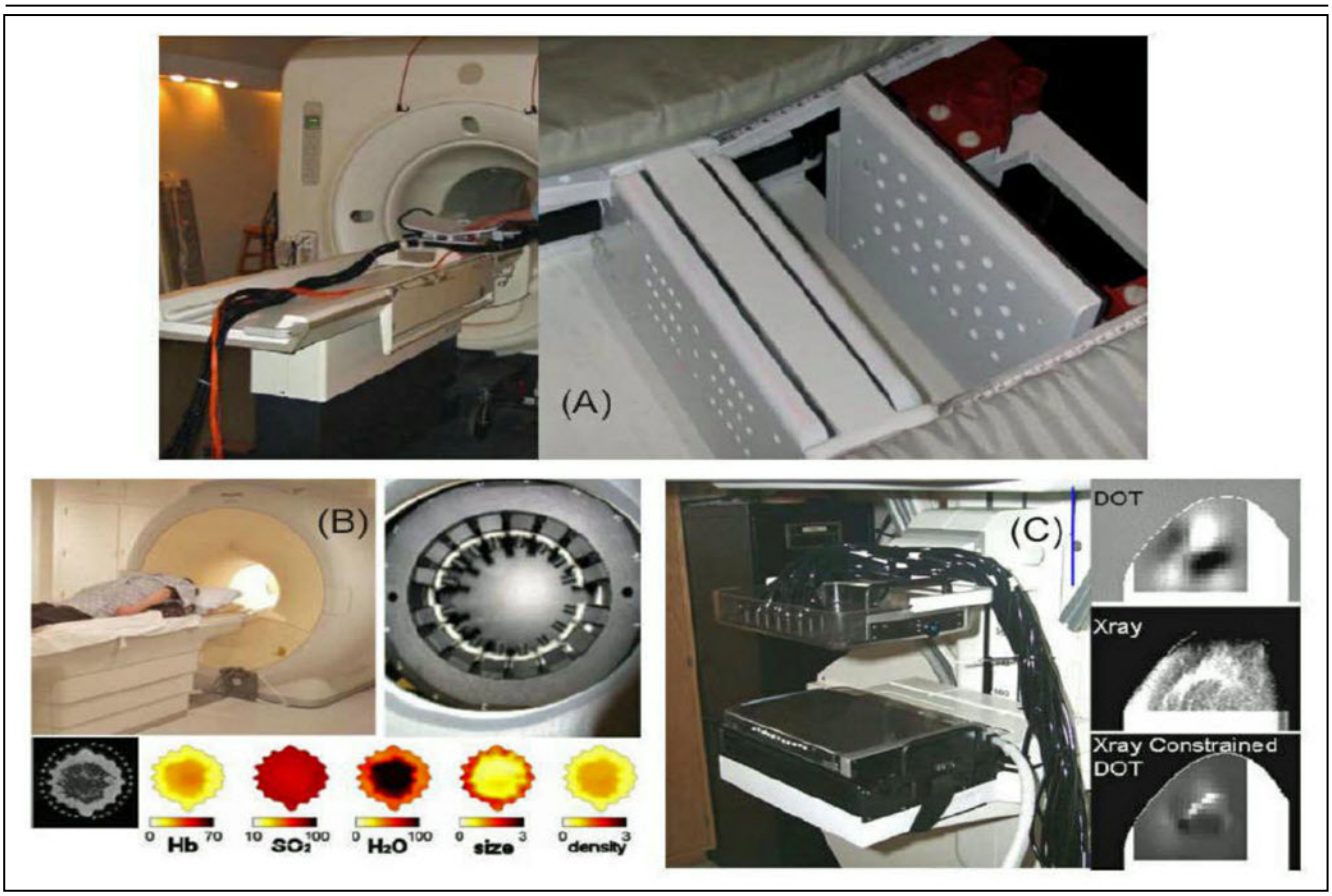

Figure 14 *Equipment that has been used to combine RI and DOT [7]*

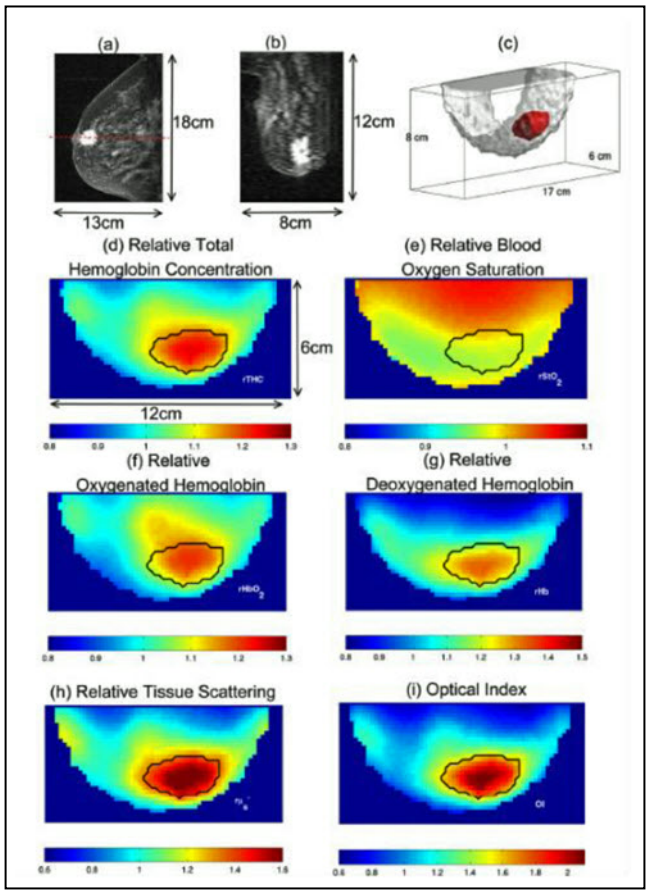

Figure 15 *MR image and DOT image of a 53-yr-old woman with a 2.2 cm invasive ductal carcinoma in her right breast. (a) Sagittal dynamic-contrast-enhanced MR (DCE MR) containing the tumour centre, (b) is the axial DCE MR slice along the red horizontal line in (a), oriented in caudalcranial view. Enhancement of gadolinium uptake in MR indicates the malignancy; (c) depicts the tumour region (in red) determined based on optical data with the MR guidance and the breast outline (in pink) in three-dimensional space. DOT images of (d) relative total haemoglobin concentration rTHC, (e) relative blood oxygen saturation rStO2, (f) relative oxygenated hemoglobin concentration rHbO2, (g) relative deoxygenated haemoglobin concentration rHb, (h) relative tissue scattering at 786 nm and (i) optical index OI are shown in caudal-cranial view with a black solid line indicating the region identified as tumor using a region-growing algorithm. High tumour-to-normal contrast in rTHC, rHbO2, rHb, and OI are visible within the region [22]*

Choe *et al.* [42] have successfully used MRI along with other radiology reports to guide a parallel plat diffuse optical tomography system into identifying tumour margins. They established that malignant cancers on average had double the optical index of normal tissue, and that malignant tissue had a significantly increased scattering, total haemoglobin, and oxy-haemoglobin concentration than normal tissue (Figures 15-17).

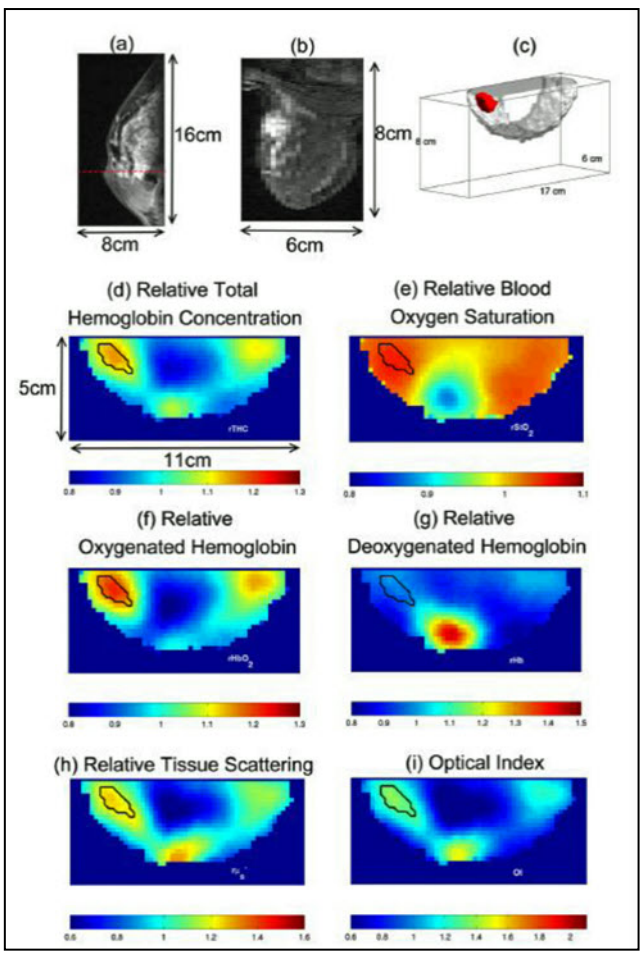

Figure 16 *MR image and DOT image of a 39-yr-old woman with ductal and lobular carcinoma in situ spanning 3 - 5 cm in her left breast. The axial DCE-MR image shows enhancement at the lesion. The black solid line indicates tumour region determined by a region growing algorithm based on this information from MRI. DOT images show elevated rTHC, rHbO2, and OI in tumour region compared to the surrounding tissue [42]*

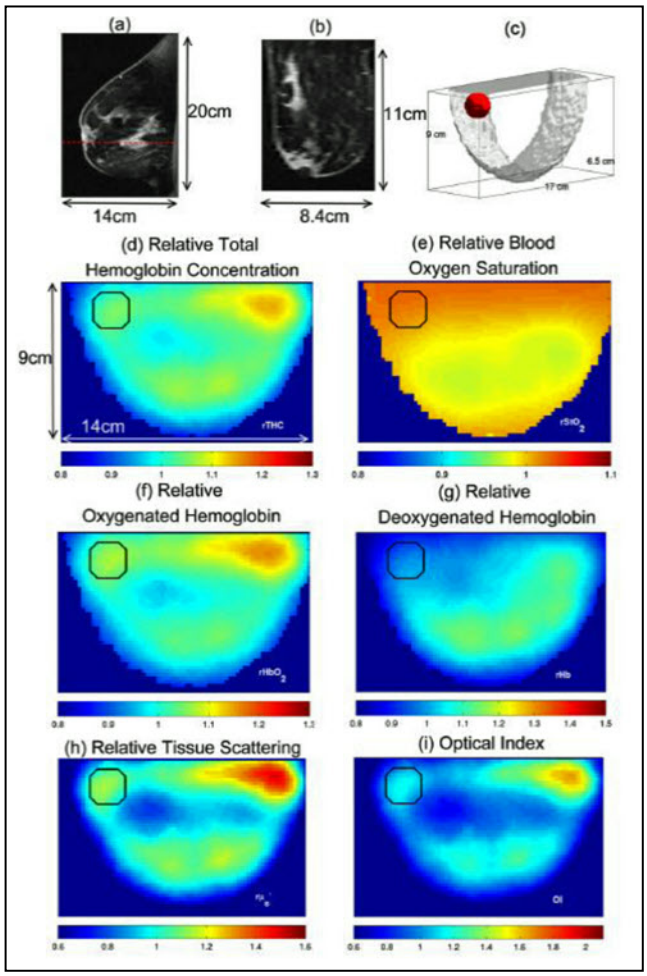

Figure 17 *MR image and DOT image of a 51-yr-old woman with a 5 mm fibro adenoma in her left breast. The DCE-MR image shows an asymmetric density exhibiting some enhancement in the lower outer quadrant. Since the optical contrast was not apparent, a spherical region was assigned as a benign lesion in DOT images (black solid line) based on the extent of gadolinium enhancement in DCE-MR image. Tumor-to-normal contrast in all parameters and OI are similar to that of surrounding tissue [42]*

Ultrasound and optical tomography

Zhu and Chen [26] have demonstrated the potential of combing diffuse optical tomography with ultrasound. In their work they co-register the images taken from the two imaging modalities. The ultrasound data is used to identify suspicious regions in the image. Then the optical data are utilized to preferentially image the lesion region over the background region by altering the accompanying voxel size in the different areas, whilst maintaining a sufficiently small number of voxels to calculate their contents. By using this reconstruction method, they can obtain 'detailed distributions of wavelength-dependent absorption and hemoglobin concentration of breast carcinoma'. This method of using the ultrasound data ensures that the optical data is well defined and less sensitive to noise. They confirmed that the regions containing breast cancer have a greater blood volume than non-malignant tissue due to angiogenesis around the cancer periphery. They could also detect in their image the necrotic core of the cancer imaged.

Xu, Yuan and Zhu [27] used the co-registered ultrasound and optical images to establish whether it was preferential to use reflection or absorption boundary conditions to generate the optical images. Reflection is suited to lesions <1.0 cm deep, whereas absorption is better for lesions >1.5 cm deep. They demonstrated that reflection geometer is better suited to lesions that are shallow in the breast, which may be appropriate for lesions close to the chest wall in a patient who is lying supine and has the breast compressed.

An alternative to this combination is offered by photo-acoustic imaging [2]. In this, NIR light is passed through the tissue and as it is absorbed heats it. The heating causes local expansion, which in turn induces a measurable acoustic wave. This wave may be detected and imaged using ultrasound equipment at the surface of the tissue. The subsequent images demonstrate regions of high optical absorption, and can render the resolution available by ultrasound. For example, Wang *et al.* [28] have used this technique to image an intact rat's brain, with a spatial resolution of 200 μm, which is far better than that achieved with the optical systems alone.

X-ray mammography and optical imaging

Li *et al.* [29] utilised a co-registered frequency domain optical imaging system using a 780 nm laser modulated at 70 MHz and 3D tomosynthesis

x-ray mammography system to establish whether images could be improved by using both modalities together. The breast was compressed as in any standard mammo graphy, in this case to 6.2 cm, and the optical images taken first. The optical assembly is then replaced with the x-ray equipment and 11 projections were taken. The x-ray data were used to provide information to assist the optical reconstruction and to vastly improve the spatial resolution of the image data (Figure 18).

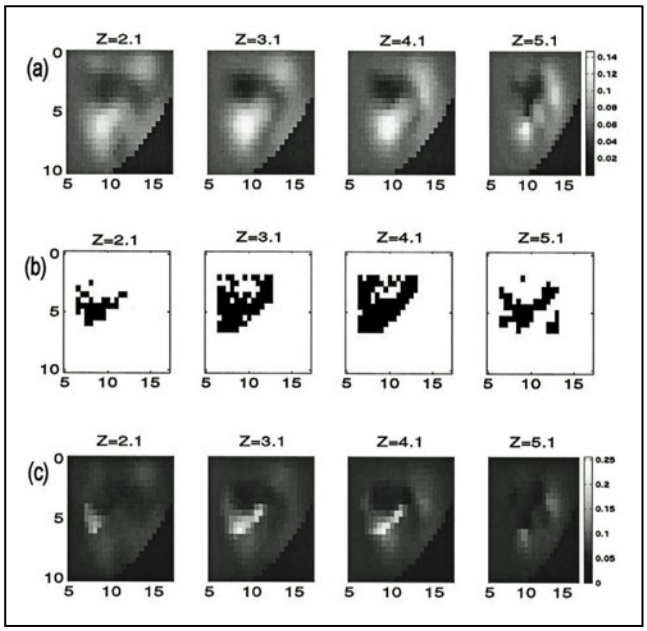

Figure 18 *(a) Optical images reconstructed without any spatial information. (b) 3D x-ray images of the same region with a threshold applied to define the spatial region of interest. (c) Optical images using the same data as used in (a) but with the additional spatial information provided in (b). The z figure in all of the data indicates the position of the slice of the breast being viewed [29]*

Radionuclide imaging and optical tomography

A number of groups have considered the use of radionuclide imaging in conjunction with optical imaging [30]. In some cases the gamma camera used is separated from the optical imaging system, whilst in others the systems are combined. Radionuclide such as Tc-99m are used for this purpose, and the gamma camera employs an appropriate collimator to create an image from the gamma emissions. The use of radionuclide and optical signals together provides complementary functional imaging information. Optical signals are currently not properly quantitative as the signal strength is a very strong function of depth in the body, which can be difficult to correct for without further information. Gamma cameras tend to be cheaper and simpler than other systems such as PET, CT or MRI [30], provide functional information, and can he useful compared to PET of being able to provide images of a number of different probes labelled with different radioisotopes that have different gamma emissions separated in energy.

Positron Emission Tomography and optical tomography

In contrast to the other techniques that have been paired with DOT, a full size PET scanner does not provide higher resolution structural information. Instead, both DOT and PET are primarily used to measure physiology within tissues [31]. A comparison between MRI, PET and optical techniques is shown in Figure 19. The efficacy of tumour treatment can depend on whether a tumour is hypoxic or not. Hypoxic tumours can be harder to treat and are often associated with increased uptake of ^{18}F-FDG - as glucose tends to be metabolised anaerobically when there is a lack of oxygen [31]. To improve this specificity of measuring hypoxia. DOT can measure the oxygenation status of tissue using endogenous contrast, i.e. without the complications of relying on tracer uptake.

"The PET system excels at performing quantitative measurements of metabolic information, and optical imaging excels at long-term cell tracking." AND "For example, simultaneous observation of genetically mani pulated disease expression by NIR fluorescence tomography and corresponding drug delivery by PET can establish non-invasively whether a drug can reach the targeted region of the diseased tissue. In addition, its application in

Parameter	Feature	PET	MRI	Optical methods		
				Confocal, multiphoton microscopy	Reflectance and raster scan	DOT
Contrast	Sensitivity to probes	High fM–pM	Low μM–mM	High fM–pM	High pM–nM	High pM–nM
	Activating probes	No	No	Yes	Yes	Yes
	Intrinsic	No	Yes	Yes		
	Nonionizing	No	Yes	Yes		
Imaging	Resolution	1–5 mm	40 μm–1 mm	~0.3–10 μm	0.1–3 mm	0.1–10 mm
	Depth	Not limited	Not limited	0.01–0.5	0.1–2 mm	0.1–50 mm
	Tomography/sectioning	Yes	Yes	Yes	No	Yes

Figure 19 *A comparison between MRI, PET and optical techniques is shown in [32].*

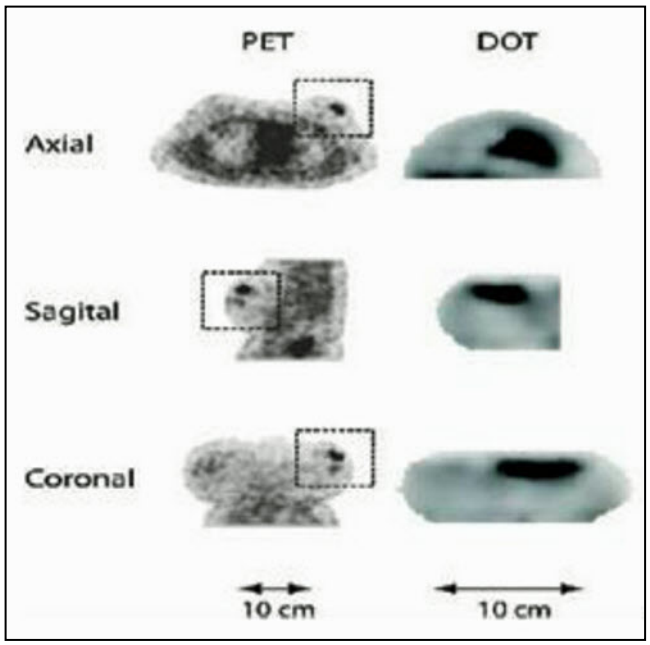

Figure 20 *Slices are showing the axial, sagittal and coronal planes of PET and DOT images [31]. The optical images show the effective attenuation coefficient (μeff) over the left breast. The rectangular boxes in the PET image denote the breast region*

mammography enables us to use two different types of test drugs simultaneously and increases the efficiency of breast cancer diagnosis" [8]. Therefore, DOT and PET could be considered complimentary measurements, and PET could be used as a tool to validate the most rapid and cost effective technique of DOT. An example of the PET and DOT images in a patient are shown in Figure 20.

It has been shown to be possible to combine contrast agents for different modalities into a single molecule, such that signals for each modality may emanate from the same place simplifying data fusion [32]. The combined PET-Optical system is exciting because of the opportunity to obtain the data from both contrast mechanisms within the same device. For the prospect of fusing optical imaging and PET data, there is a high potential for a tight correlation between the contrast data, when both signals are incorporated into a single molecular probe, then the mechanism for integrating and fusing the datasets could be explicitly modeled.

Co-registered and concurrent of PET/DOT datasets would be important for image data fusion and for the molecular probes during dynamic distribution and reporting. For pre-clinical lab studies, in which whole-body optical imaging has been demonstrated, a pair of recent simulation studies examined the feasibility of an optical/PET system. In one study, a bioluminescence-optical-PET system was evaluated [33], and another study reported an integrated Monte Carlo approach for modeling both the nuclear and the optical radiation problems [34]. In both pre-clinical and clinical studies, the combined approach would significantly reduce the obstacles commonly encountered with nuclear imaging and thus accelerate the development of PET imaging agents.

The PET-Optical hybrid imaging has currently been reported to have distinct applications as

a tool for visualization of different biological processes in experimental studies and also might accelerate the development of PET agent probes, and therefore play an advance role in the clinical management of cancer patients. Fluorescence imaging is increasingly viewed as a valuable intraoperative and diagnostic tool [35].

A hybrid PET-fluorescent agent could also serve a dual purpose where, the PET-CT imaging would delineate tumours non-invasively throughout the entire body and facilitate the preoperative staging of disease, the fluorescence tag can be used for intraoperative optical imaging to demarcate the tumour margin and guide surgical removal of the diseased tissue after the isotope on the nano-particle has been decayed (i.e., 10 half-life or 18 hrs for ^{18}F) [36].

Currently the use of optical imaging is limited to the preclinical studies and intraoperative imaging for tumour margin detection and lymph node mapping [37-38].

Conclusion

In this prospective study, data of 11 patients (4 females and 7 males) were discarded due to severe motion artifacts and/or mis registration between CT and SPECT images. There were 91 patients; their mean age was 53.24 ± 12.7 years, with a range of 30-78 years and mean height was 162.0 ± 25.18 cm. The study population had mean weight of 72.70 ± 15.56 kg. Characteristic of study population are shown in Table 1.

A significant body of research has been done on the use of optical techniques in examining breast cancer. Optical techniques have been shown to be both useful in the detection of suspicious lesion of the breast and in the monitoring of a patient's response to neoadjuvant chemotherapy. They also have the potential to be relatively cheap and provide information that is not easily available using the current standard techniques. They can often distinguish between different suspicious breast lesions. There are different methods of optical detection, including tomography, topography and spectroscopy that can be used which have different qualities and attributes, however, optical imaging when used as a tool on its own tends to have a low resolution. Spectral data can be used to give useful functional information. Images which have the benefit of other diagnostic imaging modalities to support optical processing, display improved resolution and can be used to effectively support clinical decision making. In particular, when an appropriate optical imaging agent will be successful, optical breast imaging could improve early detection of breast cancer; for example, in patients with dense breasts, the x-ray mammographic screening has very limited sensitivity, in these women due to the tumor-hiding projection of the dense glandular tissue [39-40], while near-infrared light is far less hindered by dense breast tissue. Furthermore, the optical breast imaging could also have a role in the selection of appropriate adjuvant treatment, the evaluation of response to treatment, and the fine-tuning of treatment strategy in the individual breast cancer patient. Moreover, optical imaging agents could, potentially, be used as in both processes of diagnosis and local therapy [41].

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