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FREQUENCY DEPENDENT ATTENUATION OF MALIGNANT BREAST TUMORS STUDIED BY THE FAST FOURIER TRANSFORM TECHNIQUE

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The work discussed in this paper comprises one aspect of an experimental design concerned with the use of multi-discipline examination methods to provide detailed information on the interaction of normal and malignant breast tissues with a high frequency sound field. The complete experimental design included x-ray and needle biopsy examination of the breast of a patient prior to mastectomy, followed by: x-ray examination of the excised breast (the malignant tumor remained intact in the excised breast); ultrasound visualization and FFT studies of the formalin-fixed, excised breast specimen; x-ray examination of 0.5 cm thick, whole breast sections of the tissue; and, finally, sectioning and histological staining of the primary malignant tumor region and other tissue areas of interest. Emphasis is given in this preliminary report to a study of attenuation of the sound beam as a function of frequency for specific tissue paths (i.e., from skin to back surface of the excised breast), which included (1) the malignant tumor, (2) the nipple and (3) the areola.

For the tissue path which included the malignant tumor, the FFT studies indicate that the attenuation for the full range of frequencies studied (1.1 to 4.4 MHz) was greater than that of any other area of the breast. A significant result of the investigations reported in this paper is the determination that this analytical technique is feasible and can yield data on malignant and normal regions of breast tissue which correlate with the ultrasound visualization imaging information and with the tissue structure information as revealed by histological examination.

Key words: Attenuation of areola; attenuation of breast tissue; attenuation of malignant tumors; breast cancer detection; breast carcinoma; breast examination techniques; FFT techniques for breast; histology of breast tumors; signal processing for tissue; x-ray examination of breast.

1. Introduction

At the present time, ultrasound visualization techniques, if used in conjunction with other clinical examination methods, can improve the level of success in the differential diagnosis of breast pathologies [1][1]. However, the theoretical capability of ultrasound for providing a successful method of early detection of breast cancer is not presently realized, in part because of the lack of sufficient clinical studies with this method and, in addition, because of the need for more basic experimental studies on the interaction of ultrasound and breast tissue. There is, in fact, a serious need for relatively sophisticated investigations concerned with (1) the complex structure of normal breast in terms of its interaction with sound fields and (2) the variability in structural features of malignant tumors (including those in the same pathology classification) insofar as this variability is significant to medical diagnostic data obtained by ultrasound examination of such tumors.

The experimental work discussed in this paper comprises one aspect of an overall approach of using multi-discipline examination methods, namely, x-rays, ultrasound visualization, signal processing of ultrasound transmission data (i.e., Fast Fourier Transform (FFT) techniques) and histological techniques to provide detailed information on the structural features of breast tissue and their interaction with a high frequency sound field. In the initial experimental stages,

[1]Figures in brackets indicate literature references at the end of this paper.

procedures such as the FFT are best performed on an excised breast. A special preparation, namely, an excised, formalin-fixed breast with a known intact malignant tumor, was used in the investigations discussed in this paper. Detailed examination of such breasts, by both standard and experimental breast cancer detection methods, and the correlation of the results with tissue structure information provided by histological investigations, can yield data that is pertinent to early breast cancer detection [2-8]. The rationale, validity and value of studying such fixed, whole specimens by ultrasound visualization techniques have been discussed in detail by Kelly Fry and Gallager in a previous publication [8]. Additionally, Calderon et al. have published results of an investigation on the ultrasound attenuation values of formalin-fixed breast tumors [9].

In capsule form, the overall experimental design called for collection of data first by x-ray examination of the breast of the patient prior to surgery, followed by: x-ray examination of the excised breast; detailed ultrasound visualization and FFT studies of the formalin-fixed excised breast specimen; whole breast sectioning of the tissue in blocks of approximately 0.5 cm in thickness; x-ray examination of each of these cross sections and, finally, sectioning and histological staining of the primary malignant tumor region and other tissue areas of interest.

The FFT studies were considered in the nature of a feasibility study and it is in that regard they are reported in this paper. Emphasis is given in this preliminary report to a study of attenuation of the sound beam both in the region of the malignant tumor and in other areas of the breast tissue (such as nipple and areola) as a function of frequency. As used in this paper, the term "attenuation" designates all losses in sound pressure amplitude or intensity as the acoustic beam traverses the tissue, including those due to specular reflection, scattering, refraction, absorption and diffraction.

Both the location (as revealed by x-ray examination of the whole, excised breast) and the malignant character of the primary mass (as revealed by needle biopsy) were known at the time of the ultrasound visualization and FFT studies. At the time of this writing, the histological classification of the primary malignant tumor has been determined and detailed histological studies are underway. The precise correlations between information revealed by histology, ultrasound visualization and FFT techniques will be the subject of a later paper.

2. Experimental Methods

The tissue specimen used in the subject study was an excised, formalin-fixed, left breast of a female subject who was 49 years of age at the time of the mastectomy. Since the diagnosis of breast carcinoma had been made by x-ray and needle biopsy prior to surgery, the mastectomy was carried out without a surgical biopsy so that the excised breast contained the previously detected malignant mass in an essentially undisturbed state. After excision, the breast was made to assume its approximate normal contour by pinning it to a layer of paraffin, was x-rayed and then formalin-fixed. The fixation process consisted of covering the pinned breast with 10 percent formalin solution, completely draining this solution and adding a fresh formalin solution every other day for a total period of two weeks. After the completion of this process, the breast was maintained in formalin solution except for periods of ultrasonic examination.

The instrumentation used for pulse-echo examination of the excised breast was a linear scan, B-mode visualization system which included a variety of types of transducers. Only two of these transducers were used as transmitters in the FFT studies, namely, 1.1 MHz and 4.4 MHz center frequency units. Most of the FFT studies were carried out with the 4.4 MHz unit and the results obtained with this transducer will be discussed in this paper. This transducer has a diameter of 1.9 cm, a 7.5 cm focal length, a midband frequency response of 4.4 MHz, a band width of 3 MHz just above noise, and 1 MHz at the 3 dB point.

During the visualization scanning procedures, the breast and examining transducers were completely immersed in mammalian Ringer's solution at room temperature (23 °C) so that there was direct fluid coupling of the ultrasound to the tissue. Both transverse (medial-to-lateral) and longitudinal (superior-to-inferior) scans were taken at distance intervals of 1 to 2 mm. In order to relate data recorded on the echograms to specific areas of the tissue, an anatomical landmark on the tissue (such as the center of the nipple or the center of a prominent skin discoloration over the area of abnormality) was selected and a highly reflective and attenuating acoustic target placed on this landmark. With the focus of the transducer set on the target center, the echogram of the breast tissue showed a distinct, easily identified front surface reflection and an attenuation shadow of the target. Since the linear coordinates (X and Y) were recorded for each echogram, subsequent scans of the tissue with the target removed could be directly related to the chosen anatomical landmark. These surface landmarks were subsequently used in the FFT experiments for identification of desired sound transmission tissue paths.

For the ultrasound attenuation studies in the transmission mode, the previously described axisymmetric focused transducer was used as a transmitter, and a 4 mm diameter, 10 MHz frequency, PZT ceramic sandwich-type piezoelectric probe was used as a receiver. A Panametrics Model 5050R unit pulse-excited the transmitter, and a series unit step attenuator was used to attenuate the ultrasonic received signals prior to their entrance into an amplifier receiver. The breast preparation was mounted on a three-motion coordinate system in a temperature controlled mammalian Ringer's bath (average temperature 23 °C) and positioned between the sending and receiving transducers, with the anterior aspect of the tissue facing the sending transducer (fig. 1). With this arrangement, any area of the tissue could be easily examined and the tissue could be moved in 1 mm steps in the three-axis coordinate system.

In order to record the system's reference waveform, transmitter and receiver transducers were placed facing each other and adjusted in position to receive the optimum plane wave acoustic signals. A linearity test of the system was performed by setting the attenuator unit at different values and comparing the corresponding outputs of the FFT

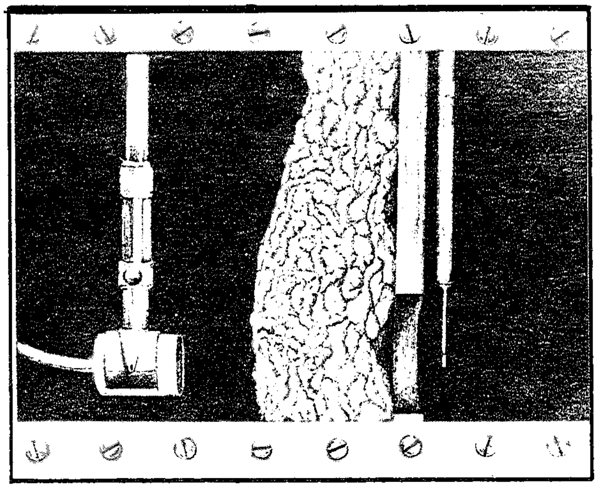

Fig. 1. Experimental arrangement of examining transducer (left), excised breast (side view) and receiving transducer.

spectrum. The system was found to be accurate to ± 1 dB in the useable frequency band, for any particular transmitting transducer. The received ultrasonic waveforms were digitized at a sampling rate of 10 or 20 nanoseconds using an eight bit Biomation Model 8100 digitizer and then transferred to a PDP-11/45 computer. Generally, four waveforms were digitized for each tissue region of interest (i.e., nipple, areola, etc.), stored on a computer disc, and later processed using a 1024 point FFT. In order to obtain attenuation and phase-angle versus frequency plots, they were deconvolved with the original system's reference waveform. The waveforms were transformed into the frequency domain and the absolute amplitude for each waveform was compared with the amplitude of the reference waveform for the relative attenuation measurement. To obtain the phase angle for each waveform, the phase was compared with the reference waveform and subsequently linearized for each frequency. For optimum frequency resolution, appropriate sampling intervals were selected on the Biomation digitizer. The output was presented in a graphical form in three different formats; namely, normalized pressure amplitude, attenuation and phase-angle spectra. The phase-angle data is presented in a separate paper [10].

The tissue was sampled at various selected regions by moving the specimen across the ultrasound beam on the three-axis system. The regions of interest chosen for this study were specific tissue paths (i.e., from skin to back surface of the specimen) which included 1) the malignant tumor, 2) the nipple and 3) the areola. In that regard, eighteen separate transmission mode studies were made in the tumor path, nine in the areola path and eight in the nipple path. In addition, the upper inner aspect of the breast was chosen as representative of normal, middle-aged, mammary adipose tissue and test ultrasound transmissions were made in that region.

Following completion of the FFT studies, the tissue was longitudinally sliced to produce whole breast sections from 5 to 8 mm in thickness. Each of these cross sections was x-rayed and the radiographs studied to determine which specific regions of the breast would be further examined by means of histological techniques. Tissue cubes 2 x 2.5 cm in overall dimensions were excised from the selected regions of interest and prepared for histological study. The primary malignant mass was included in one of these cubes of tissue.

3. Results

The ongoing histological studies indicate that the primary malignant mass was an invasive carcinoma of duct cell origin with an intermediate degree of differentiation. The mass was multinodular, fairly well circumscribed but not encapsulated, with a dense fibrotic center and a peripheral shell (3 to 4 mm thickness) of neoplastic cells. The fibrotic tissue, representing the major tumor mass, was highly collagenous but the cellular shell had a minimum deposit of collagen.

Included in the illustrations shown in this paper are duplications of the recorded system reference waveform (normalized pressure amplitude versus frequency) for sound wave transmission through Ringer's solution, compared to the waveforms recorded for sound transmission through breast tissue immersed in Ringer's solution. Such pressure amplitude graphical displays are presented in order to demonstrate the characteristics of the reference waveform and the dynamic range limitations of the system.

Before discussing the results obtained for the tissue path that included the malignant tumor, it is of interest to consider the attenuation values obtained for the areola and nipple tissue path regions of the breast which, on the basis of the x-ray examination, can be assumed normal. In calculating precise attenuation values, on the basis of the recorded, normalized pressure amplitude values, the tissue path length was taken as the distance between the anterior surface of the skin overlying the nipple or areola and the posterior surface of the breast specimen (as determined by the previously obtained ultrasound visualization images of the breast specimen). Therefore, it is emphasized here that the attenuation values shown in figures 3 and 4 are not specifically for areola or nipple, but are for the tissue path that includes these structures.

Figure 2 presents reorded pressure amplitude waveforms for four sound transits through the nipple at entrance points separated by 2 mm of surface tissue. These waveforms show the maximum variability in pressure amplitude (differences in pressure amplitude for waveforms A, B, C, D) found for the nipple region. The attenuation frequency spectrum plot for the nipple path shown in figure 3 is based on the pressure amplitude waveforms shown in figure 2 and the tissue path length (surface of nipple to back surface of the specimen) traversed by the sound wave.

Figure 4 is the attenuation frequency spectrum for the areola region of the breast. As in the case of the nipple, this data is also based on differences in pressure amplitude response curves (three sound transits through the areola region at entrance points separated laterally by 1 mm of surface tissue) and the tissue path length (areola skin to back surface of the specimen). All other sound transmissions in the areola path gave results within the range of values shown in figure 4. The tissue region of greatest attenuation, as shown in figure 4, was located closer to the nipple in comparison to the other two sound transit regions.

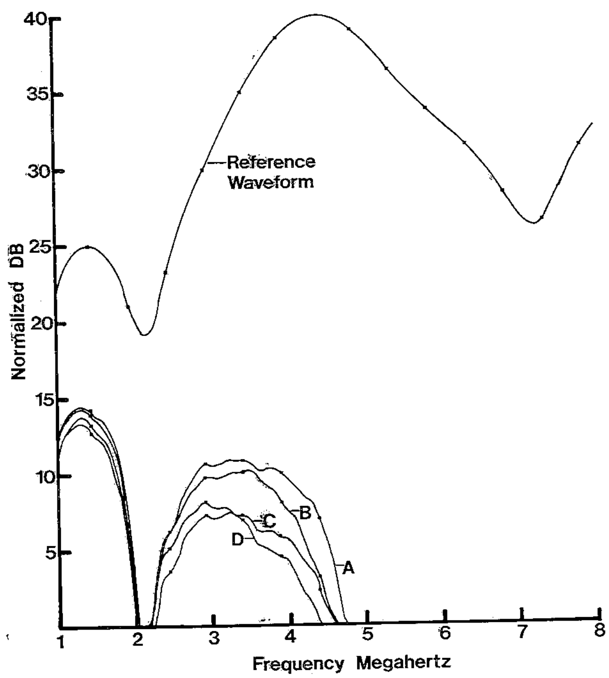

Fig. 2. Computer recorded display of: (a) reference waveform for ultrasound transmission through Ringer's solution only; (b) waveforms A, B, C, D for ultrasound transmission through four separate regions of the "nipple tissue path" of an excised, formalin-fixed breast immersed in Ringer's solution.

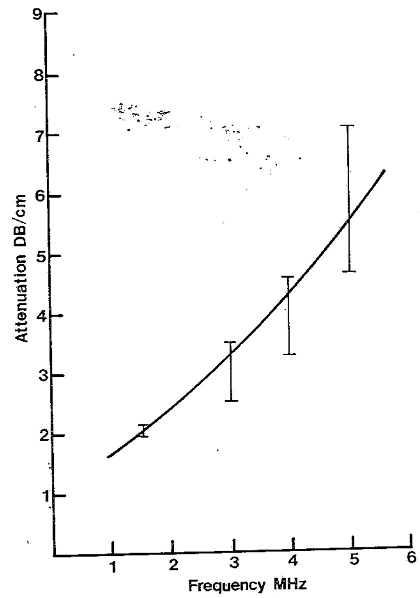

Fig. 4. Attenuation frequency spectrum for "areola tissue path" based on three sound transmissions through separate regions of the areola.

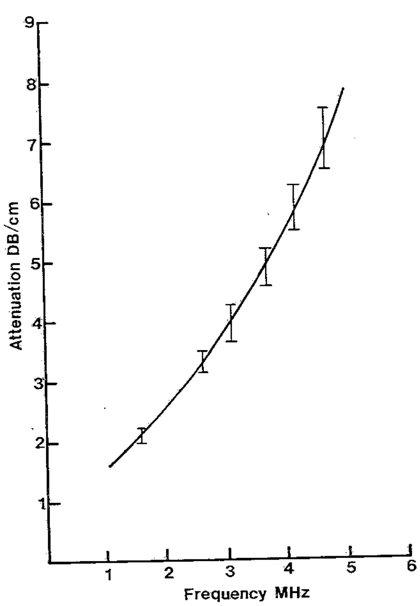

Fig. 3. Attenuation frequency spectrum for "nipple tissue path" based on waveforms shown in figure 2.

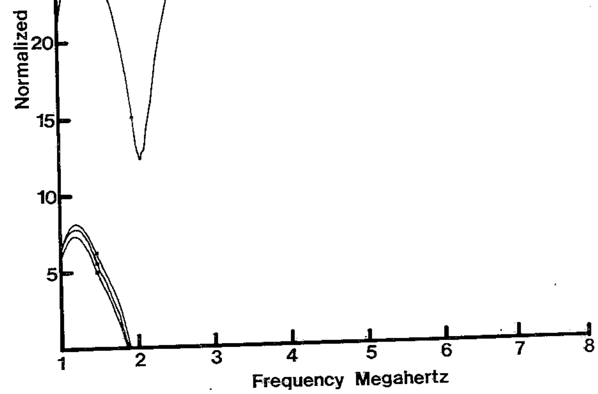

Fig. 5. Computer recorded display of: (a) reference waveform for transmission through Ringer's solution only; (b) three waveforms for ultrasound transmission in separate regions of the "tumor tissue path" of an excised, formalin-fixed breast immersed in Ringer's solution.

The waveform recordings shown in figure 5 resulted from three sound transits in the tumor tissue path, with each of the test points separated by 1 mm of tumor tissue in terms of skin surface distance. In contrast to results obtained in all other tested regions of the breast, the recorded waveform data show a total lack of recorded pressure amplitude response in the higher frequency regions. This result indicates that there is at least 40 dB of amplitude loss, for the tissue path from skin to back surface, in the frequency regions above approximately 2 MHz. At the lower end of the frequency spectrum, pressure amplitude response was recorded but, as shown later in this paper, the level of these pressure amplitudes indicates a greater attenuation for the tumor tissue path than for that of the nipple tissue path.

For the main body of the primary malignant tumor, the overlying tissue is approximately 1.5 cm in depth (from skin to anterior border of overt mass); the tumor has a diameter of 1.5 cm in depth and the tissue below the tumor is approximately 2 cm in depth. X-ray examination of the excised breast indicated the tissues surrounding the tumor were primarily fatty in nature. Consequently, if the attenuation for the 3.5 cm of tissue surrounding the tumor is considered to be that of normal breast adipose tissue and, further, if the attenuation value for such tissue is assumed comparable to that found in the present studies for tissue paths (skin to back of tissue) through other fatty regions of the breast, namely, 2.5 dB/cm at 2.0 MHz, then the tissues surrounding the tumor account for 8.8 dB of the attenuation. It should be noted that the 2.5 dB/cm value for breast adipose tissue is in general agreement with that found by Calderon et al. [9], namely 2.3 dB/cm at 2.25 MHz for formalin-fixed, excised, normal breast tissue. Deducting the 8.8 dB from the 40 dB maximum dynamic range response of the system and taking into account the 1.5 cm tumor path, it is found that the attenuation for the malignant tumor itself is 21 dB/cm at a frequency of 2 MHz. Since this value is in general agreement with that of Calderon et al. who found an attenuation of 20 dB/cm at 2.25 MHz for formalin-fixed, excised, malignant breast tumors, it is expected that the 40 dB dynamic range limitation, which represents a factor of 100 in pressure amplitude and 10,000 in intensity, is close to an adequate dynamic range response.

Carrying out the same type of calculation, using the pressure amplitude data shown in figure 5 for the lower frequencies, gives an attenuation value for the malignant mass of 8 dB/cm at a frequency of 1.5 MHz. This is calculated on the basis of 3.5 cm of normal fatty breast tissue, with an attenuation value of 2.0 dB/cm at 1.5 MHz (as found for other normal fatty regions of this breast specimen) and a 1.5 cm depth of tumor mass.

Of the total of 18 separate runs through the tumor tissue path, with the exception of two sound transits in a particular region of this path, all recorded results indicated that for frequencies above 2 MHz there apparently was total attenuation of the sound wave (i.e., within the 40 dB recording level capability of the system). The exceptional cases showed 1) a pressure amplitude waveform that was highly, but not completely, attenuated by the tumor path and thus was within the 40 dB maximum dynamic range of the system and 2) for a sound transit in an area just 2 mm laterally distant from that of number one above, a pressure amplitude waveform which had precisely the same frequency spectrum, pressure amplitude response as that found for normal fatty regions of the breast. On the basis of this result, it was assumed, prior to the histological examination, that the tumor included a border region of less density (conjectured to be a mixture of normal and neoplastic tissue) than the central mass and an adjacent region of distinct adipose tissue. Based on pressure amplitude data and the known tissue path, an attenuation value of 13 dB/cm at a frequency of 2 MHz was calculated for this border area of neoplastic tissue.

The histological studies, to date, clearly show adipose tissue immediately adjacent to and surrounding the malignant mass, thus accounting for the characteristics of the waveform which duplicated those of the fatty regions of the breast. The 3 to 4 mm thick neoplastic shell located adjacent to the adipose tissue and surrounding the fibrotic center of the tumor presumably accounted for the 13 dB/cm attenuation value.

4. Discussion

At the present time, in clinical studies concerned with the use of pulse-echo methods for breast examination, differential diagnosis is primarily based on the characteristics of the wall of the tumor, the presence and nature of the echoes from the internal structure of the tumor and the existence or absence of a shadowing phenomenon resulting from the attenuation of acoustic energy by a malignant mass. In evaluating each of these parameters, considerable emphasis and reliance is placed on the so-called "attenuation shadow" which, when present, is generally considered to be indicative of the presence of a malignant mass. However, precise knowledge regarding attenuation characteristics of normal, benign and malignant breast tissue is extremely limited. This is a serious deficit since its consequence may be misdiagnosis of the benign or malignant nature of a breast tumor.

Considerable care should be used in interpreting attenuation shadows produced by pulse-echo examination of breast, with specific regard to the question of whether normal or benign tissues can produce significant shadowing effects. In that regard, Kobayashi has found that fat necrosis results in an attenuation shadowing comparable to that produced by a malignant mass, as judged by pulse-echo visualization [11]. Calderon et al.'s studies at a frequency of 2.25 MHz of formalin-fixed excised breast tissue gave values of 20 dB/cm for malignant masses, 9 dB/cm for benign masses and approximately 2.3 dB/cm for normal breast tissue surrounding the tumors [9]. Although there is a significant difference between attenuation values for benign and malignant tumors as found by these investigators, it must be realized that in the clinical pulse-echo methods, differential diagnosis is made on the basis of a comparison between the image pattern of the overt mass and that of the surrounding normal tissue. Therefore, the Calderon et al. data indicate that for pulse-echo techniques in which the sound beam makes two passes through the breast, common sized benign tumors (2 cm and above) with an attenuation of 9 dB/cm could result in shadowing in relation to surrounding normal tissue with an attenuation value of 2.3 dB/cm. Additionally, the first author of this paper recently found, in the case of several clinical patients, each with an overt, benign mass within the breast (identified by x-ray examination and confirmed by surgical biopsy), that the echograms obtained using standard pulse-echo methods at frequencies of 4.4 MHz to 5.0 MHz displayed distinct shadows in the region of the mass. The significance of this result, insofar as the present paper is concerned, is the recognition of the need for quantitative attenuation data on multiple types of benign and malignant breast tumors, as opposed to simple visual inspection of shadow phenomena of such masses and consideration of whether signal processing techniques may provide some of the needed data [12].

The FFT studies discussed in this paper, for the tissue path which included the malignant tumor, showed that the attenuation for the full range of frequencies studied (1.1 to 4.4 MHz) was greater for this tissue path than for that of any other area of the breast. Further, these findings were consistent with those found in the visualization echograms, that is to say, even at a frequency of 1.1 MHz, this specific tumor could be recognized by "pale shadowing," while at the higher frequencies the attenuation shadow was more opaque and formed a distinctive border in relation to adjacent tissue.

From the viewpoint of possible in vivo breast examinations by FFT methods, it is of interest that in the present study the dual structural components of the tumor (as shown by the two attenuation values) and the adipose tissue surrounding the tumor were recognized prior to any histological investigations. Further, the finding that the total malignant mass was attenuating but the greater attenuation was in the region of fibrosis agrees with earlier studies [8] relating attenuation (as judged by nonquantitative pulse-echo methods) of breast tumors with specific tumor tissues (as revealed by detailed histological studies). The highly collagenous nature of the primary malignant mass combined with its high attenuation values and the minimum collagen content of the surrounding cellular shell is of interest in regard to the relative importance of elastic properties versus physical structural make-up for sound reflection and transmission through overt tissue masses [13]. The ongoing histological studies and the preliminary phase-angle data may provide some information on this aspect [10].

There are many factors, both tissue and instrumentation related, associated with the attenuation in the nipple path region as determined by the FFT ultrasound transmission studies discussed in this paper. Included in the tissue aspects are the nonuniform structure of the skin surface and the variable tissue components within the nipple and in the regions deep to the nipple. Although the above factors may be significant, information which is relevant to present pulse-echo clinical techniques can be derived from the preliminary FFT data without complete analysis of such parameters. In that regard, for example, the results shown in figure 3 are important in relation to detection of an overt breast mass located in the region directly posterior to the nipple. If pulse-echo techniques are applied to scan directly over the nipple region, there may be a lack of success in detecting such masses (particularly at frequencies of the order of 5 MHz) because of their location in the attenuating path of the nipple. For the purposes of tumor detection, therefore, the tissues deep to the nipple should be viewed by scanning from the side regions of the breast and by using lower frequencies. These two approaches to visualizing structures deep to the nipple were successfully applied by the present authors in the case of the excised breast discussed in this paper, and breasts studied in vivo.

To accomplish the overall aim of the studies carried out in this preliminary investigation, that is, to correlate x-ray, visualization, FFT analysis and histological findings, requires extensive and time-consuming investigations. However, if some of the significant parameters that are relevant to differential diagnosis of breast tumors by ultrasonic techniques are to be determined by methods other than the necessarily slow process of interpreting ultrasound clinical data, such detailed investigations are necessary. A significant result of the investigation reported in this paper is the determination that this computer based, signal processing technique is feasible and can yield data on malignant and normal regions of breast tissue. It also appears evident from these experiments that similar investigations could be carried out on freshly excised whole breast tissue. If such investigations are successful, then this technique could be considered for application to breast patient examination. Success in that regard could lead directly to development of an ultrasound breast examination technique which might eventually limit the need for surgical biopsy to a small number of exceptional cases.

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