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REVIEW

Diffuse optical imaging of the healthy and diseased breast: A systematic review

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Abstract Screening X-ray mammography is limited by false positives and negatives leading to unnecessary physical and psychological morbidity. Diffuse Optical Imaging using harmless near infra red light, provides lesion detection based on functional abnormalities and represents a novel diagnostic arm that could complement traditional mammography. Reviews of optical breast imaging have not been systematic, are focused mainly on technological developments, and have become superseded by rapid technological advancement. The aim of this study is to review clinically orientated studies involving approximately 2,000 women in whom optical mammography has been used to evaluate the healthy or diseased breast. The results suggest that approximately 85% of breast lesions are detectable on optical mammography. Spectroscopic resolution of tissue haemoglobin composition and oxygen saturation may improve the detectability of breast diseases. Results suggest that breast lesions contain approximately twice the haemoglobin concentration of background tissue. Current evidence suggests that it is not possible to distinguish benign from malignant disease using optical imaging techniques in isolation. Methods to improve the performance of Diffuse Optical Imaging, such as better spectral coverage with additional wavelengths, improved modelling of light transport in tissues and the use of extrinsic dyes may augment lesion detection and characterisation. Future research should involve large clinical trials to determine the overall sensitivity and specificity of optical imaging techniques as well as to establish patient satisfaction and economic viability.

Keywords Diffuse optical imaging · Optical mammography · Optical tomography · Near infrared spectroscopy · Breast cancer

Introduction

Background

Breast cancer is the commonest cancer and cause of cancer related deaths in females in the United Kingdom (UK) [1]. In 2003, as many as 36,500 women were diagnosed with breast cancer [1]. Mortality can be reduced by early detection and appropriate therapy [2] and as a result many countries offer women screening. In the UK, women between 50 and 70 years of age are invited to attend screening X-ray mammography. Despite recent evidence to suggest that successful screening is life saving [3] the technique is hampered by false positives and negatives [4, 5]. Consequently, many women undergo further assessment with core biopsy, leading to unnecessary physical and psychological morbidity. Additionally, X-ray mammography requires ionising radiation and has limited benefit in

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younger women due to the increased density of their breasts [6]. The technique does not permit an evaluation of vascularity nor can it provide quantitative information regarding tissue function and composition. These limitations have fuelled research to develop alternative techniques such as Ultrasound (US), Magnetic Resonance Imaging (MRI) and Diffuse Optical Imaging (DOI) in the hope of providing clinically viable adjuncts to X-ray mammography.

Continuous illumination of the breast to produce shadow images or ‘‘diaphanography’’ was first described in 1929 [7]. The development of medical optical imaging modalities utilizing harmless near infrared (NIR) light has been a major goal of biomedical optics research in the last decade. One of the most potentially useful applications is in breast imaging. DOI employs NIR light to produce images and to resolve spectroscopic information about the composition of tissues. When DOI is applied to the study of breast tissues, it is often referred to as Optical Mammography (OM). Unlike conventional X-ray mammography, OM is a non-invasive, non-ionising, low-cost technique that requires little or no breast compression. Additionally, it has the potential to delineate physiological properties of the tissue such as haemoglobin concentration (HbT), blood oxygen saturation (SO_2) and water and lipid content, thus affording lesion detection based not only on structural changes but also on functional abnormalities. As a result, OM represents an entirely new diagnostic arm.

Optical breast imaging technology

Most optical breast imaging techniques rely on a relatively simple concept. NIR light is capable of being detected after it has been transmitted across several centimetres of breast tissue. Within the breast, light is both absorbed and scattered. The number of absorption events per unit length is referred to as the absorption coefficient (μ_a). The dominant light absorbing molecules (chromophores) in biological tissue are oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (HHb). The fact that these chromophores have different absorption spectra at NIR wavelengths enables spectroscopic resolution of HbT concentration and SO_2. The number of scattering events per unit length of tissue is known as the scattering coefficient (μ_s), although tissues are more often characterised in terms of the transport scatter coefficient (μ_s'), which is the effective number of isotropic scatters per unit length. Most biological tissues are very highly scattering. Photons take lengthy and irregular paths such that the optical ‘‘pathlength’’ is often several times the separation between the source and detector. As a result mathematical models of the transport of light within tissue are required in order to determine the tissue properties or derive information about their spatial distribution.

DOI techniques use measurements of transmitted light to produce spatially resolved images. Images of the absorption or scattering properties of the tissue, or other physiological parameters such as HbT and SO_2 may be generated. Broadly, two different imaging approaches have been adopted: *Transillumination*, where sources and detectors are arranged at opposite sides of the breast (Fig. 1a), and *Tomographic*, where sources and detectors are placed over the available surface enabling as much of the entire volume to be sampled as possible (Fig. 1b). Transillumination yields two-dimensional projection images (comparable to X-ray mammograms), and generally requires breast compression. Compression can be performed between arrays of sources and detectors, or between transparent plates over which one or more source-detector pairs are scanned on each side. Tomographic methods yield three-dimensional maps of the optical properties within the breast.

Three distinct technologies have been used for imaging systems, known as Continuous wave, Time resolved and Frequency domain.

Continuous wave

Continuous wave (CW) devices continuously emit light at constant amplitude or modulated at low frequency. CW systems simply measure the attenuation of light across the breast. CW devices are relatively inexpensive and compact but have a number of disadvantages including (a) an inability to distinguish the internal absorption and scattering properties of the tissue [8], and (b) a strong sensitivity to variation in the surface coupling.

Time domain

Time Domain (TD) techniques involve illuminating the breast with short (picosecond) pulses of light. TD systems detect the temporal distribution or ‘‘times of flight’’ of photons as they exit the breast tissue. The optical properties of the tissue are inferred from the shape of the temporal distribution. Though TD techniques are expensive, costs have been reduced with the recent introduction of Time Correlated Single Photon Counting (TCSPC) systems and pulsed laser diodes. Some applications of TD technology have relied on a ‘‘time gating’’ approach to isolate early (least scattered) photons, to increase the spatial resolution.

Frequency domain

Frequency Domain (FD) systems deliver light continuously but the amplitude is modulated at frequencies of the order of tens to hundreds of megahertz. Information on the optical properties of the tissues is obtained by measuring

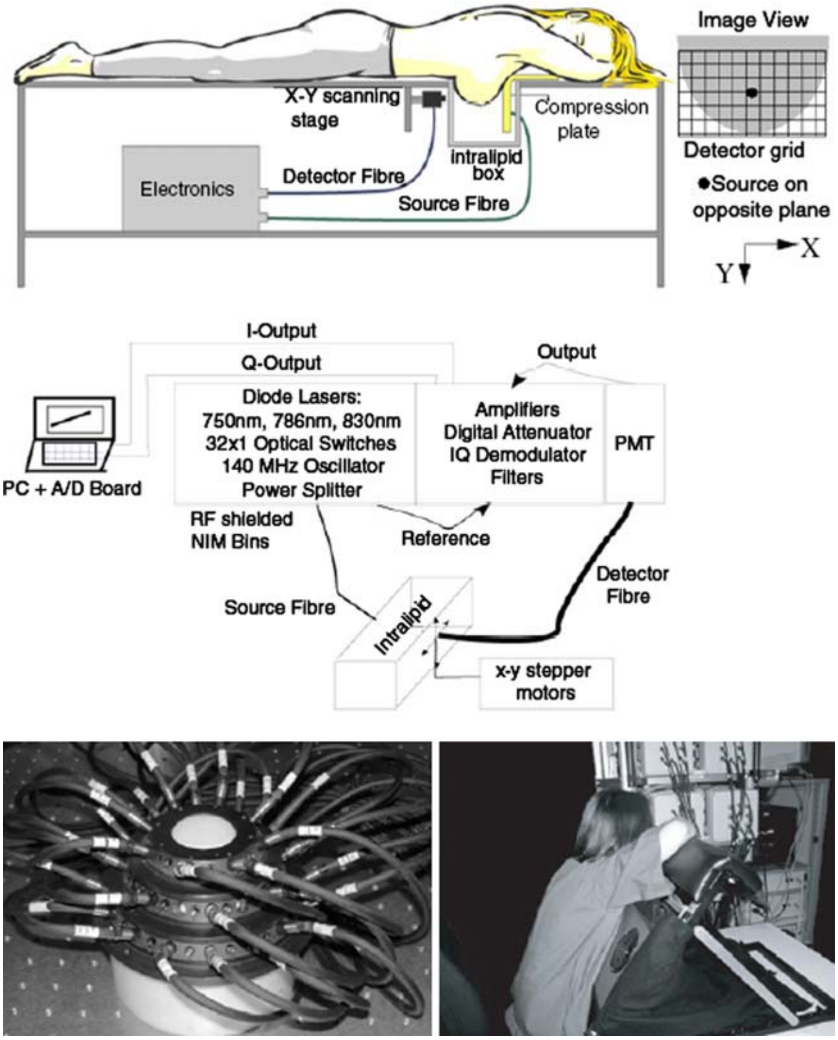

Fig. 1 (**a**) Transillumination geometry. Subject is shown in the prone position, with breast inserted into an intralipid tank through an aperture in the table. Soft compression is applied on the source plane and detector scans a 2D grid on the opposite plane. Published in Durduran T, Choe R, Culver JP et al. (2002) [21]. Bulk Optical Properties of healthy female breast tissue. Physics in Medicine and Biology 47:2847–2861. Republished with permission from the Institute of Physics Publishing. (**b**) Tomographic geometry. Arrangement of source-detector fibre bundles attached to three inter-connecting rings (left). Illustration of the patient interface consisting of two rings mounted on an adjustable frame. Published in Yates T, Hebden JC, Gibson A et al. (2005) [35]. Optical Imaging of the breast using a multichannel time resolved imager. Physics in Medicine and Biology 50:2503–2517. Republished with permission from the Institute of Physics Publishing

the amplitude decay and phase shift (delay) in comparison to a reference signal. In principle, FD systems can acquire exactly the same information as TD systems, providing they acquire data over a large range of frequencies. A detailed comparison of a FD and TD system has recently been published by Nissilä et al. [9].

Aims and scope of the review

Whilst review articles pertaining to DOI of the breast have been published previously [10–14], in most instances they are not systematic and have been superseded by the fast pace of technological development. Furthermore, previous reviews have focused on the medical physics and the development of the technology. This article systematically reviews the literature with regard to clinical studies in which optical imaging has been utilised to evaluate the healthy or diseased breast(s). We aim to provide a summary of the current state of DOI that is both thorough and comprehensible to the breast clinician. Specifically we aim to investigate the capacity of DOI to differentiate healthy from diseased tissue, and distinguish benign from malignant pathology.

Materials and methods

Literature search criteria

The literature search was performed using Medline, Ovid, Embase, and Cochrane databases. The following MeSH headings were used: ‘‘Near Infrared Spectroscopy’’, ‘‘Optical Tomography’’, ‘‘Optical Mammography’’, ‘‘Diffuse Optical Imaging’’, ‘‘Breast’’, ‘‘Carcinoma’’ and ‘‘Cancer’’. The ‘‘Related Articles’’ function was utilised to broaden the search, and all abstracts, studies, and citations were scanned and reviewed. Studies were limited to those in the English language. The latest date for this search was 1st August 2006.

Data extraction

Two reviewers (D.L and O.W), independently extracted the following data from each study: first author, year of publication, study population characteristics, study design, number of subjects, and outcome measures. Three reviewers (D.L, L.E and D.P) extracted or calculated the average optical properties of the tissues from each article, if this data were available. Three authors (A.G, L.E and J.H) critically reviewed the DOI technology and design limitations of each study.

Inclusion and exclusion criteria

In order to enter our review, studies had to be clinically orientated (defined as involving five or more subjects) and utilise DOI to evaluate either the healthy or diseased human breast. Studies limited to the assessment of tissue phantoms (artificial/synthetic tissues) and animal studies were excluded.

Results

Study Identification

Ninety-one publications were identified in the initial search. Sixty-five articles were excluded following title and abstract review. These included five articles evaluating alternative techniques, one editorial, three review articles, and 33 articles without patient data, of which nine articles focused entirely on evaluating tissue phantoms. In addition 23 articles included data on fewer than five patients and were subsequently excluded despite initial review. This left 26 studies that were investigated in detail. Examination of the references revealed a further eight studies that fulfilled the inclusion criteria. In total, this left 34 studies for inclusion and data extraction. (Please see Fig. 2 for systematic search strategy and results). The details of the included articles are summarised in Table 1.

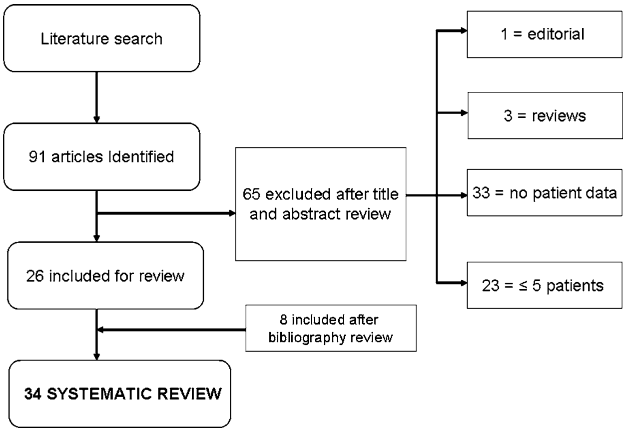

Fig. 2 Systematic search strategy

Study demographics and case mix

At least 577 healthy volunteers [15–25], have undergone breast assessments with DOI. Investigations of healthy subjects have focused on the variability in optical properties of the breast with menstrual cycle, menopausal status and/or demographic factors such age and body mass index (BMI) [15–25]. A total of at least 350 women have been recruited for DOI studies on the suspicion of a breast lesion or abnormality on X-ray mammography and have undergone optical measurements of the suspicious region as well as a reference region from the same or contralateral breast [26–30]. Approximately 213 patients were selected for optical imaging after cyto-histological characterisation of the lesion [31–36]. For a number of articles, totalling 773 patients it was not possible to determine whether patients were recruited before or after biopsy [19, 37–42]. We identified only three studies that specifically recruited a subset of healthy control subjects for comparison with patients bearing breast lesions [36, 43]. In total, this review contains data from optical imaging experiments involving at least 1,913 women.

Can optical imaging provide information on tissue composition of healthy breast tissue?

Absorption and scattering properties and background tissue components

Absorption and scattering coefficients are commonly used to derive values for clinically relevant tissue constituents such as HbT and SO_2, such that these parameters can be compared between healthy and diseased breasts. It is vital to appreciate optical properties of normal breast tissue if we are to make sense of the comparisons with benign and malignant disease.

Data for average μ_a and μ_s' of background normal breast tissue were extractable from a number of articles [15, 16, 18, 21, 25, 27, 31, 34, 35, 37, 39]. This data has been summarised in Table 2. The table reflects the remarkable consistency in absorption and scattering properties between studies, despite varying methodologies and apparatus. The calculated global average absorption and scattering properties of healthy breast tissue are as follows: (600–700 nm: $\mu_a = 0.04 \pm 0.02$ cm^{-1}, $\mu_s' = 10 \pm 5$ cm^{-1}); (700–800 nm: $\mu_a = 0.04 \pm 0.02$ cm^{-1}, $\mu_s' = 8 \pm 4$ cm^{-1}); (800–900 nm: $\mu_a = 0.05 \pm 0.03$ cm^{-1}, $\mu_s' = 8 \pm 4$ cm^{-1}).

Table 1 Study synopsis and outcome measures of included articles

References	Study synopsis		NIR imaging domain	*N*			Outcome measures
	Patient category	Reference region		Total	Breast lesion	Healthy/control	
Yates [35]	1, 2a, 2b	ii/iv	2	24	21	3	2
Grosenick [33]	2b	ii	2	154	154	–	2, 6
Grosenick [34]	2b	ii	2	87	87	–	1, 3
Grosenick [32]	2b	ii	2	93	65	–	1, 2, 3
Grosenick [31]	2b	ii	2	35	26	–	1, 2, 3
Spinelli [26]	2a	ii	2	190	190	–	1, 3
Spinelli [15]	1	–	2	150	150	–	1, 3, 4
Taroni [37]	2#	ii	2	194	194	–	1, 2, 3, 4
Taroni [38]	2#	ii	2	43	43	–	6
Taroni [39]	2#	ii	2	101	101	–	1, 2
Shah [16]	1	–	3	14	–	14	1, 3, 4
Shah [17]	1	–	3	31	–	31	1, 3, 4
Intes [27]	1, 2a	ii	2	49	49	–	1, 2, 3, 4
Pogue [36]	1, 2a, 2b	iii	3	11	2	9	1, 3, 4
Pogue [18]	1	–	3	46	–	46	1, 3
Hsiang [52]	2b	ii	3	6	6	–	3, 6
Srinivasan [19]	2#	ii	3	6	6	–	1, 3, 8
Srinivasan [20]	1	–	3	24	–	24	1, 3
Durduran [21]	1	–	3	52	–	52	1, 3, 4
Durduran [43]	1, 2b	ii,iii	1	7	5	2	5, 6
Chance [40]	2#	ii	1	166	44	72	3, 7
Zhu [28]	2a	ii	3	65	65	–	3, 7
Zhu [29]	2a	ii	3	6	6	–	3, 8
Zhu [30]	2a	ii	3	18	18	–	1, 3
Moesta [41]	2#	ii	3	20	20	–	6
Cerussi [22]	1	–	3	28	–	28	1, 3, 4
Cerussi [44]	1/2b	ii	3	31	1	30	1, 3, 4
Simick [23]	1	–	1	92	–	92	9
Gu [42]	2#	ii	1	6	6	–	1
Pifferi [24]	1	–	2	6	–	6	1, 3
Van Veen [50]	1/2b	ii	1	24	24	–	1, 2
Suzuki [25]	1	–	2	30	–	30	1, 4
Ntziachristos [51]	2a	ii	2	10	10	0	3
Poplack [45]	1	–	3	23	–	23	1, 3

Patient Category. 1 = Healthy subjects; 2 = Abnormality on X-Ray Mammography (a) DOI assessment prior to biopsy/FNAC, (b) DOI assessment following biopsy/FNAC, # ? Recruited before or after biopsy

Reference Region. (i) DOI of abnormal tissue/breast only; (ii) Subject used as own control, reference from normal area of same or contralateral breast; (iii) Specific healthy control group; (iv) Phantom or Reference media

NIR Imaging Domain. (1) Continuous Wave Domain; (2) Time Domain; (3) Frequency Domain

Outcomes. (1) Absorption and Scattering Coefficients; (2) Lesion detectability against predefined criteria (includes details of missed lesions); (3) Tissue Constituents (HbT, SO_2, Water, Lipid content); (4) Correlations between optical properties and demographics; (5) Blood flow; (6) Tumour contrast at different wavelengths; (7) Sensitivity and Specificity of Optical Mammography; (8) Correlations of optical properties with Micro-vessel Density (Mvd); (9) Outcomes from Principal Component Analysis

Tissue components and correlations with demographics

A number of articles investigated if breast optical properties varied in an expected manner with demographic factors such as age and BMI [15, 16, 20–22, 27, 44]. Correlations between spectroscopically resolved tissue constituents and demographic factors, would establish a level of confidence in optical imaging techniques.

Table 2 Summary of absorption and scattering parameters for healthy volunteers

References	Healthy patients (Combined)						Healthy pre-menopausal						Healthy post-Menopausal					
	μ_a			μ_s			μ_a			μ_s			μ_a			μ_s		
	600–700	700–800	>800	600–700	700–800	>800	600–700	700–800	>800	600–700	700–800	>800	600–700	700–800	>800	600–700	700–800	>800
Grosenick [31]	0.04 ± 0.01	0.04 ± 0.01	–	12 ± 2	10 ± 2	–	–	–	–	–	–	–	–	–	–	–	–	–
Intes [27]	0.05	–	–	11	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Yates [35]	–	0.01	–	–	–	–	–	0.007	–	–	–	–	–	–	–	–	–	–
Taroni [39]	–	0.05 ± 0.01	0.05 ± 0.01	–	11 ± 1	10 ± 1	–	–	–	–	–	–	–	–	–	–	–	–
Suzuki [25]	–	0.005 ± 0.001	–	–	1 ± 0	–	–	–	–	–	–	–	–	–	–	–	–	–
Taroni [37]	–	–	–	–	–	–	–	–	–	–	–	–	0.07	0.05	–	10	9	–
Grosenick [34]	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	11 ± 1	10 ± 1	8 ± 0	–	–	–	–	–	–	–	–	–	–	–	–
Durduran [21]	–	0.04 ± 0.003	0.05 ± 0.03	–	9 ± 0	8 ± 2	–	–	–	–	–	–	–	–	–	–	–	–
Spinelli [15]	0.05 ± 0.01	0.04 ± 0.01	0.10 ± 0.07	13 ± 0	11 ± 2	12 ± 0	–	–	–	–	–	–	–	–	–	–	–	–
Shah [16]	–	–	–	–	–	–	0.05 ± 0.2*	–	0.04 ± 0.2*	10 ± 10*	–	–	0.02 ± 0.06*	–	0.02 ± 0.06*	10 ± 10*	–	10 ± 10*
Pogue [18]	0.01 ± 0.16	0.05 ± 0.04	0.005 ± 0.02	1 ± 0	1 ± 0	1 ± 0	–	–	–	–	–	–	–	–	–	–	–	–
Poplack [45]		0.05 ± 0.02*			12 ± 2*													
Global average	0.04	0.04	0.05	10	8	8	–	–	–	–	–	–	–	–	–	–	–	–

μ_a, average absorption coefficient (cm^{-1}) rounded to 2DP or 3DP; μ_s, average scattering coefficient (cm^{-1}) rounded to nearest whole number; *, units originally in mm^{-1} converted to cm^{-1} for consistency

These studies have found good correlations between BMI, lipid density and HbT concentration [15, 20, 21]. Specifically, the higher the BMI, the greater the lipid density and the lower the HbT concentration [21, 22, 27, 44, 45]. In contrast, the majority of investigators have found no clear correlations between age and HbT concentration or blood volume [20, 21, 25]. Only four studies comment on a relationship between HbT concentration and age [15, 16, 22, 44]. Spinelli et al. [15], observed a trend of decreasing HbT concentration with advancing age. The observed correlation between HbT and age appeared to be weak and the authors do not provide a correlation coefficient nor do they comment further on it in the text. The trend observed by both Cerussi et al. [22, 44] and Shah et al. [16], consisted of an increasing HbT concentration with advancing age in pre-menopausal women and a decreasing HbT concentration in women over 50 years of age.

Tissue components and menstrual cycle/menopausal status

The results of studies comparing spectroscopically resolved breast tissue components, between pre- and post-menopausal women [17, 22, 44] are summarised in Table 3. The global average HbT concentration and SO_2 for pre-menopausal and post-menopausal women are as follows: Pre-menopausal ($HbT = 34 \pm 9$ µmol/l, $SO_2 = 75 \pm 2\%$); Post-menopausal ($HbT = 14 \pm 0$ µmol/l, $SO_2 = 80 \pm 4\%$). The results suggest that the breasts of pre-menopausal women contain proportionally higher concentrations of haemoglobin [17, 22, 44]. However, it should be noted that relevant data were only extractable from three studies.

We identified only two studies that commented on changes in breast composition associated with fluctuations in the menstrual cycle [16, 18]. The results suggest that average HbT concentration increases during the luteal phase of the menstrual cycle [16, 18]. These findings are consistent with MRI studies demonstrating that blood flow and breast parenchymal water increase by as much as 50 and 25%, respectively, following ovulation [46, 47].

Tissue components and correlations with radiographic density/breast density

Evidence suggests that women with denser breasts are at an increased risk of breast carcinoma and should be monitored more closely [48, 49]. DOI may provide a non-ionising method for determining at-risk women if correlations between tissue composition and density can be demonstrated. As a result some studies have evaluated spectroscopically resolved breast tissue components as a function of radiological density [15, 18, 20, 23].

In general, the results suggest that denser breasts contain a greater proportion of water, lipid, HbT concentration and are prone to greater scattering, whilst SO_2 concentration does not appear to vary greatly with breast density [15, 18, 20, 23, 45]. However, it is difficult to draw parallels between these studies due to the variability in study design and definitions of radiographic density. For example, some investigators have classified radiographic density as low (<25%), medium (25–75%) or high (>75%) [23], whilst others have used 4 point scales [20] or a 5-point parenchymal reference pattern [15].

Can optical imaging detect breast lesions/abnormalities?

Visibility scoring system

The ability of OM to detect or visualise breast lesions had often been determined using a reference scale [31–33, 35, 37]. The most commonly used criteria is the Visibility Grading System (VGS) which is described in Table 4. In the majority of cases the detectability of a lesion is classified depending upon its contrast with respect to background properties, following retrospective comparison with X-ray Mammography. Pooling the results, the total number of cases subjected to such an analysis is 212, of which 179 lesions were detectable in either both or one OM view. This suggests that the lesion detection rate of OM is approaching 85%. As shown in Fig. 3, the ability of OM to detect breast lesions has been primarily based on increased absorption and HbT concentration vs. background breast tissue.

Two articles included patients with both benign and malignant lesions [35, 37]. Yates et al. [35] used a tomographic approach to image the breasts of three healthy subjects and 19 patients bearing breast lesions. Lesion detectability approached 90%, but the visibility score was far higher for cysts (average = 5) than for cases of suspected malignant lesions (average = 2.5). Taroni et al. [39], utilised TD to study a comparatively large population of patients ($n = 194$) including 169 benign lesions and 56 malignant lesions over a 3-year period. Lesion detection rate for cysts, fibroadenoma and cancer were 79, 37 and 83%, respectively, the latter being primarily influenced by lesion size.

A few reports restricted detectability to malignant lesions [31–33]. These articles, all conducted by the same author [31–33], describe results from 154 patients undergoing optical imaging. In the first of these reports, Grosenick et al. [31], observed a lesion detection rate of OM of only 65%, suggesting that ‘‘missed’’ cases were due to difficulties differentiating lesion from glandular tissue or due to lesion proximity to the axilla and chest wall (outside the scanning range). In two subsequent studies, Grosenick et al. report substantially improved detectability rates for

Table 3 Summary of haemoglobin concentration and oxygen saturation in healthy volunteers

References	Healthy (combined)		Healthy pre-menopausal		Healthy post-menopausal	
	HbT	SO_2	HbT	SO_2	HbT	SO_2
Pogue [36]	32 ± 5	–	–	–	–	–
Srinivasan [19]	20	65	–	–	–	–
Grosenick [31]	17 ± 8	74 ± 3	–	–	–	–
Spinelli [26]	16 ± 4	74 ± 9	–	–	–	–
Taroni [39]	20 ± 7	71 ± 8	–	–	–	–
Chance [40]	–	70	–	–	–	–
Grosenick [33]	17 ± 6	74 ± 7	–	–	–	–
Ntziachristos [51]	18 ± 5*	69 ± 6	–	–	–	–
Durduran [21]	34 ± 9	68 ± 8	–	–	–	–
Spinelli [15]	16 ± 5	66 ± 9	–	–	–	–
Pogue [18]	22 ± 7	61 ± 1	–	–	–	–
Pifferi [24]	16		–	–	–	–
Srinivasan [20]	22 ± 8	58 ± 9	–	–	–	–
Cerussi [22]	–	–	40 ± 3	73 ± 6	14 ± 1	83 ± 1
Shah [17]	–	–		74 ± 6		75 ± 8
Cerussi [44]	–	–	27	77	14	82
Poplack [45]	24 ± 12	69 ± 9				
Global average	21 ± 6	68 ± 5	34 ± 9	75 ± 2	14 ± 0	80 ± 4

HbT, haemoglobin concentration (μmol/l); SO_2, oxygen saturation (%); *, units originally mM converted to μmol/l for consistency

histologically validated carcinomas [32, 33]. The first of these studies involved 65 cases of which 53 were detectable in at least one view (81% detection) [32] and the latter involved 102 patients of which 92 had detectable lesions (90% detection) [33]. Superior detection rates might be due to improvements made to TD technology, involving the inclusion of additional NIR wavelengths. Despite the improved detection rates, in approximately 30% of cases the cancerous lesion was hardly perceivable, undetectable or only identified based on prior knowledge of lesion location. Overall these results suggest that approximately 10% of malignant lesions might still be missed on OM, especially if these are small in nature. Moreover, the VGS might prove to be too crude a tool to detect benign lesions such as fibroadenomas.

Table 4 The visibility grading system

Score	Definition
0	Lesion not visible
1	Hardly perceivable change in transmittance, indicating presences of an inhomogenity
2	Weak contrast, tumour only detectable providing exact location of inhomogenity is known
3	Contrast of tumour clearly distinguishable yet inferior to other inhomogenities
4	Contrast of tumour similar to that of other inhomogenities
5	Contrast of tumour dominates mammogram

We identified two papers that specifically addressed methods that improve tumour contrast [38, 41] of OM. Taroni et al. [38], observed increasing tumour contrast at shorter wavelengths, possibly reflecting stronger absorption due to haemoglobin. In a further study, the best contrast for malignant lesions was obtained after correction for edge effects but was possibly biased by the use of only readily visible tumours, the proportion of excluded patients and the lack of comparisons with benign lesions [41].

Intra-operative detection

One study explored the ability of optical imaging to detect breast cancer intra-operatively [50]. In this study by Van Veen et al. [50], 74% of tumours studied were detectable using a handheld probe. The detection rate is low considering all the prior knowledge and it is possible that the results were adversely affected by the difficulty of intra-operative probe stabilisation, limited depth resolution and imaging of overlapping areas of diseased and normal tissue at the surgical resection margin.

Do breast lesions have different spectroscopic properties from background tissue?

Table 5 illustrates the results of spectroscopically resolved tissue constituents for benign and malignant lesions. There

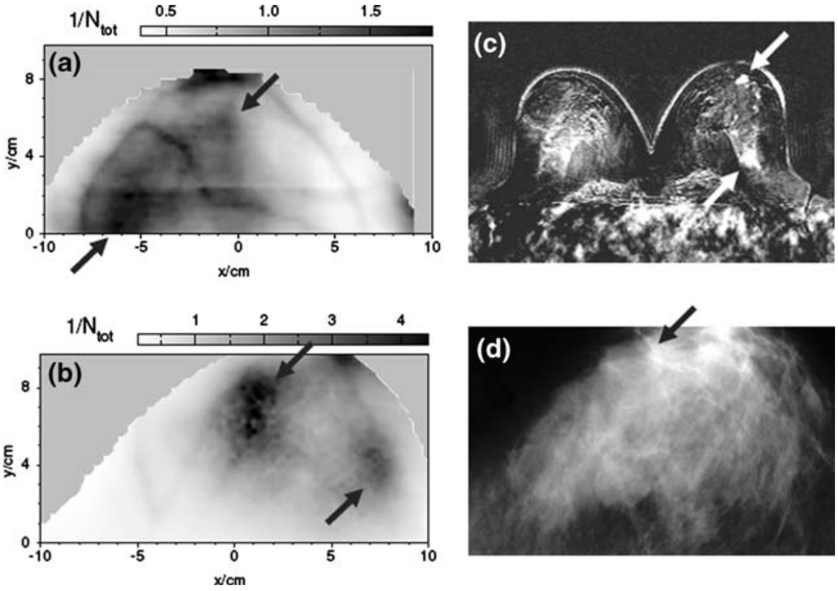

Fig. 3 Mammograms of a patient with a multicentric ductal carcinoma, indicated by the arrows. (**a**) Optical mammogram of the left breast in Craniocaudal projection. (**b**) Corresponding Mediolateral projection. (**c**) MR mammogram, (transversal slice). (**d**) X-ray mammogram, of the left breast in Mediolateral projection. The optical mammograms display inverse photon counts $1/N_{tot}$ at 670 nm. The X-ray mammogram does not show the carcinoma close to the chest wall. Published in Grosenick D, Moesta KT, Muller M et al. (2005a) [33]. Time domain optical mammography: I. Recording and assessment of mammograms of 154 patients. Physics in Medicine and Biology 50:2429–2449. Republished with permission from the Institute of Physics Publishing

is little data available for benign cysts and global averages could not be calculated. The overall average HbT concentration and SO_2 for benign fibroadenoma and malignant lesions are as follows: fibroadenoma (HbT = 54 ± 13 µmol/l, SO_2 = 69 ± 3%); malignant disease (HbT = 65 ± 34 µmol/l, SO_2 = 66 ± 24%). These results suggest that breast lesions contain at least twice the HbT concentration of healthy background breast tissue (HbT = 21 ± 6 µmol/l, SO_2 = 68 ± 5%). This is supported by evidence suggesting that breast lesions have greater HbT concentrations vs. background tissues [19, 21, 26, 27, 31, 36, 40]. Our findings do not support an obvious difference in SO_2 between background tissue and breast lesions. In fact there is limited consensus in literature regarding SO_2 values at tumour foci with some reports suggesting lower saturations [19, 31], and others unable to demonstrate a clear difference [26].

Spinelli et al. [26], demonstrated larger HbT concentrations in malignant tumours than the surrounding local and bulk background tissue, but could not find any

Table 5 Summary of haemoglobin concentration and oxygen saturation for breast diseases

References	Cyst		Fibroadenoma		Malignant disease	
	HbT	SO_2	HbT	SO_2	HbT	SO_2
Zhu [28]	28.0 ± 14.6	–	46 ± 18	–	88 ± 25	–
Pogue [36]	–	–	55	–	68	–
Zhu [30]	–	–	67	–	119	–
Taroni [39]	–	–	27 ± 11	71 ± 11	28 ± 9.2	68 ± 16
Ntziachristos [51]	–	–	60 ± 10*	67 ± 2	130 ± 100*	60 ± 9
Zhu [29]	–	–	–	–	60	–
Hsiang [52]	–	–	–	–	35	–
Srinivasan [19]	–	–	–	–	29	54
Spinelli [26]	–	–	–	–	50 ± 20	78 ± 20
Grosenick [33]	–	–	–	–	53 ± 32	72 ± 14
Global average	–	–	54 ± 13	69 ± 3	65 ± 34	66 ± 24

HbT, haemoglobin concentration (µmol/l); SO_2, oxygen saturation (%); *, units originally mM converted to µmol/l for consistency

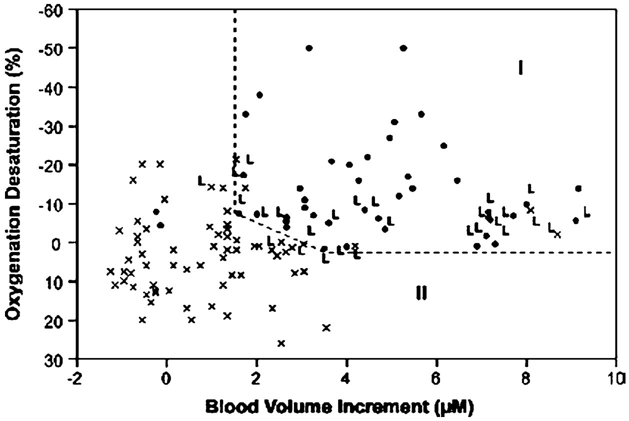

Fig. 4 A two-dimensional nomogram display of NIR breast cancer data. The abscissa is relative increments of blood concentration in units of micromolar concentration change with respect to the average cancer-free value. The ordinate represents incremental change with respect to the average cancer-free value in percent change of haemoglobin saturation. Verified cancers are indicated with a dot and cancer-free breasts plotted with an X. The nomogram is divided into two parts, one containing the verified cancers (I) and the other containing the cancer-free breasts (II). Published from Chance B, Nioka S, Zhang J et al. (2005) [40]. Breast cancer detection based on incremental biochemical and physiological properties of breast cancers: a 6-year, two-site study. Academic Radiology 5:379–388. Republished with permission from Elsevier

particular trend for SO_2, nor for scattering properties. Srinivasan et al. [19] demonstrated higher HbT concentrations (34–86%), and reduced SO_2 in three cases of invasive cancer relative to the surrounding tissues. Intes et al. [27] were able to identify benign and malignant breast lesions using a ''SoftScan'' technique primarily on the basis of increased blood volume. In two articles, Grosenick et al. [31, 34] demonstrated considerably higher absorption and scattering foci at tumour foci vs. background tissue. Additionally, the average HbT concentration was observed to be 2.5 times larger than that of healthy tissue [34]. The authors initially observed reduced SO_2 values at tumour locations [31], though subsequent analysis failed to reveal differences in saturation between lesions and healthy breast tissues [34].

Only one article provided specificity and sensitivity values to describe the ability of DOI to detect malignancy based on spectroscopic information. This study performed by Chance et al. [40] was a 6 year, two site trial that involved the use of a multiwavelength handheld device, operating in CW domain. Data was acquired from 166 patients of whom 44 patients had confirmed malignancy and the remainder classified as ''non-cancer patients''. Blood volume and saturations were calculated with reference to a similar location on the contralateral healthy breast. The results are summarised in the 2D normogram of blood volume vs. oxygen saturation in Fig. 4. In this graph, verified cancers are labelled as a dot whilst cancer free breasts are denoted with an ''X''. The normogram can be divided into two zones, one containing the verified cancers (I) and the other containing cancer-free breasts (II). This technique was able to distinguish cancer from non-cancer bearing breasts with 96% sensitivity and 93% specificity, with an area under the curve of 95%. Overall, only four false positives and two false negatives were identified as small cancers (6 and 7 mm), in which the blood volume increment is significantly underestimated.

Whilst the results of spectroscopic detection of breast lesions are encouraging, it should be remembered that the majority of these studies involved small sample sizes [19, 27, 31, 36], were hampered by the exclusion of cases in which the lesion was outside the region of interest [27] and are strongly influenced by the methods used to obtain estimates bulk/background healthy tissue and lesion size and location [19, 26, 31, 34, 36].

Can optical breast imaging differentiate benign from malignant disease?

A number of studies specifically addressed the ability of Optical Imaging to differentiate benign from malignant breast lesions [19, 26–28, 30, 36, 42, 51]. Several articles failed to demonstrate convincing evidence of differences between benign and malignant lesions [26, 36, 42], possibly through study design limitations. Gu et al. [42], observed lower scattering and absorption vs. healthy tissue in six patients with breast cysts. The authors suggested that distinguishing benign from malignant lesions is possible since the latter show increased absorption and scattering compared to healthy tissue. Of note, this study [42] did not include subjects with malignancy and comparisons were made with historical histological data. Spinelli et al. [26], only considered scattering properties of benign lesions and therefore could not compare tissue composition between benign and malignant disease. Pogue et al. [36], included only two patients with breast disease of which only one patient had a confirmed malignancy (invasive ductal carcinoma) and one fibroadenoma. Despite the marginally greater HbT concentration in the malignant case (68 vs. 55 µmol/l), the sample size is too small to draw firm conclusions. Additionally, tissue sampling (FNAC) occurred prior to DOI evaluation, the authors could not differentiate the HbT changes related to intrinsic properties of tumours from the changes due to host response to biopsy.

Only a few studies provide some evidence to suggest that Optical Imaging technology can distinguish benign from malignant pathology [19, 27, 28, 30, 51]. These articles involve both FD [19], TD [27] and combined US and MRI approaches [28, 30, 51]. The results suggest that malignant disease can be differentiated from benign disease on the basis of blood volume, saturation or both. Srinivasan et al. [19], using FD technology, observed that the contrast between lesion and background for HbT concentration was more marked for malignant than benign lesions and that average HbT correlated well with microvessel density. Malignant tumours were observed to have variable reductions in the SO_2 levels as compared to healthy breast tissue, which was not the case for benign disease. Interestingly, benign disease was dominated by changes in scattering properties, suggesting that these might prove valuable for future discrimination. Intes et al. [27], observed that malignant lesions had significantly greater HbT concentrations ($P = 0.0184$), water content and lower SO_2 levels relative to surrounding tissue than did benign lesions.

Investigators have sought to improve lesion discrimination by combining optical techniques with either US [28, 30] or MRI techniques [51]. These modalities enhance optical imaging through the provision of structural information about the lesion size and location. Employing combined optical techniques, investigators have demonstrated increased HbT concentration at tumour foci, good correlations between HbT concentration and microvessel density and have witnessed reductions in HbT concentration in response to chemotherapy [29, 52]. Moreover, the use of combined-techniques providing structural and functional tissue information, has led to improvements in lesion discrimination [28, 30, 51].

In a study of 19 patients, Zhu et al. [30] demonstrated a 2-fold greater average HbT concentration (86 vs. 46 μmol/l) in subjects with invasive cancer ($n = 2$). In a subsequent trial, 65 consecutive women with 81 breast lesions were assessed using a similar protocol [28]. Similarly, both the maximum and average HbT were significantly higher in the malignant group as compared to the benign group. Interestingly, when a maximum HbT of 95 μmol was used as the threshold value the sensitivity, specificity, positive predictive value and negative predictive value were 100, 96, 73 and 100%, respectively. In addition, Zhu et al. [28] observed different patterns of HbT concentration between benign (>diffuse) and malignant lesions (>localised). It is important to consider that across two trials only 10 patients with malignant disease were evaluated, and a much larger trial would be required to confirm these findings. Despite the benefits of US to provide more accurate estimations of lesion location and prevent an underestimation of HbT concentration, it is worth noting that lesions had to be visible on US for the combined technique to function. It is unlikely that such a technique would be valuable for screening. Similar results were obtained by Ntziachristos et al. [51], using a hybrid MRI and DOI approach. The authors found that breast cancers contained decreased SO_2 and higher HbT concentrations compared to benign lesions. The small sample size ($n = 10$) unfortunately prevented any further evaluation of sensitivity or specificity.

The differentiation of benign from malignant disease has also been demonstrated using handheld optical probe to image regional blood flow across tumours [43]. Durduran et al. [43], were able to stratify patients into three broad groups based on the nature of the blood flow distribution. Specifically, subjects with healthy breast showed very little variability in flow (2.7% variation), benign tumours showed a moderate increase (153%) over healthy tissue and malignant group wherein blood flow increased to 230% of healthy tissue. The authors do not elaborate on the way in which average healthy tissue flow was defined and the sample size ($n = 7$) is too small for any conclusions to be drawn on the ability of such devices to differentiate benign and malignant lesions.

Discussion

To the best of our knowledge this is the first clinically orientated systematic review article of DOI of the breast. We specifically focused on clinical studies in which DOI has been employed to study the healthy and diseased breast. DOI has the potential to provide clinically useful functional information on breast tissues and has tremendous potential to complement traditional X-ray mammography. The last decade has witnessed some particularly interesting insights into functional properties of healthy and diseased breasts as a result of this technology.

There is a good consensus between studies regarding the absorption and scattering properties of healthy breast tissue, despite considerable variations in methodology. In general, the relationship between spectroscopically resolved breast tissue composition and population demographics is as anticipated. Moreover, the fact that optical properties correlate with demographic information supports the notion that optical measurements can provide valuable information about breast tissue composition. The data suggests that the breast is non-uniform, and that the composition of healthy breast tissue is affected by physiological changes that occur over the course of a women's lifetime. For example, HbT concentrations of the breast appear to elevate in the luteal phase consistent with research demonstrating parenchymal cellular proliferation [53] and increasing vascular fibroglandular tissue [54] in phase II of the menstrual cycle. The observation of greater HbT concentrations in younger pre-menopausal women is in good agreement with the involution of glandular tissue and its replacement by adipose in peri-menopausal and post-menopausal women [55].

There is an increasing body of evidence to suggest that women with higher radiographic density breast tissue are at increased risk of developing invasive breast cancer [48, 56]. It has since been suggested that women with higher radiographic density should be screened at an earlier age and more frequently than those with lower density [49]. It is possible that DOI may provide a viable, cost-effective, non-ionising alternative to screening such patients given the limitations of X-ray mammography in assessing younger patients with dense breasts. The reviewed data suggests that optical imaging may be able to differentiate radiographic density based on HbT concentration and water content. Women with higher radiographic breast density contain a greater proportion of water and haemoglobin. It is possible that spectroscopically resolved components might be able to predict radiographic density and therefore determine which patients are at increased risk, enabling stratified follow-up. However, further studies involving larger sample sizes are required before optical imaging modalities can be reliably used in a predictive capacity.

It appears that OM is capable of distinguishing lesions from healthy background tissue. This is largely due to differences in the absorption and scattering properties between bulk and diseased tissue. The current analysis suggests that OM is capable of detecting up to 85% of lesions. This value is comparatively low considering that the majority of studies have involved retrospective comparisons with X-ray mammography [33, 35, 37]. Fibroadenomas and small malignant lesions are consistently problematic [37], the latter possibly due to the limited spatial resolution of DOI techniques. Enhanced detection rates have been observed through the spectroscopic resolution of tissue composition [40] and by combined different imaging modalities [28–30, 51]. Breast lesions can be distinguished from healthy tissues primarily on the basis of increased HbT concentration and reduced oxygen saturation, consistent with increased vascularisation associated with tumours [57].

Tumour angiogenesis may play a role in facilitating growth and metastatic potential of malignancy [58], and yet despite such vigorous angiogenesis, insufficient oxygen may be delivered to tumours, rendering them relatively hypoxic [40]. Theoretically, DOI might be capable of distinguishing breast cancer from benign tissues on the basis of HbT concentration and oxygen saturation. The current evidence for such discrimination between benign and malignant disease is scarce. Only a few studies provide evidence to suggest that such contrast is possible [19, 27, 28, 30, 51]. Moreover, our results (Table 5) do not support differences between fibroadenoma and malignant disease based on HbT concentration and saturation alone. It seems likely that to differentiate the malignant potential of lesions based on intrinsic contrast requires multimodal strategies, with little potential to replace traditional mammographic screening. It is anticipated that improved characterisation of malignant and benign lesions, will be achieved through ongoing technological advances such as methods to improve the spatial resolution, enhanced modelling of light transportation in breast tissues, the use of additional NIR wavelengths, as well as the use of external dyes such as Indocyanine Green (ICG) that may improve lesion contrast [59].

It is surprising that there is limited comparison between traditional X-ray mammography and DOI in terms of patient comfort. Despite some investigators commenting that optical techniques involve less compression and there are few reports containing objective data [60, 61]. Additionally, the economic implications of complementing X-ray mammography, with optical imaging for diagnostics and monitoring response to treatment have yet to be discussed. If optical imaging of the breast is to progress from a research tool to a clinically viable adjunct to X-ray mammography, patient satisfaction and cost-effectiveness needs to be addressed. Such an analysis would undoubtedly help determine which method (handheld puck, breast pendent, subject prone, liquid interface, etc) to pursue in the future.

Conclusion

DOI provides functional information about the tissue under investigation and represents a novel approach to understanding the healthy and disease bearing breast. Optical imaging techniques using NIR light may have the potential to assist the identification and characterisation of breast lesions as well as monitor the response to therapy. Large robust clinical trials are now required to establish the sensitivity and specificity of DOI for lesion detection and to establish patient satisfaction and economic viability.

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