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Preliminary clinical evaluation of a combined optical Doppler ultrasound instrument for the detection of breast cancer

[1]J BRITTENDEN, MD, FRCSG, [2]D WATMOUGH, PhD, [1]S D HEYS, MD, PhD, FRCSG and [1]O EREMIN, MD, FRACS, FRCSE

Departments of [1]Surgery and [2]Medical Physics, University of Aberdeen, Medical School, Foresterhill, Aberdeen AB9 2ZB, UK

Abstract

Mammography is widely used for imaging the breast, but is known to be less effective in evaluating the younger dense breast. In this study the ability of telediaphanography in conjunction with Doppler ultrasound (TDDU) to detect breast carcinomas was assessed. Light absorption, determined by the number of blood cells per unit volume of breast, results in the detection of an opaque lesion. Subsequent Doppler ultrasound detects the neovascularization at the periphery of tumours.

In total, 178 patients were investigated without prior knowledge of the mammographic findings. This consisted of 69 patients presenting to the symptomatic breast clinic with normal mammograms and 109 patients with mammographic detected abnormalities (mean age 54 years). There were 95 neoplastic lesions. The sensitivity and specificity were: telediaphanography alone 73% and 82%; TDDU 61% and 92%, respectively. TDDU was less sensitive for small and impalpable tumours, and did not detect ductal carcinoma *in situ* (26 false negatives, mean diameter of 1.1 cm (SD of 0.3 cm)). Subsequent Doppler ultrasound did not further increase the sensitivity of the examination, but did increase the specificity. Patients with locally advanced breast cancers showed dramatic changes on repeated optical/Doppler examinations, in concordance with response to chemotherapy. The combined optical/Doppler instrument, with its low sensitivity, is not suitable for screening, even in the young dense breast, but may have a role in assessing the response of large tumours to chemotherapy.

Mammography is currently the "gold standard" for imaging the breast and for screening for breast cancer in the 50 to 64-year-old age group [1]. The Forrest report has recommended that work on other non-invasive techniques should continue in the search for an effective way of screening younger women with dense breasts and where mammography has not been shown to be effective [2, 3].

There has been sporadic interest in the use of telediaphanography to examine the female breast since it was first demonstrated that light could be used to image malignant tumours [4]. The degree of light absorption is determined by the number of blood cells per unit volume of breast tissue [5]. Cysts appear translucent, whereas blood filled cysts, haematomas and neoplastic tumours appear opaque. The sensitivity of telediaphanography has been found to vary widely (48–94%), depending on the equipment used and the number and size of tumours analysed [6–8].

Doppler ultrasound has been reported to be of value in detecting the neovascularization at the periphery of palpable neoplastic tumours [9]. The characteristic signals detected by Doppler ultrasound from neoplastic lesions arise from rapid blood flow in arterial-venous shunts [9]. Neovascularization is thought to occur once the tumour reaches a critical size (1–2 mm), following which the tumour grows exponentially [10]. Tumour angiogenesis in patients with breast cancer has been shown to be an indicator of poor prognosis [11]. The initial results obtained with Doppler ultrasound of the breast have been encouraging. Britton et al obtained a sensitivity of 91% and specificity of 89% in detecting palpable breast cancers [12]. The procedure is impractical for impalpable lesions, due to the time required for the very narrow Doppler beam to scan accurately all the breast tissue [13, 14]. The present study combined telediaphanography and Doppler ultrasound (TDDU) to image the breasts of women with suspected malignancy detected on prior mammography. Telediaphanography was used initially to detect opaque lesions, which on subsequent Doppler ultrasound scanning would be examined for tumour induced neovascularization. The aims of this study were: (1) to determine if technical innovations could improve on previously documented sensitivities of telediaphanography; (2) to determine the sensitivity and specificity of Doppler ultrasound in combination with telediaphanography; and (3) to determine

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if large tumours, which are often difficult to assess using standard imaging modalities, both in terms of their original volume and subsequent response to therapy, could be evaluated using this method.

Materials and methods

Patients

The study population consisted of 178 patients, presenting to the Surgical Breast Unit, Aberdeen Royal Hospitals, NHS Trust, over a 12 month period. The study was approved by the Joint University of Aberdeen and Grampian Health Board Ethical Committee. There were two groups of patients, which consisted of: (1) 69 patients presenting to the symptomatic breast clinic with normal mammograms; and (2) 109 patients undergoing investigations or treatment for mammography-suspected breast cancer. The mean age was 54 years, with 19 patients being under 50 years of age. All were examined without prior knowledge of the mammogram report.

Materials and procedure

The Aurascan (Aurora Instruments Ltd, Aberdeen, UK) which is designed to examine the female breast using light and 8 MHz Doppler ultrasound was used in the study. In a darkened room, the superior, medial and lateral aspects of the breast were examined using a filtered light source (short wavelength pass filter, Ealing Optics Division, Watford, UK, and Tungsten halogen bulb, 12 V, 75 W, Thorn A1/230 with reflector), placed against the inferior surface. Areas of increased absorption were noted. Both the normal and abnormal breasts were imaged using an infrared sensitive television camera (Link Electronic Ltd, Andover, Hampshire, UK). Images were captured in a frame store, digitized and stored on floppy discs. Once an abnormality was detected, the Doppler probe, which has a diameter of 10 mm, was positioned on the margin of the suspected lesion. Continuous wave Doppler ultrasound was used, with an effective beam width of 2–3 mm and penetration of 3 cm (range up to 8 cm) [9, 14, 15]. Once a signal was obtained, it was processed and displayed in isometric form [14] on the same Commodore Amiga 2000 computer used to process and display the optical images. The isometric display was used to guide location of the Doppler probe so that the signal with the greatest Doppler frequency (up to 4 kHz) and amplitude was recorded.

Technical aspects

The technique was easy to learn. It required two people, one to operate the camera and controls, the other to position the light source. The first month of the study was considered a learning period and data were not collected. Several modifications in technique were made at this time to improve accuracy, and to use the Aurascan to its maximum potential.

It is particularly important in screening to be able to detect small tumours. Telediaphanography may not detect small superficial tumours if the area being examined is saturated with light. It is therefore, necessary to set the brightness at the minimal level sufficient for uniform illumination of the tissues in order to prevent this occurring. An optical filter was included in the light source (blocking region beyond 810 nm and cut-off wavelength about 690 nm) to enhance contrast of small lesions by increasing the fraction of radiation which would be absorbed by the neoplasm (maximum 570 nm) (13).

For large carcinomas or for very dense breasts, an unfiltered torch was used to delineate tumour margins. Both torches were used with interchangeable light guides with circular, semicircular and slit cross-sections. These were required to allow for the thorough examination of the variable sizes of breasts and lesions encountered. For example, too large an entrance pupil leads to images spoiled by leakage of excess light and by backscatter. Also, small lesions close to the chest wall may be missed unless a slit or semicircular end piece is used. In all cases, the entire breast was visualized by varying the position of the light source and, if necessary, the end piece prior to recording an image. An important factor that only became apparent during the study, was that some lesions were visualized but could not be recorded by the infrared camera. This led us to consider whether there might be an angular dependence of contrast for some of the lesions observed by transillumination of tissues. Further investigation demonstrated that viewing the affected breast at an angle of 45°, in some cases resulted in the cancer becoming lost in the dark background on the periphery of the breast. Thereafter, all images were recorded with the light axis normal to the superior surface of the breast.

Analysis of results

A scoring system was required to quantify the performance of the instrument and analyse the results. A system used by radiologists for interpreting mammograms which allocates a number from -2 to $+2$ as follows: -2 benign; -1 likely benign; 0 undiagnostic; $+1$ suspicious; $+2$ malignant, was adapted. When interpreting optically produced images, asymmetry between the two breasts with dilated blood vessels, along with an area of increased density (shadow) would be scored as $+1$. A definite opacity would rate as $+2$. In view of the very narrow beam width from the Doppler transducer, ultrasound was only performed once a lesion was detected by light imaging ($+1$ or $+2$). A Doppler signal was regarded as abnormal if it exhibited any of the following characteristics: asymmetrical or larger amplitude; higher frequency components (higher flow velocities) than contralateral site; and continuous flow through diastole and systole [14]. Figure 1a shows a typical Doppler display obtained from the periphery of a neoplasm, which can be contrasted with Figure 1b showing the typical trace obtained from an artery.

Results

All patients found the procedure, which did not use breast compression, to be painless and acceptable. There were 95 neoplastic tumours in this series of 109 patients with abnormal mammograms; TDDU detected 69. Of the 69 tumours detected by both modalities, 28 were

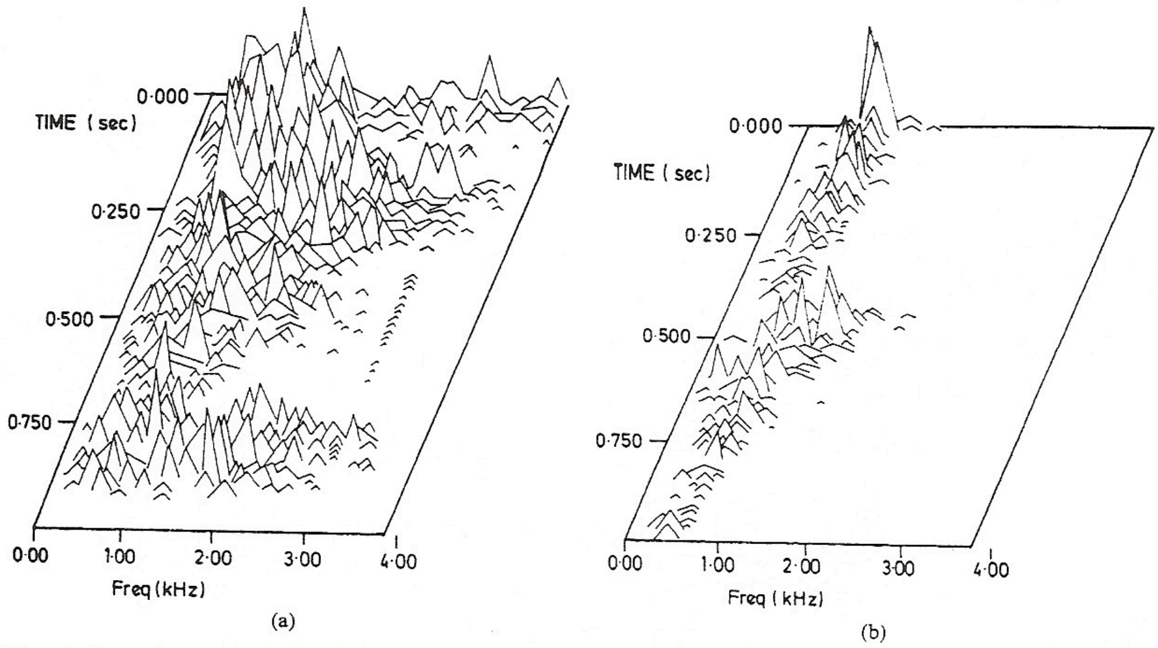

Figure 1. Isometric display of blood flow obtained by Doppler from (a) periphery of a breast cancer and (b) from an artery. Velocity in X axis, time in Y axis. Vertical display represents signal amplitude.

subsequently excised. The average diameter of the pathology specimen was 1.65 cm with a standard deviation of 0.65 cm. Although transillumination was positive in all these cases Doppler signals were only detected in 24 out of 28.

One patient refused operation, and the remaining 40 tumours were large, measuring in excess of 4 cm diameter on clinical examination. These lesions were not excised but confirmed to be malignant by trucut biopsy or fine needle aspiration cytology prior to undergoing primary therapy with chemotherapy, followed by radiotherapy. In seven of these 40 tumours no Doppler signal was elicited.

In the series of 109 patients with abnormal mammograms, there were 14 mammographic false positives, of which five were also falsely positive on telediaphanography, with only one being positive on Doppler. The 14 false positives on mammography arose mainly because of suspicious calcification or radial scars. TDDU detected 26 false negatives. The average size of tumour missed by TDDU was 1.1 cm, with a standard deviation of 0.3 cm. Eight of the tumours not detected by TDDU were ductal carcinomas *in situ* (DCIS). The pathology of the remainder of cancers missed by telediaphanography were: 12 ductal; four tubular; one lobular and one inflammatory. DCIS are pre-invasive lesions, which are not associated with neovascularization and, therefore, would not be expected to be detected using this modality.

In the 69 patients with normal mammograms there were 10 false positives on telediaphanography, of which five were also falsely positive on Doppler ultrasound. These results are summarised in Table I, along with the sensitivities and specificities. The positive predictive value for telediaphanography was 82%, and the negative predictive value was 72%. Further analysis of the clinical size of the tumours with reference to detection showed that TDDU was less sensitive for smaller and non-palpable tumours although the numbers are small (Table II). In addition, 25 of the patients with large primary tumours who subsequently underwent chemotherapy, were examined throughout their treatment. All these patients achieved a complete or partial response to therapy, which was reflected in a dramatic change in the images obtained with telediaphanography. Figures 2a–c represent typical images obtained in a patient with a T3 tumour which had a partial clinical and pathological response to chemotherapy.

Table I. Sensitivity and specificity of TDDU

	True negative (no cancer)	True positive (cancer)
Negative telediaphanography	68	26
Positive telediaphanography (positive Doppler)	15 (9)	69 (58)
Total	83	95

Sensitivity for telediaphanography (+Doppler) = 73 (61).
Specificity for telediaphanography (+Doppler) = 82 (92).

Table II. Number of tumours detected with reference to patient's age and tumour size

	TDDU	Mammogram
Under 50 years old	16	19
Over 50 years old	53	76
Not palpable	4	14
Less than 2 cm	8	13
Greater than 2 cm	57	68

Discussion

To the best of our knowledge, this is the first study to use a modality combining light and Doppler ultrasound to examine the female breast. Results obtained with this combined approach, were compared with mammography which is recognized to be the "gold standard". Although involving a small and select group of patients, the number of neoplastic lesions in this study is comparable to some of the larger studies using light alone [5]. The use of Doppler ultrasound is limited, primarily due to its very narrow beam, to assessing palpable lesions or lesions detected by TDDU [14, 16]. In common with other studies, we found the use of Doppler ultrasound to be time-consuming with signals often being detected in only one region at the periphery of the tumour [9]. The signals were often very noisy and highly dependent on the angle of the beam, and pressure applied. Small movements of the Doppler probe result in loss of the signal, which could be difficult to relocate. The Doppler detection of abnormal blood flow in any future study would be markedly improved by transducers capable of simultaneously interrogating larger tissue volumes (*i.e.* by larger Doppler transducers).

In this study, the use of Doppler ultrasound did confirm that abnormal blood flow at the periphery of the lesion, as originally described by Wells et al [9], does occur and is associated with carcinoma detected by transillumination. The initial report by Wells et al [9], involved only three patients with breast cancer. However, the larger study by Burns et al [14] involved 394 patients, 55 of whom had breast cancer. In this group of patients, 4% showed no difference from the contralateral side. In the remainder, Doppler signals were of (i) larger amplitude, (ii) higher frequency, or (iii) showed continuous flow through diastole and systole. All three characteristics were detected in 73% of patients with breast cancer. However, in this study the size of the cancers is not stated and the results were interpreted by ear and not by the isometric display as in this study. The fact

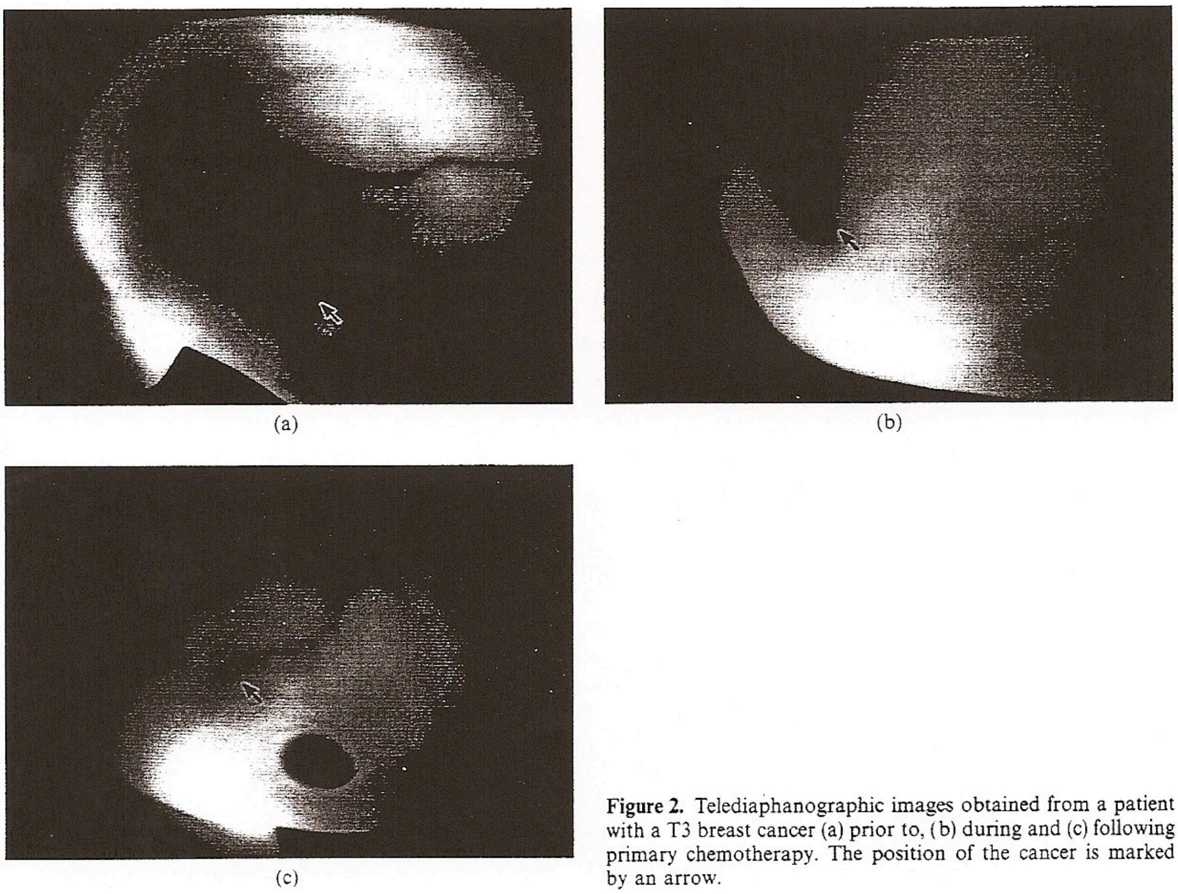

Figure 2. Telediaphanographic images obtained from a patient with a T3 breast cancer (a) prior to, (b) during and (c) following primary chemotherapy. The position of the cancer is marked by an arrow.

that Doppler ultrasound was not detected in all tumours detected by TDDU, may be a reflection of difficulties associated with the procedure. Alternatively there may be a volume threshold effect for smaller tumours. For the larger tumours (>4 cm), a Doppler signal was not obtained in 11 cases, predominantly where the tumours were diffuse, clinically inflammatory carcinomas. Overall, the use of Doppler ultrasound did marginally increase the specificity of TDDU.

Several refinements in the technique of light scanning have been discussed and implemented in an attempt to improve detection rates. The chance observation that the image obtained depended critically on the angle of view, may affect the detection rate, especially of small tumours. However, in this study all tumours which could be visualized by the examiners could be recorded by adjusting the position of the cameras. In subsequent studies care will be necessary to ensure that the camera is normal to the skin surface.

However, the sensitivity of TDDU is significantly lower than that obtained for mammography in this series, particularly for smaller and non-palpable tumours. TDDU also does not detect DCIS, due to the lack of neovascularization in these lesions. To date, for women less than 50 years old, there is no national screening programme. Although TDDU is of value in examining dense breasts, where mammography is less sensitive, its reduced sensitivity does not make it suitable for screening [17]. It may, in combination with Doppler ultrasound, be of value in assessing patients with locally advanced breast cancer, both in determining initial size and subsequent response to treatment. Mammography is often inaccurate in assessing the response of tumours to neoadjuvant chemotherapy. This may be the one area of clinical practice in which this technique is superior. Further studies would need to compare TDDU and Doppler, with clinical examination, mammography and ultrasound imaging.

In conclusion, the combined optical/Doppler ultrasound instrument evaluated in this study achieved a lower sensitivity compared with mammography, making it unsuitable for screening purposes. It may, however, have a role in assessing the response of large tumours to chemotherapy.

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References

1. FORREST, A P M and ROBERTS, M M, Breast cancer: screening for breast cancer, *Br. J. Hosp. Med.*, *23*, 8–21 (1980).
2. FORREST, A P M, Breast cancer screening; report to the health ministers of England (HMSO, London) (1986).
3. FLETCHER, S W, BLACK, W, HARRIS, R ET AL, Report of the International Workshop on Screening for Breast Cancer, *J. Natl Cancer Inst.*, *85*, 1644–1656 (1993).
4. CUTLER, M, Transillumination as an aid to diagnosis of breast lesions, *Surg. Gynaecol. Obstet.*, *48*, 721–729 (1929).
5. WATMOUGH, D J, Diaphanography; mechanisms responsible for the images, *Acta. Radiol. Oncol.*, *21*, 11–15 (1982).
6. DOWLE, C S, TEW, J, MANHIRE, J ET AL, An evaluation of transmission spectroscopy in diagnosis of symptomatic breast lesions, *Clin. Radiol.*, *39*, 375–377 (1987).
7. SICKLES, E A, Breast cancer detection with transillumination and mammography, *AJR*, *142*, 841–844 (1983).
8. BARTRUM, R J and CROW, H C. Transillumination light-scanning to diagnose breast cancer: a feasability study, *AJR*, *142*, 409–414 (1984).
9. WELLS, P N T, HALLIWELL M, SKIDMORE R ET AL, Tumour detection by ultrasonic doppler blood flow signals, *Ultrasonics*, *15*, 231–232 (1977).
10. FOLKMAN, J, Tumour angiogenesis, *Cancer*, *3*, 355–413 (1979).
11. HORAK, E R, HARRIS, A L, STUART, N and BICKNELL, R, Angiogenesis in breast cancer. Regulation, prognostic aspects, and implications for novel treatment strategies, *Ann. N Y Acad. Sci.*, *698*, 71–84 (1993).
12. BRITTON, P D and COULDEN, R A, The use of duplex Doppler ultrasound in the diagnosis of breast cancer, *Clin. Radiol.*, *42*, 99–401 (1990).
13. WATMOUGH, D J, Son et Lumiere; a new combined optical and Doppler ultrasound approach to the detection of breast cancer, *J. Biomed. Eng.*, *10*, 119–123 (1988).
14. BURNS, P N, HALLIWELL, M, WELLS, P N T and WEBB, A J, Ultrasonic Doppler studies of the breast, *Ultrasound Med. Biol.*, *8*, 127–143 (1982).
15. MINASIAN, H and BAMBER, J C, A preliminary assessment of an ultrasonic Doppler method for the study of blood flow in human breast cancer, *Ultrasound Med. Biol.*, *8*, 357–364 (1982).
16. WHITE, D N and CLEDGETT, P R, Breast carcinoma detection by ultrasonic Doppler signals, *Ultrasound Med. Biol.*, *4*, 329–335 (1978).
17. KEY, H, DAVIES, E R, JACKSON, P C and WELLS, P N T, Optical attenuation characteristics of breast tissue at visible and near infra-red wavelengths, *Phys. Med. Biol.*, *36*, 591–602 (1991).