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*C. Tobias*

PROPOSED PROTOCOL FOR APPLICATION OF THE EMI TOTAL BODY  
SCANNER FOR EVALUATION OF BREAST DISEASES

Investigators: Harry K. Genant, M.D., Edward A Sickles, M.D.,  
Cornelius A. Tobias, Ph.D., Eugene V. Benton, Ph.D.,  
and Kay H. Woodruff, M.D.

INTRODUCTION

1. Objective: The primary objective of this study is to determine the efficacy of the EMI total body scanner in the detection and characterization of benign and malignant diseases of the breast.

We plan to compare the sensitivity and specificity of the EMI total body scanner with two other new imaging modalities: (a) direct radiographic magnification using a micro-focus tube and the single screen, single emulsion Lo-Dose recording system, and (b) heavy particle radiography using the Bevalac facility at the Lawrence Berkeley Laboratory in Berkeley, California. Clinical evaluations will be performed on breast specimens obtained immediately following mastectomy and on patients selected on the basis of clinical findings and conventional mammography.

2. Background:

(A.) Breast carcinoma is currently the most common cause of cancer death in American women, producing over 32 thousand deaths per year in the United States<sup>1</sup>. Periodic clinical examinations (either self-examination or examination by a physician), if performed expertly and regularly, can be expected to detect many breast cancers, but often such tumors do not become palpable until they have metastasized to an extent where cure is no longer possible<sup>2</sup>. Conventional mammographic examinations, including film mammography and xeromammography have proved more useful in the early detection of breast malignancy, especially in women over 40-50 years of age<sup>3,4</sup>. These imaging modalities are not infallible, with a reported false negative detection rate of up to 5 percent<sup>3,5</sup>. Furthermore, in younger women, glandular breast tissue is abundant and often appears uniformly dense with conventional mammographic techniques<sup>4</sup>. These techniques provide little contrast between normal dense mammary tissue and small mass lesions, making detection of occult breast cancer all the more difficult.<sup>4</sup>

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(B.) Computerized tomography provides a unique approach to possible early detection of breast carcinoma. It generates images with high levels of contrast by virtue of its ability to detect very small differences in tissue attenuation coefficients<sup>6</sup>. This technique is rapidly replacing pneumoencephalography in diagnosis of many neurologic disorders<sup>7,8</sup>, and promises to be valuable when applied to other areas of the body<sup>9</sup>. Computerized tomography (CT) scanning is reported to be capable of producing excellent images of breast tumors<sup>9</sup>, but a systematic study of the usefulness of this system in studying breast diseases has not been performed. It has the potential, however, for superior imaging not only of microcalcifications (an important radiographic sign of malignancy, especially in occult breast carcinoma<sup>4</sup>), but also of mass lesions, especially with the use of contrast enhancement techniques. The procedure is easy to perform, and causes minimal discomfort and radiation to the patient.

(C.) Another approach to improving early detection of breast cancer involves the use of direct radiographic magnification using a micro-focus tube. The efficacy of this approach has already been demonstrated in diagnosis of many skeletal disease processes<sup>10,11</sup>, but application to mammography has yet to be accomplished. By taking advantage of the increased resolution provided by small focal spot size, the increased contrast produced by air-gap magnification, and the ten-fold reduction of exposure permitted by the use of the Lo-Dose single screen, single emulsion recording system<sup>12</sup>, imaging of smaller lesions should be possible. This technique promises not only to enhance imaging of microcalcifications but also to delineate small mass lesions not detectable by conventional non-magnification techniques.

(D.) A novel approach to detecting small breast masses is the use of a uniform monoenergetic beam of heavy particles for imaging the breast. The Bevalac facility at the Lawrence Berkeley Laboratory takes heavy atoms such as carbon, oxygen, and neon, strips all the electrons off these atoms, and then accelerates the resultant heavy charged particles to energies of approximately 250 MeV per nucleon<sup>13</sup>. Working in Berkeley, two of the investigators (Drs. Tobias and Benton) have recently developed an imaging system using these heavy particles<sup>14</sup>. It has been found that very small density differences in regions less than 1 cm in diameter can be detected with ease, potentially allowing for early detection and localization of breast carcinoma in cases where the density difference between tumor and normal tissue is too small to be detected by conventional methods<sup>15</sup>. Pilot studies on breast specimens obtained immediately following mastectomy have shown contrast differences between tumor and normal breast tissue much larger than those seen with conventional mammography. (Illustrations to be supplied.) These images are similar in

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contrast but of higher clarity than those reported for proton mammography<sup>16</sup>. Disadvantages of this approach include the limited number of Bevalac facilities, inaccessibility of these facilities to hospitalized or infirm patients, and expense.

3. Rationale: The rationale for the proposed study of the EMI whole body scanner is that small differences in attenuation coefficients within normal and abnormal breast tissue may permit imaging of subtle pathologic changes not detectable by other available techniques. This holds the most promise in allowing earlier detection of breast carcinoma in younger women with dense breasts, in whom conventional mammography is most unreliable. Application of contrast enhancement techniques, which have proved so valuable in study of intracranial neoplasms<sup>9</sup>, may provide for even further sensitivity in early diagnosis of cancer. Our approach will include intensive studies of breast specimens immediately following mastectomy, and examination of patients selected on the basis of clinical findings and conventional mammography. With each patient serving as her own control, comparisons between conventional and experimental imaging systems will be facilitated.

#### SPECIFIC AIMS

We hope to determine the sensitivity and specificity of CT scanning in detection and localization of benign and malignant diseases of the breast. Studies on breast specimens obtained fresh from mastectomy will provide valuable in vitro data on the capabilities, limitations, and dosimetry of the EMI scanner, as well as indicating the need for any necessary design alterations in equipment. This information will be applied to the in vivo study of breast abnormalities in selected patients.

#### METHODS OF PROCEDURE

1. In vitro studies of breast tissue obtained at surgery. Breast specimens obtained immediately following mastectomy will be studied (approximately four per month) by the three new imaging modalities discussed above: (A) CT scanning, under the direction of Drs. Genant and Sickles, (B) direct radiographic magnification, under the direction of Dr. Sickles, (C) heavy particle radiography at the Lawrence Berkeley Laboratory, under the direction of Drs. Tobias and Benton. This will not always be possible since only a limited amount of Bevalac time can be assigned to heavy particle radiography studies. Each specimen will then be cut into sections approximately 1 cm thick, along the plane of section used

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in the CT scan. Photographs will be taken to facilitate precise radiographic/pathologic correlation. Direct radiographic magnification and heavy particle radiography of the sections will also be performed.

Data analysis will proceed as follows: CT scans of breast specimens will be compared visually with the corresponding direct magnification radiographs and heavy-particle radiographs, as well as with routine pre-operative conventional mammograms. Attention will be focused on the ability to detect abnormal masses, microcalcifications, and other radiographic signs of malignancy. These comparisons will be performed blindly and independently by several of the investigators.

Comparisons of the image properties of direct radiographic magnification mammography with those of conventional mammography will be performed. Measurements of modulation transfer function, Wiener spectra, and scattered radiation will provide quantitative comparisons of resolution, noise, and contrast. Studies on the image characteristics of the CT scanner are described elsewhere in this protocol (see proposal by Smith et al.)

All specimens will also be submitted for careful gross and histopathologic examination, under the direction of Dr. Woodruff. Special attempts at correlating imaging studies with pathologic findings will indicate the incidence of detection of breast abnormalities, as well as those of false positive and false negative results. Histopathologic identification of all unknown images visualized by the newer imaging techniques will allow for determination of the specific capabilities and limitations of these methods.

2. In vivo studies in selected volunteer human patients. One hundred paid adult female subjects over 40 years of age will be studied. Age was chosen to minimize radiation effect. Patients will be selected on the basis of (a) clinical findings indicating suspicion of breast malignancy or (b) abnormalities on conventional mammography which suggest the possibility of malignancy. We will especially seek patients with a history of prior unilateral mastectomy for cancer because of the known increased incidence of a second primary carcinoma contralaterally\*, because of minimization of radiation effect if there is known co-existent metastatic disease, and because of presumed increased patient motivation. Informed consent will be obtained. Approximately ten patients will be studied per month.

Conventional mammograms will be obtained on all patients. Each

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patient will then undergo (a) CT scanning of both breasts, (b) direct radiographic magnification mammography using a micro-focus tube and the Lo-Dose recording system (one craniocaudal and one lateral exposure of each breast), and (c) heavy particle mammography at the Lawrence Berkeley Laboratory, if possible (one craniocaudal and one lateral exposure of each breast). Should it be known that a patient will undergo breast biopsy and/or mastectomy, the (pre-operative) CT scan will be performed twice, once before and once after intravenous injection of sodium diatrizoate. Initially a dose of 100 ml of 50% diatrizoate will be injected as a bolus and the CT scan will be obtained 15 minutes later. This arbitrary technique will be modified if indicated by the initial results of the study of contrast enhancement by Korobkin et al., described elsewhere in this program project grant proposal.

The total radiation dose to the breast for all studies is estimated to be approximately 6-8 rads, depending on individual variations in breast size. Dosimetry measurements using thermoluminescent dosimeters in the form of lithium fluoride powder encapsulated in polyethylene cylinders<sup>17</sup> will be performed on the first ten patients in order to accurately determine absorbed radiation dose.

**SIGNIFICANCE**

This study may lead to widespread use of CT scanning in detection of breast carcinoma and other mammary disorders. Should the CT scanner prove capable of detecting, localizing, and characterizing breast carcinoma at an earlier stage than presently possible, at acceptable levels of radiation dose, the clinical course and medical management of this disease may be significantly altered. Breast carcinoma will probably continue to be a common malignancy in American women, but with earlier detection of cancers, prior to development of metastases, its mortality may be greatly reduced.

**COLLABORATIVE ARRANGEMENTS**

Drs. Maurice Galante, Nicholas Petrakis, and Thomas Hunt, of the Department of Surgery, U.C.S.F., will aid in selection of patients with evidence of breast carcinoma and in referral of patients with suspected breast carcinoma.

Dr. Kunio Doi (Department of Radiology, University of Chicago School of Medicine, Chicago, Illinois) will help in the quantitative evaluation of the image properties of the direct radiographic magnification technique. He will help in generating and interpreting the Wiener spectrum data, and in the computer-assisted derivation of modulation transfer functions.

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Dr. Leo Seidlitz, of the Department of Radiology, U.C.S.F., will aid in analyzing thermoluminescent dosimetry results.

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