Reprinted from SPIE Vol. 419—Application of Optical Instrumentation in Medicine XI

The Rationale and Efficacy of Applying Multiple Imaging Techniques for Breast Examination: X-Ray Mammography and Ultrasound Visualization

Elizabeth Kelly-Fry

Department of Radiology, Indiana University School of Medicine
Life Sciences Research Division, Indianapolis Center for Advanced Research, Inc.
926 West Michigan Street, Room A-32, Indianapolis, Indiana 46223

Abstract

Since failure to biopsy a malignant mass during a relatively early stage of its development will result in a severely shortened life span for the patient, breast imaging techniques must be capable not only of detecting a mass, but of differentiating between the image characteristics of a benign and a malignant tumor. Ideally, the applied technique should be equally capable when used to examine the young breast and the older breast. The specific advantages and disadvantages of x-ray mammography and of ultrasound visualization, as well as the rationale of balancing the disadvantages of one technique with the advantages of the other, are discussed in this presentation.

Introduction

The endpoint of most current breast examinations is to determine whether there is an isolated, discrete mass within the breast which has imaging characteristics that differ from the immediately surrounding tissue and, on the basis of these characteristics, to make a judgement whether or not surgical biopsy should be carried out to confirm the possible malignant nature of the mass. Statistically, most masses found in the breast are of a benign nature. Further, the common existence of such benign masses in both the young and the older breast and, in some cases, the recurring nature of such masses, precludes a recommendation that all discrete breast masses should be surgically biopsied. However, failure to biopsy a malignant mass during the stage of its development when malignant cells have not yet migrated to the lymph nodes will result in a severely shortened life span for the patient.[1,2] Consequently, breast imaging techniques must not only be capable of detecting a mass, but also of differentiating between the sometimes subtle differences between imaging characteristics of benign and malignant tumors. Further, the applied techniques must be equally capable of detecting and differentially diagnosing masses in the young and in the older breast. For the most commonly used instrument technique for breast examination, namely, x-ray mammography, this latter requirement cannot be satisfied in all cases since breast tissue components and their architectural distribution change with the aging process to an extent that a mass which is distinctly delineated in images of the older, fatty breast may not be discernible in images of the young dense breast due to relatively small differences in density between the mass and the surrounding tissue components.

X-ray mammography has many advantages for breast examination including the capability of detecting microcalcifications and tissue masses less than 0.5 cm in diameter; however, it cannot meet all of the requirements for detection and accurate differential diagnosis, and such capability should not be expected from this one modality.[2,3] Rather than applying x-ray mammography as the sole breast imaging instrumentation technique, emphasis should be placed on developing and applying other imaging modalities for those specific cases where x-ray mammography is not diagnostic, or where its ionizing character is inappropriate in terms of a patient's age or other patient parameters. Further, advantage should be taken of the multiple diagnostic information provided by applying x-ray mammography and one or more additional imaging modalities when a firm differential diagnosis cannot be obtained, with certainty, by any of the individual examination techniques. This paper is primarily concerned with the capability of ultrasound visualization for breast examination when applied in conjunction with x-ray mammography and when used as a single examination technique.

Background of the Breast Cancer Problem in the United States

For the past forty years, for women in the United States, death from all causes has been decreasing, with the exception of death related to breast cancer, i.e., although there may be some recent gains, there has been little significant change in death rate for that specific malignant disease.[4,5] In terms of survival time, some progress has been made but, unfortunately, this is accompanied by an increasing incidence in breast cancer which is of the order of 1% per year.[6] If a malignant tumor is localized to the breast, approximately 85% of the women will survive for five years after diagnosis but, if it has spread to the lymph nodes, then only approximately 55% will survive that first five-year period. Spread of the malignant cells beyond the lymph nodes is an extremely ominous sign, and only 10% of these patients survive that five-year period.[7] However, if malignant tumors can be detected

while they are in the noninvasive stage and/or are less than 5 mm in diameter (so-called "minimal breast cancers"), the life span for the average patient can be close to normal, that is, it is of the order of 20 years following diagnosis.[8] Unfortunately, however, for white women in the United States, the median survival time following the diagnosis of breast cancer is approximately 7 years, while for American black women, it is approximately 4 years.[4] Early detection, in association with advances in the treatment of breast cancer, is the key to decreasing the high death rate from this disease.[9] In that regard, therefore, one may ask the question "Is this essentially constant death rate due to the fact that the techniques used to examine the breast are not capable of detecting malignant masses when they are of the order of 5 mm in greatest diameter, or does it mean that most of the women in the age ranges associated with high breast cancer incidence are not being examined?" There are many complex factors associated with mortality rates from breast cancer which are significant to the above question, including the possible systemic nature of breast cancer, and the growth rate of the malignant cells; these will not be considered in this discussion since the influences of such factors are not resolved.[3 9]

In respect to the above question, the most important fact is that the two most common means of breast examination in the United States are manual palpation and x-ray mammography. Since over 90% of women who develop breast cancer detect their own malignant masses, it can be assumed that of these two examination techniques, manual palpation is the most commonly used. This does not mean, however, that a large percentage of women use self breast examination; a 1977 survey by the American Cancer Society of a selected population indicated that only 24% of women said they practiced breast self examination monthly.[4] Although the percentage of patients doing self breast examination probably has increased since that time, it is nevertheless reasonable to assume that most patient-detected breast masses have been accidentally found because of their large size. If a physician carries out this examination, the smallest tumor will be of the order of 1 cm in size,[10] while if the patient carries out a breast self examination, it has been estimated that the smallest detected tumor will be of the order of 1.6 cm in size.[11] Clearly, then, one answer to the previously raised question is that the most commonly used method to examine the breast, namely, the application of the human hand, is not an effective means for detecting small masses and, therefore, has only limited benefit in terms of the life span of the breast cancer patient.

The second most commonly used technique for examination of the breast, x-ray mammography, is capable of detecting small breast masses and thus of exerting a significant influence in respect to the life span of the breast patient. However, in the United States, this technique is not widely used in terms of the number of women at risk for breast cancer. The population considered at risk for breast cancer are women over the age of 35; in the United States, there are approximately 53 million in that age range.[12] Based on a 1977 figure, approximately 4% of that population (2 million) receive an x-ray mammography examination.[13] Obviously, the wide gap between the number of patients at risk and the number of patients being examined by the most widely used instrumentation modality is at least partly associated with the current dilemma that exists in the United States in regard to screening for breast cancer. It is not the purpose of this presentation to analyze the breast screening problem, but one aspect of this problem is relevant to the subject of this paper, namely, if breast masses in symptomatic patients of all ages can be accurately diagnosed, using either a single or multiple examination modality, there is a reasonable possibility that efforts might subsequently be directed to further development of these techniques to make them appropriate for screening. Screening is one of the most significant tasks in terms of breast cancer; however, a clear differentiation should be made between the techniques and instrumentation required for screening and that required for the symptomatic subject. It was this general philosophy that underlies the work of the author and her associates in regard to the development of ultrasonic techniques which can provide, used either singly or in combination with x-ray mammography, a high diagnostic accuracy in terms of symptomatic patients.[14-20]

Advantages and Limitations of X-ray Mammography

In terms of an efficient clinical procedure, x-ray mammography allows fast examination of both breasts, and provides two-dimensional images of total breast volume which can be read in a relatively short time. Its most significant advantages are: (1) the capability of detecting a mass less than 5 mm in diameter within the breast and defining its wall structure.[10] Since, in general, for those subjects who are at a higher risk for breast cancer in terms of their age, there is usually a large percentage of fat within their breasts (classically, the middle-aged subject), the capability of x-ray mammography to sharply outline malignant masses in such breasts is critically important; (2) imaging the flecks of calcium particles, generally referred to as microcalcifications, which often accompany malignant breast disease. There is considerable variation in the medical literature regarding the range of size of such particles, but it can be indicated that their average size is of the order of 500 microns, with a size range extending from 50 microns to 2 mm. Conventional x-ray mammography techniques demonstrate microcalcifications in 30 to 50% of breast cancers.[21] Current state-of-the-art ultrasound breast examination instruments are capable of demonstrating the presence of calcifications in the millimeter range, but they are not capable of detecting

microcalcifications of the type most generally associated with malignant pathologies, namely, those in the micron size range.[16]

Apart from questions regarding possible deleterious effects of ionizing radiation, it is reasonable to ask why it is necessary to consider other breast imaging modalities when x-ray mammography has so many advantages. The diagnostic limitations of x-ray mammography associated with the physics of its radiation is relevant to this question. Radiographic contrast, in terms of diagnosis, is generally defined as a difference in density on the photographic film between two areas of interest such as a dense mass and the surrounding tissue. This contrast is dependent on the inherent properties of the two tissue components in terms of differential x-ray absorption, miscellaneous instrumentation factors, and the characteristics of the film. At the present level of development of x-ray mammography, sufficient fat must be present in the breast to provide adequate image contrast; fat, which absorbs the least amount of x-ray radiation, provides a radiolucent background for the mass of interest, while other radio-opaque breast tissues do not.[10]

In the majority of cases that are routinely examined by x-ray mammography, namely, the middle-aged subject, fat is a normal component of the breast, and masses only a few millimeters in size can be imaged with this technique. However, other cases for which the low density fat background is not available, and for which x-ray mammography cannot provide good diagnostic images are not uncommon.[3 10] The most obvious example of this condition is the dense breast of the young woman, including those who are pregnant or lactating. Although some young subjects may have breasts which have sufficient fat in them to allow adequate x-ray mammography imaging, on the average, subjects under the age of 30 do not constitute good candidates for x-ray mammography. Also, dense breasts can be found for pre-menopausal subjects who are over the age of 30, and they are sometimes found for post-menopausal women. Additionally, there is a large number of subjects of all ages whose breasts may have a normal component of fat for their age range but, in addition, also exhibit large areas of dense fibrous tissue which may be associated with benign conditions such as mammary dysplasia, fibrocystic disease, or fibrosing adenosis. Carcinomas located in such regions of tissue density may not be detected by x-ray mammography since the contrast between the malignant mass and the surrounding tissue is not sufficient.[3 10]

As indicated previously, x-ray mammography is particularly beneficial in regard to detecting the type of microcalcifications often associated with the presence of malignant masses. However, in some cases, calcifications are detected which are not completely characteristic of the type of microcalcifications associated with carcinoma, nor the usually larger, more amorphous calcifications associated with benign masses.[22] When such calcifications are found and no associated mass is discernible on the mammogram, the radiologist is confronted with a serious problem in regard to whether or not a surgical biopsy should be recommended. In many of these cases, an occult mass may not actually be present but, in some, a mass is present and the failure to detect it with x-ray mammography is associated with the fact that the mass is located in a dense region of the breast.[25]

Background - Ultrasound Visualization Techniques and Instrumentation

A number of instrumentation designs and technique approaches to ultrasound mammography have been used by various investigators; recent publications[23-25] devoted to breast ultrasound seminars and international meetings provide current information on progress in that field. The B-mode linear scan ultrasound system used in a clinical-research study by the author and associates over approximately a 4-year period to examine a symptomatic population has been described in previous publications.[15-20] Prior to the clinical studies, investigations were carried out on the significance to breast diagnosis of lateral resolution, to the degree that such resolution is provided by a narrow acoustic beam.[19] The frequency ranges investigated were from 1.6 to 10 MHz, with f numbers ranging from 5 to 1.25. Possible transducer designs were considered in terms of their application to imaging the uncompressed and the compressed breast. On the basis of the above outlined studies, as well as other factors associated with simplicity of design and imaging of structures beneath the nipple-areolar region, the transducers were designed for the case of the compressed breast. Based on a series of theoretical and experimental investigations, it was determined that the beam width should be less than 1 mm at 3 dB, of the order of 1 mm at 6 dB, and approximately 2 mm at 20 dB pressure amplitude points for adequate lateral resolution. In terms of these conditions, coupled with the condition of a compressed breast, an f/2, 3.5 to 4 MHz transducer can provide excellent imaging of the breast tissues; the frequency can be increased to as high as 7.5 MHz, but differentiating between benign and malignant masses on the basis of acoustic shadowing at this frequency becomes more difficult. The breast can be scanned from either the sitting, standing, prone, or supine position, but our investigations showed that there are unique advantages to the supine position which can affect the accuracy of diagnosis.[15 19]

In determining the benign or malignant character of a breast mass on the basis of its ultrasound image, the primary characteristics evaluated were: (1) whether or not the wall

of the tumor was well demarcated from the surrounding tissue and whether it exhibited a smooth or jagged structure; (2) whether the internal echo pattern of the mass was homogeneous, non-homogeneous, or non-visible; and (3) the degree of attenuation shadowing in terms of marked, moderate, or slight; (this degree of attenuation was judged by the blackness of the shadow and was not associated with the width of the shadow). The volume location of all of these three parameters was noted, but particular emphasis was placed on the volume location of the attenuation shadow, that is, whether or not the attenuation was evident over the entire volume, or only over a small portion of the mass; this volume location was determined by 1 mm scanning throughout the mass.[20] The presence or absence of posterior enhancement and/or lateral shadowing was also noted, but the absence of this phenomena was not considered significant since earlier experimental studies indicated that it was related to both the structural features of the mass and variable features of the sound field.[17] If a disturbed architectural pattern, as imaged by ultrasound, was noted, the possible presence of a malignant mass was considered, and efforts were increased to obtain other diagnostic information.[18]

Over a 46-month period, 1892 subjects were examined, and a total of 73 cases of biopsy-confirmed carcinoma masses were found in this primarily symptomatic population.[19] A diagnostic accuracy of 95% was obtained for the ultrasound mammography technique. Combined x-ray and ultrasound mammography yielded 100% accuracy. The clinical-research program under which these results were obtained has now been completed.*

Discussion

For ultrasound imaging systems, the magnitude of an echo is dependent on the magnitude of the difference in acoustic impedance between two interfaces; the larger the difference, the more intense the echo. The characteristic impedance of biological and non-biological materials is dependent on the value of their acoustic velocity and their density. Acoustic velocity is dependent on both density and elasticity of materials but, in the case of biological materials, has a significant association with elasticity, a tissue characteristic which probably has an association with the benign or malignant character of a breast mass. It can be expected that future sophisticated tissue characterization investigations will provide additional diagnostically relevant information on this and other tissue characteristics of breast masses which will further increase diagnostic accuracy. However, present ultrasound instrumentation has sufficient sensitivity to differentiate the small differences in acoustic impedance between various normal breast tissues and between normal and pathological tissue, and thus can provide good contrast images of these tissues. The strongest rationale for the use of ultrasound mammography is that, for those specific cases where x-ray mammography cannot clearly delineate the mass from the surrounding normal tissue, ultrasound visualization can provide good contrast images. Common examples are ultrasonically detected benign masses in the very dense breast of a young woman,[17] and benign masses located within isolated dense regions of the breasts of older subjects.[16]

The tomographic aspect of ultrasound imaging in respect to evaluating primary imaging characteristics such as wall structure, internal echo pattern, attenuation, and architectural patterns, over the full volume of the mass, is particularly significant in regard to diagnosis because it takes into account varying structural features of malignant masses within different regions of the tumor. For those cases where adequate imaging is obtained by both modalities, the confirmation by ultrasound visualization of certain features revealed by x-ray mammography, such as wall structure,[18 20] and the addition of other types of information such as internal echo structure and unique characteristics of attenuation, increases the accuracy of diagnosis. Basic to the arguments presented in this paper for application of both x-ray and ultrasound mammography is the presumption that, for both modalities, only instruments designed for the specific purpose of breast examination will be used.

* This research was supported by the Grace M. and Ralph W. Showalter Residuary Trust, the Department of Radiology of Wishard Memorial Hospital, and by the Indianapolis Center for Advanced Research, Inc.

References

1. Seidman, H.: Cancer of the Breast: Statistical and Epidemiological Data. Amer. Cancer Society, Inc., May 1969.

2. Gold, R. H. and Bassett, L. W.: Section 1. X-ray Mammography: History, Controversy, and State of the Art. In Mammography, Thermography, & Ultrasound in Breast Cancer Detection. L. W. Bassett and R. H. Gold, Eds., Grune & Stratton, New York, 1982, pp. 3-11.

3. Buchanan, J. B., Spratt, J. S. and Heuser, L. S.: Tumor Growth, Doubling Times, and the Inability of the Radiologist to Diagnose Certain Cancers. In The Radiologic Clinics of North America, J. N. Wolfe, Ed., W. B. Saunders Co., Philadelphia, 1983, pp. 115-126.

4. The Breast Cancer Digest: A Guide to Medical Care, Emotional Support, Educational Programs, and Resources. U.S. Dept. of Health, Education, and Welfare; Public Health Service, National Institutes of Health; NIH Pub. No. 80-1691, December 1979.

5. Strax, P., Ed.: Control of Breast Cancer Through Mass Screening, PSG Pub. Co., Inc., Littleton, MA, 1979.

6. Venet, L., Ed.: Breast Cancer: A Practical Guide to Diagnosis and Treatment. SP Medical & Scientific Books, New York, 1979.

7. Bassett, L. W. and Gold, R. H., Eds.: Mammography, Thermography, & Ultrasound in Breast Cancer Detection. Grune & Stratton, New York, 1982.

8. Frazier, T.: Prognosis and Treatment in Minimal Breast Cancer. Amer. J. Surg. 133:697-701, 1977.

9. Moskowitz, M.: Section 4. Benefit and Risk. In Mammography, Thermography, & Ultrasound in Breast Cancer Detection. L. W. Bassett and R. H. Gold., Eds., Grune & Stratton, New York, 1982, pp. 129-139.

10. Gold, R. H. and Bassett, L. W.: Section 2. Mammographic Features of Malignant and Benign Disease. In Mammography, Thermography, & Ultrasound in Breast Cancer Detection. L. W. Bassett and R. H. Gold., Eds, Grune & Stratton, New York, 1982, pp. 13-52.

11. Kirch, R. L. A. and Klein, M.: Prospective Evaluation of Periodic Breast Examination Programs. Cancer 41(2):728-736, 1978.

12. U. S. Bureau of Census 81; Current Population Report CP25 #917.

13. Food & Drug Administration: A Look at FDA's Program to Protect the American Consumer from Radiation. DHEW Pub. No. (FDA)77-8032, Rockville, MD, April 1977, 18 pp.

14. Kelly-Fry, E., Fry, F. J. and Gardner, G. W.: Recommendations for Widespread Application of Ultrasound Visualization Techniques for Examination of the Female Breast. In Ultrasound in Medicine, Vol. 3A, D. White and R. E. Brown, Eds., Plenum Pub. Corp., New York, 1977, pp. 1085-1088.

15. Kelly-Fry, E.: Breast Imaging. Chapter 24 in Diagnostic Ultrasound Applied to Obstetrics and Gynecology. R. E. Sabbagha, Ed., Harper & Row, New York, 1980, pp. 327-350.

16. Harper, P. and Kelly-Fry, E.: Ultrasound Visualization of the Breast in Symptomatic Patients. Radiology 137(2):465-469, 1980.

17. Harper, A. P., Kelly-Fry, E. and Noe, J. S.: Ultrasound Breast Imaging--The Method of Choice for Examining the Young Patient. Ultrasound Med. Biol. 7:231-237, 1981.

18. Harper, A. P., Jackson, V. P., Bies, J., Ransburg, R. and Kelly-Fry, E.: A Preliminary Analysis of the Ultrasound Imaging Characteristics of Malignant Breast Masses as Compared with X-ray Mammographic Appearances and the Gross and Microscopic Pathology. Ultrasound Med. Biol. 8(4):365-368, 1982.

19. Kelly-Fry, E. and Harper, A. P.: Factors Critical to Highly Accurate Diagnosis of Malignant Breast Pathologies by Ultrasound Imaging. Third World Federation of Ultrasound in Medicine and Biology Proceedings; Brighton, UK, July 26-30, 1982, Pergamon Press; in press.

20. Harper, A. P., Kelly-Fry, E., Noe, J. S., Bies, J. R. and Jackson, V. P.: Ultrasound in the Evaluation of Solid Breast Masses. Radiology 146(3):731-736, 1983.

21. Sickles, E. A.: Further Experience with Microfocal Spot Magnification Mammography in the Assessment of Clustered Breast Microcalcifications. Radiology 137:9-14, 1980.

22. Egan, R. L., McSweeney, M. B. and Sewell, C. W.: Intramammary Calcifications Without an Associated Mass in Benign and Malignant Diseases. Radiology 137:1-7, 1980.

23. Raymond, H. W. and Zwiebel, W. J., Eds.: Seminars in Ultrasound: Ultrasound Mammography. Grune & Stratton, Vol. III(1), 1982.

24. Third World Federation of Ultrasound in Medicine and Biology Proceedings; Brighton, UK, July 26-30, 1982, Pergamon Press, London; in press.

25. Jellins, J. and Kobayashi, T., Eds.: Proceedings, International Congress on the Ultrasonic Examination of the Breast; June 10-12, 1983. John Wiley & Sons, Ltd., Sussex, UK; in press.