Quantification of lesion size, depth, and uptake using a dual-head molecular breast imaging system

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A method to perform quantitative lesion analysis in molecular breast imaging (MBI) was developed using the opposing views from a novel dual-head dedicated gamma camera. Monte Carlo simulations and phantom models were used to simulate MBI images with known lesion parameters. A relationship between the full widths at 25%, 35%, and 50% of the maximum of intensity profiles through lesions and the true lesion diameter as a function of compressed breast thickness was developed in order to measure lesion diameter. Using knowledge of compressed breast thickness and the attenuation of gamma rays in soft tissue, a method was developed to measure the depth of the lesion to the collimator face. Using the measured lesion diameter and measurements of counts in the lesion and background breast region, relative radiotracer uptake or tumor to background ratio (T/B ratio) was calculated. Validation of the methods showed that the size, depth, and T/B ratio can be accurately measured for a range of small breast lesions with T/B ratios between 10:1 and 40:1 in breasts with compressed thicknesses between 4 and 10 cm. Future applications of this work include providing information about lesion location in patients for performing a biopsy of site and the development of a threshold for the T/B ratio that can distinguish benign from malignant disease. © 2008 American Association of Physicists in Medicine. [DOI: [10.1118/1.2885371](https://doi.org/10.1118/1.2885371)]

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I. INTRODUCTION

In the last few years, several laboratories have worked to develop dedicated molecular breast imaging (MBI), a technique which uses specialized small field-of-view gamma cameras for the detection of breast cancer.¹⁻⁷ These dedicated cameras have a considerable advantage over conventional gamma cameras because of their minimal dead space at the edge of the detectors. In the absence of this dead space, positioning of the breast directly on the camera is possible, and consequentially spatial resolution is improved with less distance between breast lesions and the detector. In addition, the dedicated detectors, especially those employing solid-state technology, offer superior intrinsic spatial resolution and energy resolution compared to conventional systems.⁸

We have previously reported a sensitivity of 74% for breast lesions <10 mm in diameter in clinical studies performed with a single semiconductor-based gamma camera.⁹ To further improve this sensitivity, we have recently developed a novel dual-head dedicated breast imaging system. This system (Fig. 1) comprises two identical opposing cadmium zinc telluride (CZT) detectors and performs planar imaging of the breast under light compression. Recent clinical studies performed in our laboratory with a dual-head system have shown an increase in sensitivity to nearly 90% for lesions ≤10 mm.^{10,11}

In addition, the simultaneous acquisition of opposing breast views provides the opportunity to quantify lesion parameters such as lesion size, depth to the collimator face, and relative uptake of radiotracer. Determination of these parameters is typically only possible with tomographic imaging

methods. However, in the specialized situation of planar dedicated breast imaging, soft tissue in the breast is compressed to a uniform breast thickness and the separation between opposing detector heads is small. In many cases, uptake in the lesion can be approximated as homogeneous and nearly spherical in shape. These factors allow the use of relatively simple mathematical techniques to determine the lesion size, depth, and uptake with two opposing dual-head planar breast images. Knowledge of these parameters may be important in patient management and in distinguishing benign from malignant lesions.

The objectives of this study were (1) to develop a method for performing quantitative lesion analysis in dual-headed dedicated molecular breast imaging that can determine the size, depth to the collimator, and relative tracer uptake of a lesion and (2) to determine the accuracy with which these parameters can be calculated.

II. MATERIALS AND METHODS

II.A. Monte Carlo simulation

A Monte Carlo simulation program (MCNP5, Los Alamos National Laboratory) was used to simulate the detection of breast lesions with a dedicated dual-head gamma camera. MCNP is a general purpose Monte Carlo code for simulation of particle transport in a user-defined geometry.¹² Use of MCNP by our laboratory to model breast imaging with a single dedicated gamma camera has previously been described.¹³

FIG. 1. Dual-head dedicated breast imaging system comprising two identical opposing CZT detectors.

The geometry of the simulated gamma camera and breast are shown in Fig. 2. This model used the previously developed geometry for a single-head dedicated breast system in order to simplify the simulation. To create pairs of opposing dual-head images with this simulation, the orientation of the breast was rotated 180° in the z direction. The simulated gamma camera was designed to model the LumaGem 3200s (Gamma Medica-Ideas, Northridge, CA), a dedicated breast imaging detector currently used for patient studies in our laboratory. The simulated detector comprised a 96×128 array of CZT elements with dimensions of 1.6×1.6 mm² and thickness of 5 mm. The total active area was 15×20 cm². The simulated lead collimator was a parallel, hexagonal-hole, low energy high-sensitivity collimator with a hole diameter of 2.54 mm, a hole length of 25 mm, and a septal

FIG. 2. Schematic of gamma camera and breast geometry simulated with the Monte Carlo code.

thickness of 0.3 mm. Lead shielding with thickness of 4 mm surrounding the outer surface and underside of the detector was also modeled. The modeled CZT had a density of 5.76 g/cm³ and atomic fraction of Cd_(1-x)Zn_xTe, where $x = 0.1$ and the modeled lead had a density of 11.33 g/cm³.

The simulated breast was a 15×20 cm block of water with a thickness of 4, 6, 8, or 10 cm. This range of thicknesses was chosen to encompass the compressed breast thicknesses measured in patient exams performed in our laboratory with a dedicated dual-head system. The 10th percentile, median, and 90th percentile values for breast thickness in over 75 patients were 4.5, 6.5, and 8 cm for cranio-caudal (CC) views and 4.8, 7, and 8.4 cm for mediolateral oblique (MLO) views.

To determine an appropriate tumor shape for the Monte Carlo model, MBI images of 55 biopsy-proven breast cancers were randomly selected for analysis. Using terminology analogous to the American College of Radiology Breast Imaging Reporting and Data System,¹⁴ the mass shape on MBI was classified as either round, oval, lobular, or irregular. Of the 55 tumors, 49 were determined to be either round or oval in shape, one was lobular in shape (bilobed), and five tumors were irregular with either linear uptake or diffuse radiotracer uptake that did not form a discrete mass. Therefore, we estimate that approximately 90% of the cancers detected with MBI are either round or oval. The size of these round and oval breast cancers, given as the maximum length in three dimensions, was determined from the pathology report following excision of the tumor or mastectomy.

The mean and standard deviation of the three dimensions was determined for each of the round or oval tumors. The range of the mean tumor dimensions was 4–20 mm. In cases where the standard deviation of the three dimensions was less than 10% of the mean, the tumor was assumed to have a spherical shape, otherwise it was assumed to have an ellipsoid shape, where the major axis was the maximum tumor dimension and the minor axis was the minimum tumor dimension. In the 49 round or oval tumors, the ratio of the major axis:minor axis ranged from 1.0 to 2.4. The mean $\pm$ SD of the major axis:minor axis ratios was 1.5 ± 0.3 .

Based on this analysis, the simulations were initially performed using spherical tumors as a first approximation of the tumor shape. Diameters of the spherical tumors varied between 4 and 20 mm, which gave tumor volumes of 33.5–4190 mm³. Additional simulations were performed using tumors in the shape of ellipsoids with the same total volumes as the spherical tumors and major axis:minor axis ratios of either 1.4, 2.0, or 2.4. The depth of the tumors with respect to the collimator face of the lower detector head was varied between 1 cm and (total breast thickness – 1 cm).

Because previous simulations have shown only a minor contribution of scatter from the torso and its organs in the dedicated breast image, an adjacent torso was not modeled in this simulation. Furthermore, our previous studies have demonstrated that when a standard energy window ($\pm 10\%$) is employed, the fraction of detected photons that undergo Compton scattering is less than 15% for detectors with en-

ergy resolutions of 10% or better.¹³ Therefore, the effects of Compton scatter were assumed to be negligible for the purposes of this study.

The radioisotope used in the simulation was Tc-99m, emitting gamma rays with an energy distribution of 142.6 keV for 1.4% of photons and 140.5 keV for 98.6% of photons. For each simulation, the uptake of Tc-99m in the tumors relative to the background breast tissue (T/B ratio) was set to one of three values; 40:1, 20:1, or 10:1. This range of T/B ratios was chosen to represent the degree of uptake that we have observed in over 200 MBI studies performed in patients with breast cancer. Although the T/B uptake of Tc-99m sestamibi in breast tumors was previously reported as 3:1–12:1,¹⁵ comparison of clinical studies with phantom simulations performed using clinically relevant count densities and breast thicknesses suggests that the actual ratio may be higher than this and more on the order of 20:1.¹⁶ Ratios of activity concentration were created by simulating the appropriate number of particles per volume started in each tumor and the breast tissue. For the purposes of simulations performed in this study, radiotracer uptake in the tumors was assumed to be homogenous.

The energy and location of particles captured in the CZT elements were recorded and used to create the simulated breast images acquired with the lower and upper detectors. An energy resolution of 3.8% full width at half maximum (FWHM) at 140 keV, which matched that of the LumaGem system, was simulated by convolving the energy of each particle with a Gaussian blurring function. A standard energy window of $\pm 10\%$ was applied. The number of total particle histories run in each simulation was adjusted to produce a count density of 1020 counts/cm² (26 counts/pixel) in an area of normal breast tissue in the simulated image. This count density corresponds to the median count density obtained in patient studies performed on the LumaGem system in our laboratory.

II.B. Image analysis methods

II.B.1. Diameter measurement

As a lesion moves deeper in the breast or farther away from the detector head, its apparent diameter increases due to the loss of resolution with distance from the collimator face. For example, a lesion closer to the lower detector head appears smaller in the lower detector image than in the upper detector image. Therefore, a geometric mean image of the two opposing images was created to provide a consistent lesion size on which to perform a measurement of diameter for a given breast thickness. Performing the geometric mean essentially places the depth of the lesion in the middle of the breast, at half the total compressed breast thickness.

In order to measure the diameter of each simulated spherical tumor, a relationship between the shape of the pixel intensity profiles through each tumor and the known tumor diameter was developed. The FWHM is typically used to measure the size of an object at a particular distance from the

source. However, the three-dimensional shape of the spherical tumors creates a nonlinear relationship between FWHM and the true diameter.

To derive a relationship between the tumor diameter and the width of the measured count profile, a profile analysis was performed on geometric mean images for breast thicknesses of 4, 6, 8, and 10 cm acquired with a high T/B ratio of 40:1 and with the tumors located 1 cm deep to the lower detector and 3, 5, 7, and 9 cm from the upper detector in the respective images. In each image, four count profiles were obtained across the center of each tumor at angles of 0°, 45°, 90°, and -45°. The count profiles were corrected for background counts by subtracting the minimum value of the profile. The full width of each count profile at 10%, 15%, 20%, 25%, 30%, 35%, 40%, and 50% of the maximum value was measured. Averages of the four angular count profiles were calculated and a second order polynomial fit was used to relate the full width of the count profile at each percentage to the true diameter. The full widths at 25%, 35%, and 50% were selected for use as standard curves relating measured and true diameter for each breast thickness.

II.B.2. Depth measurement

Using equations for attenuation of photons in soft tissue, the depth of the tumor with respect to the lower collimator face was calculated as follows. The counts in the lower detector image are described as N_L in Eq. (1) and the counts in the upper detector image are N_U as given in Eq. (2), where N_O is the number of unattenuated photons, μ is the attenuation coefficient of soft tissue (0.153 cm⁻¹), t is compressed breast thickness, and d is tumor depth. These equations can be solved for N_O and set equal to each other to determine an equation for tumor depth, d , as given in Eq. (3a),

$$N_L = N_O \cdot \exp(-\mu d), \quad (1)$$

$$N_U = N_O \cdot \exp(-\mu(t-d)), \quad (2)$$

$$d = \frac{\mu t - \ln[(N_L/N_U)]}{2\mu}. \quad (3a)$$

Equation (3a) was modified to account for counts only coming from the tumor by subtracting the background counts. Also, a correction was applied to the upper head counts to adjust for possible differences in detector sensitivity. These modifications are shown in Eq. (3b), where T_L and T_U are the sum of counts in an identical region of interest (ROI) placed on the tumor in the lower and upper head images, respectively, and B_L and B_U are the sum of counts in an identical ROI placed in a uniform background breast tissue region of the lower and upper head images, respectively,

$$d = \frac{\mu t - \ln[(T_L - B_L)/((T_U - B_U) \cdot (B_L/B_U))]}{2\mu}. \quad (3b)$$

To facilitate more precise placement of ROIs, images were interpolated by a factor of 10 using a linear interpolation algorithm to resample the images with a pixel size of 0.16×0.16 mm². The linear algorithm calculates the resampled

sampled pixel intensities by examining the neighboring intensities of the original image and integrating them based on their proportional distance from the projected resampling position.

In developing the depth measurement method, it was observed that the measured depth depends on the size of the ROI relative to the size of the tumor. To determine the appropriate size of ROI to use for an accurate depth measurement, ROIs of various sizes were applied to each tumor diameter of 4–20 mm in the images acquired with a T/B of 40:1, tumor depth of 1 cm relative to the lower detector, and breast thicknesses of 4, 6, 8, and 10 cm. A second order polynomial fit was used to relate ROI diameter to the error in the estimate of depth for each tumor diameter. These relationships were used to calculate the ROI size that would give the minimum error in depth as a function of tumor diameter. Using the tumor diameter determined as described above, the appropriate ROI size was determined in order to provide an accurate measurement of tumor depth. This same ROI was also used in measurement of the T/B ratio, described below.

II.B.3. Relative uptake measurement

Using ROI size determined as described above, counts in the tumor and breast background region ROIs from the lower and upper detector images were used to calculate the T/B uptake ratio according to Eq. (4), which takes the ratio of the geometric mean of the tumor regions to the geometric mean of the background regions and corrects for differences in the ROI volumes. In this equation V_{Bkgd} is the volume of the background breast tissue which is the background ROI area multiplied by the breast thickness. V_{Tumor} is the estimated tumor volume calculated by assuming a spherical tumor shape with the previously determined diameter. V_{Tumor} is raised to the power of F , which is a constant of 0.99 that was empirically determined to provide a more accurate measure of the T/B ratio

$$T/B \text{ ratio} = \frac{\sqrt{(T_L \cdot T_U)} - \sqrt{(B_L \cdot B_U)}}{\sqrt{(B_L \cdot B_U)}} \cdot \frac{V_{\text{Bkgd}}}{(V_{\text{Tumor}})^F}. \quad (4)$$

II.B.4. Validation of techniques

After developing the diameter, depth, and uptake measurement methods on Monte Carlo simulated images of spherical tumors with a T/B ratio of 40:1, these methods were validated in other Monte Carlo simulations acquired with lower T/B ratios of 20:1 and 10:1. Additional validation of the methods was performed on phantom simulations of a compressible breast model that was imaged on the dual-head MBI system. The compressible breast phantom was constructed using two compressible 3000 ml saline bags coupled to a water tank. Six lesions with diameters of 6.2, 7.9, 9.9, 12.4, 15.4, and 19.8 mm were simulated using small refillable plastic spheres (Hollow Sphere Set, Data Spectrum Corp., Chapel Hill, NC), positioned between the two saline bags. Water and Tc-99m at T/B ratios of approximately 40:1, 20:1, and 10:1 were placed in the spheres. The actual ratios

in phantom simulations were verified as 37.8:1, 19.0:1, and 9.9:1 by measuring the activity of aliquots from the tumor and background solutions in a dose calibrator.

From geometric mean images, count profiles were generated as previously described for each sphere and each breast thickness. Using the previously derived relationships between profile width and tumor diameter for each breast thickness, an estimate of tumor diameter was obtained from an average of the diameters determined with the 25%, 35%, and 50% full width count profiles.

The calculations of the tumor depth and T/B ratio are dependent upon an accurate measurement of tumor diameter. The equation for calculating depth [Eq. (3b)] is strictly valid only for a point source and does not directly depend on diameter, however, the ROI size used to perform the depth measurement is determined from the previously measured tumor size. The T/B ratio is directly dependent on tumor volume [Eq. (4)], which is calculated using the measured tumor diameter.

Hence, in order to validate the techniques for calculating these parameters without the confounding effects of errors in tumor diameter, they were calculated both with the measured and known true diameters of each simulated tumor. Using both the measured and known tumor diameter and the known breast thickness, the appropriate ROI sizes for minimum error in depth were selected and depth was calculated by applying these ROIs to the upper and lower head images to measure the sum of counts in the tumor and background regions. Using the same ROIs, and calculating the tumor volume with the tumor diameter, the T/B ratio was calculated. Differences in measurements using the true and measured diameters were assessed for statistical significance using a two-tailed paired t test with 95% confidence interval.

To quantify the sensitivity of these measurements to errors in tumor diameter, the calculations for the depth and T/B ratio were performed on a set of Monte Carlo simulated dual-head images after setting the tumor diameter to 1 mm greater and 1 mm less than the known true diameter for each tumor. These images were acquired with 6 cm breast thickness, tumor depth of 2 cm from the lower detector, and a T/B of 40:1.

The expected change in the T/B measurement was calculated by manipulating Eq. (4) as follows. The T/B ratio is inversely proportional to the tumor volume raised to the factor $F=0.99$ and therefore the T/B ratio is inversely proportional to the diameter, d , cubed and raised to the power of 0.99 as shown in Eq. (5). The change in the T/B ratio for a given fraction of the true diameter can thus be calculated as given in Eq. (6), where k is the fraction of the true diameter. For example, if tumor diameter is underestimated by 5%, $k=0.95$, and the change in the T/B is 1.165, or the T/B is overestimated by 16.5%,

$$T/B \text{ ratio} \propto \frac{1}{(V_{\text{Tumor}})^F} = \frac{1}{\left[\frac{4}{3}\pi(d/2)^3\right]^{0.99}}, \quad (5)$$

$$\text{Change in } T/B \text{ ratio} = \frac{1}{(k^3)^{0.99}}. \quad (6)$$

In order to test the effect of detector pixel size on measurements of the tumor diameter, depth, and T/B ratio, validation studies were also performed on images that acquired a larger pixel size. These images were created by downsampling the original images acquired with $1.6 \times 1.6 \text{ mm}^2$ pixels by a factor of 4 to obtain images with a pixel size $3.2 \times 3.2 \text{ mm}^2$.

Thus far, these techniques were developed and validated using spherical models of tumors. To explore the ability of these techniques to be used on tumors with an elongated, ellipsoidal shape, we simulated tumors with the same volumes as the spherical tumors ($33.5\text{--}4190 \text{ mm}^3$) and major axis:minor axis ratios of 1.4, 2.0, and 2.4 to encompass the range of tumor dimensions observed in our clinical studies. Separate simulations of the ellipsoidal tumors were performed with the major axis orientated in the x – y plane and x – z plane, in order to simulate both the CC and MLO views of the tumors. In these simulations, the center of each tumor was placed 3 cm deep in a 6 cm-thick breast and the T/B ratio was 20:1. The same methods developed for measuring the diameter, depth, and T/B ratio with spherical tumors were applied to the ellipsoidal tumors, with the exception that both major axis and minor axis diameters were measured using the CC and MLO simulated views, and the ellipsoidal volume was calculated and used for subsequent T/B calculations.

Last, to illustrate the future application of these quantitation techniques in patient images, measurements of the tumor diameter, depth, and T/B ratio were performed in an example set of MBI images from a patient with breast cancer. The patient was imaged using the dual-head MBI system comprising two LumaGem detectors. Registered lower and upper detector breast images were acquired simultaneously of the breast, first while the breast was positioned for a CC view and then for a MLO view for a total of 10 min/view. Measurements of tumor diameter were compared with those obtained from histological exam and ultrasound. The location of the tumor as determined by imaging with mammography and ultrasound, and the tumor histology and grade were recorded for comparison with measured depth and T/B ratio.

III. RESULTS

III.A. Image analysis results

III.A.1. Tumor diameter results

All measurements of tumor diameter were performed on the geometric mean of the upper and lower detector images. Figure 3 shows an example of the opposing images and the geometric mean image of simulated tumors placed 1 cm from the lower detector (and 5 cm from the upper detector) in a breast with a compressed thickness of 6 cm and a T/B ratio of 40:1. From geometric images obtained at T/B ratios of 40:1, Fig. 4 shows the correlation between the measured full width at 25%, 35%, and 50% of the maximum intensity profiles at various breast thicknesses and true tumor diameter.

FIG. 3. Simulated images of nine tumors $<2 \text{ cm}$ in diameter placed 1 cm from the lower detector head in a 6 cm-thick breast. Shown are (a) the lower detector image, (b) the upper detector image, and (c) the geometric mean of the opposing images.

Using the data presented in Fig. 4, Table I illustrates the average errors in the measurement of tumor diameter in images obtained from Monte Carlo simulations or from phantom studies. Results are listed for tumors that were clearly visible in the geometric mean image and the applicable tumor diameters for each breast thickness and T/B ratio are listed. The diameter measurements were performed on eight tumor diameters in Monte Carlo simulations and six tumor diameters in phantom simulations. Tumors were placed at three tumors depths within the breast, for a total of 24 measurements in Monte Carlo simulations and 18 measurements in phantom simulations for each breast thickness and T/B ratio. The average error in measured diameter was less than 0.4 mm for all Monte Carlo and phantom simulations evaluated in this study. However, with increasing breast thickness and decreasing T/B ratio, the technique is limited to larger tumor sizes as listed in Table I. For example, in a thin breast (4 cm) with high T/B , the technique was able to be applied to tumors $\geq 6 \text{ mm}$ in diameter; in thicker breasts (10 cm) with lower T/B ratios (10:1), the technique was limited to tumors $\geq 10 \text{ mm}$ in diameter because of poor count statistics for tumors smaller than these diameters at the specified T/B ratios.

III.A.2. Depth results

In developing the methodology to measure tumor depth, it was found that the ROI size applied to each tumor must be large enough to include all the counts from the tumor in both the upper and lower detector images. To determine the appropriate ROI size, the error in measured tumor depth was plotted as a function of ROI diameter. Figure 5 shows an example of the effect of different ROI sizes on the estimation of tumor depth for an 8 cm-thick breast. Similar results were obtained for breasts thicknesses of 4, 6, and 10 cm. For each tumor diameter, there is a range of appropriate ROI diameters which produce a low ($\pm 1 \text{ mm}$) error in measurement of tumor depth. The zero crossing of each curve was used to determine the best ROI diameter to use for tumor depth measurement. Figure 6 shows the ROI diameter that produced no error in depth as a function of the true diameter for each breast thickness.

Using both the true and measured tumor diameters, the appropriate ROI sizes were determined and used in the measurement of tumor depth. This allowed an evaluation of the

FIG. 4. Curves relating the measured tumor diameter to true diameter using the full width at (a) 25%, (b) 35%, and (c) 50% of the maximum intensity profile for compressed breast thicknesses of 4, 6, 8, and 10 cm.

errors in measurement of tumor depth per se and the compound effects of errors in tumor diameter on depth measurements. Results for the error in measured depth with both the Monte Carlo and phantom images are shown in Table II. Depth results were averaged from a total of 24 measurements (eight tumor diameters placed at three tumors depths) in Monte Carlo simulations and 18 measurements (six tumor

diameters placed at three tumor depths) performed for each breast thickness and T/B ratio. Using true tumor diameter from the Monte Carlo simulated images, the average error in depth was less than ± 0.5 mm for all breast thicknesses and T/B ratios, except for tumors in a 10 cm-thick breast at a T/B of 10:1, in which the error was 1.6 mm [Table II(a)]. For phantom simulated images, the average error in depth and the standard deviation of the measurements was slightly higher than those performed on the Monte Carlo images, which we believe may be partly attributed to minor shifting of the tumor placement in the compressible breast phantom upon compression. For both phantom and Monte Carlo simulated images, results showing the error in measured depth using the measured tumor diameter in Table II(b) were not significantly different than those obtained using the true tumor diameter.

III.A.3. Relative uptake results

Errors in the measurement of the T/B ratio for Monte Carlo simulations and phantom studies are shown in Table III. Again, the results were averaged from a total of 24 measurements in Monte Carlo simulations and 18 measurements in phantom simulations performed for each breast thickness and T/B ratio. Results in Table III(a) were calculated using a tumor volume derived from the true diameter of the simulated tumors and illustrate the error in the T/B ratio independent of any error in measurement of tumor diameter. For the Monte Carlo studies, results show the average errors in the T/B ratio to be less than $\pm 5\%$ for all breast thicknesses, except at the T/B of 10:1, where the error was nearly -9% at a 4 cm breast thickness. For the phantom studies, the average errors in the T/B ratio were less than $\pm 4\%$ for a T/B of 40:1, but the error increased to up to 16% for a T/B of 20:1 and up to 30% for a T/B of 10:1. Results in Table III(b) were calculated using a tumor volume derived from the measured diameter of the simulated tumors. As can be seen from a comparison of Tables III(a) and III(b), the errors in the measurement of the tumor diameter increase the variability in the estimates of the T/B ratio at all tumor depths and for all T/B ratios.

III.B. Limitations for smaller tumors

Although the diameter, depth, and T/B ratio measurements were performed on Monte Carlo and phantom simulated tumors with diameters of 4–20 mm, the results were only reported in Tables I–V for those tumors that were clearly visible in the images and for which reasonably accurate measurements could be obtained. We have demonstrated in previous simulations of MBI that when using clinically observed count densities, a considerable amount of image noise is present for T/B ratios less than 20:1, which limits the ability to detect sub-10 mm tumors.¹⁶ The count statistics for small tumors and low T/B ratios are further impacted by increasing breast thickness. In this study, it was found that the smallest tumor diameter for which the diameter, depth, and T/B could consistently be measured accurately was 6 mm when either the breast thickness was low (4 cm) or the

TABLE I. Error in measured diameter for geometric mean images obtained by phantom studies and Monte Carlo simulations.

Breast thickness (cm)	Error in measured tumor diameter (mm) Average $\pm$ SD (applicable tumor diameters)				
	$T/B=40:1$ (phantom studies)	$T/B=20:1$ (phantom studies)	$T/B=10:1$ (phantom studies)	$T/B=20:1$ (Monte Carlo data)	$T/B=10:1$ (Monte Carlo data)
4	0.0 ± 0.3 (≥ 6 mm)	-0.2 ± 0.6 (≥ 6 mm)	-0.4 ± 0.5 (≥ 6 mm)	-0.1 ± 0.4 (≥ 6 mm)	0.1 ± 0.4 (≥ 6 mm)
6	-0.2 ± 0.4 (≥ 6 mm)	-0.2 ± 0.3 (≥ 8 mm)	-0.3 ± 0.8 (≥ 8 mm)	0.0 ± 0.5 (≥ 8 mm)	0.0 ± 0.4 (≥ 8 mm)
8	-0.2 ± 0.5 (≥ 6 mm)	-0.1 ± 0.9 (≥ 8 mm)	0.0 ± 0.8 (≥ 10 mm)	-0.2 ± 0.3 (≥ 8 mm)	-0.1 ± 0.5 (≥ 10 mm)
10	-0.1 ± 0.4 (≥ 8 mm)	0.1 ± 0.7 (≥ 10 mm)	-0.2 ± 0.8 (≥ 10 mm)	0.0 ± 0.4 (≥ 10 mm)	-0.1 ± 0.5 (≥ 10 mm)

T/B ratio was high (40:1). The limits for tumor diameters given in Tables I–III demonstrate that the lower limit for applicable tumor diameters increases with greater breast thickness and lower T/B ratio. For tumor diameters below these limits, inconsistent measurements were obtained due to poor count statistics. In some cases a depth was calculated which was outside the region of the breast and the T/B ratio could be underestimated by as much as 50%.

III.C. Dependence of depth and uptake calculations on diameter measurement

Figure 7 shows the effect of a 1 mm underestimation or overestimation of tumor diameter on the T/B ratio. Both measured error and calculated errors [from Eq. (5)] are shown for tumors at a depth of 2 cm in a 6 cm-thick breast. The measured percent change in the T/B ratio closely agreed with that calculated using Eq. (5) and shows that the T/B ratio is highly dependent on accurate measurement of tumor diameter. By comparison, measurement of tumor depth was within ± 1 mm of the true value indicating that the depth is nearly unchanged for small errors in the diameter measurement.

III.D. Effect of pixel size

Using Monte Carlo simulated images, Table IV compares the measured diameter, depth, and T/B ratio for a set of opposing images acquired with tumors located 1 cm deep to the lower detector in a 6 cm-thick breast and with both pixel

sizes of 1.6×1.6 mm² and 3.2×3.2 mm². Measurements of the depth and T/B ratio were performed using both the known true diameters and the measured diameters. For tumors with diameters of 8 mm or greater, the results showed minor changes in the measured depth and T/B ratio for each pixel size, demonstrating that the methods developed for the 1.6×1.6 mm² pixels can be applied to larger pixels as well. However, for tumor diameters less than 8 mm, the diameter measurements were less accurate due to decreased spatial resolution with the larger pixel size, which consequently led to a less accurate measurement of the depth and T/B ratio, as described in the previous section. The simulated 4 mm tumors were unable to be adequately imaged with either pixel size, and therefore, the diameter, depth, and T/B ratio could not be accurately measured.

III.E. Application to ellipsoidal tumors

Table V displays results from measurements on ellipsoidal tumors. The Monte Carlo simulation was used to simulate these ellipsoidal tumors placed 3 cm deep in a 6 cm-thick breast with a T/B ratio of 20:1. All measurements were performed by applying the same methods developed for spherical tumors, except that the diameters of both the major and minor axes were measured and used to calculate the tumors ellipsoidal volume for use in the T/B calculations. The re-

FIG. 5. The error in measured tumor depth as a function of ROI diameter for tumors with diameters of 4–20 mm in an 8 cm-thick breast.

FIG. 6. Curves to determine the appropriate ROI diameter that gives the minimum error in measured depth for tumor diameters of 4–20 mm and breast thicknesses of 4, 6, 8, and 10 cm.

TABLE II. Error in measured tumor depth for pairs of dual-head images obtained by phantom studies and by Monte Carlo simulations using (a) the true tumor diameter and (b) the measured tumor diameter.

		Error in measured depth (mm) using true tumor diameter Average $\pm$ SD (applicable tumor diameters)				
(a)	Breast thickness (cm)	$T/B=40:1$ (phantom studies)	$T/B=20:1$ (phantom studies)	$T/B=10:1$ (phantom studies)	$T/B=20:1$ (Monte Carlo data)	$T/B=10:1$ (Monte Carlo data)
	4	-0.2 ± 4.0 (≥ 6 mm)	-2.1 ± 9.5 (≥ 6 mm)	3.2 ± 12.1 (≥ 6 mm)	0.1 ± 1.4 (≥ 6 mm)	0.1 ± 2.2 (≥ 6 mm)
	6	1.0 ± 4.1 (≥ 6 mm)	0.8 ± 2.7 (≥ 8 mm)	2.6 ± 6.9 (≥ 8 mm)	-0.1 ± 0.9 (≥ 8 mm)	0.2 ± 1.6 (≥ 8 mm)
	8	0.6 ± 3.8 (≥ 6 mm)	-1.8 ± 6.3 (≥ 8 mm)	-2.9 ± 7.9 (≥ 10 mm)	-0.2 ± 1.0 (≥ 8 mm)	0.5 ± 1.3 (≥ 10 mm)
	10	-0.1 ± 5.3 (≥ 8 mm)	-0.5 ± 7.4 (≥ 10 mm)	-3.9 ± 7.4 (≥ 10 mm)	0.0 ± 1.2 (≥ 10 mm)	1.6 ± 2.0 (≥ 10 mm)
		Error in measured depth (mm) using measured tumor diameter Average $\pm$ SD (applicable tumor diameters)				
(b)	Breast thickness (cm)	$T/B=40:1$ (phantom studies)	$T/B=20:1$ (phantom studies)	$T/B=10:1$ (phantom studies)	$T/B=20:1$ (Monte Carlo data)	$T/B=10:1$ (Monte Carlo data)
	4	0.4 ± 4.1 (≥ 6 mm)	-2.1 ± 9.3 (≥ 6 mm)	2.6 ± 9.7 (≥ 6 mm)	-0.3 ± 1.4 (≥ 6 mm)	-0.8 ± 2.4 (≥ 6 mm)
	6	1.1 ± 4.1 (≥ 6 mm)	0.0 ± 3.0 (≥ 8 mm)	1.9 ± 5.1 (≥ 8 mm)	-0.2 ± 1.1 (≥ 8 mm)	0.5 ± 1.5 (≥ 8 mm)
	8	0.5 ± 3.7 (≥ 6 mm)	-1.1 ± 6.7 (≥ 8 mm)	-3.0 ± 6.9 (≥ 10 mm)	0.0 ± 1.3 (≥ 8 mm)	0.9 ± 1.5 (≥ 10 mm)
	10	-0.1 ± 5.5 (≥ 8 mm)	1.5 ± 5.4 (≥ 10 mm)	0.6 ± 2.6 (≥ 10 mm)	0.2 ± 1.4 (≥ 10 mm)	2.0 ± 1.9 (≥ 10 mm)

sults given in Table V are the average and standard deviation of the error in each measurement for six ellipsoidal tumors with minor axis diameters of 8–20 mm.

The results show that minor axis diameter was able to be measured with approximately the same degree of accuracy as for the spherical tumors (Table I). The major axis diameter, however, was underestimated by 1.5 ± 1.4 mm and 2.0 ± 1.8 mm for the ellipsoidal tumors with major:minor axis ratios of 2.0 and 2.4, respectively.

The depth measurements for the ellipsoidal tumors had errors of less than 1 mm and were comparable to the depth measurements performed on the ellipsoidal tumors (Table II).

The depth measurements obtained using the measured major and minor axis diameters were nearly identical to those using the true diameters.

The error in the measured T/B ratio using the true major and minor axis tumor diameters was higher for the ellipsoid tumors than the spherical tumors (Table III), although not statistically significantly different. The T/B ratios obtained using the measured major and minor axis diameters were not significantly different from those obtained using the true diameters. However, there was greater variability in the T/B ratios obtained with measured diameters, as shown by the increase in standard deviation for these measurements. When

TABLE III. Error in measured relative tumor to background ratio (T/B ratio) for pairs of dual-head images obtained by phantom studies and by Monte Carlo simulations using (a) the true tumor diameter and (b) the measured tumor diameter.

		Error in measured T/B ratio (% error) using true tumor diameter Average $\pm$ SD (applicable tumor diameters)				
(a)	Breast thickness (cm)	$T/B=40:1$ (phantom studies)	$T/B=20:1$ (phantom studies)	$T/B=10:1$ (phantom studies)	$T/B=20:1$ (Monte Carlo data)	$T/B=10:1$ (Monte Carlo data)
	4	$2.1 \pm 4.9\%$ (≥ 6 mm)	$-8.3 \pm 10.3\%$ (≥ 6 mm)	$-17.2 \pm 11.0\%$ (≥ 6 mm)	$-4.3 \pm 1.8\%$ (≥ 6 mm)	$-8.9 \pm 2.2\%$ (≥ 6 mm)
	6	$-1.2 \pm 5.0\%$ (≥ 6 mm)	$-10.6 \pm 6.8\%$ (≥ 8 mm)	$-24.2 \pm 11.4\%$ (≥ 8 mm)	$-1.9 \pm 3.0\%$ (≥ 8 mm)	$-3.1 \pm 8.5\%$ (≥ 8 mm)
	8	$-2.8 \pm 5.9\%$ (≥ 6 mm)	$-16.2 \pm 7.6\%$ (≥ 8 mm)	$-25.5 \pm 10.9\%$ (≥ 10 mm)	$-1.6 \pm 3.3\%$ (≥ 8 mm)	$-1.5 \pm 5.5\%$ (≥ 10 mm)
	10	$-3.4 \pm 7.7\%$ (≥ 8 mm)	$-15.9 \pm 8.2\%$ (≥ 10 mm)	$-19.4 \pm 3.2\%$ (≥ 10 mm)	$-5.3 \pm 3.8\%$ (≥ 10 mm)	$-3.6 \pm 6.1\%$ (≥ 10 mm)
		Error in measured T/B ratio (% error) using measured tumor diameter Average $\pm$ SD (applicable tumor diameters)				
(b)	Breast thickness (cm)	$T/B=40:1$ (phantom studies)	$T/B=20:1$ (phantom studies)	$T/B=10:1$ (phantom studies)	$T/B=20:1$ (Monte Carlo data)	$T/B=10:1$ (Monte Carlo data)
	4	$2.8 \pm 8.3\%$ (≥ 6 mm)	$0.3 \pm 14.5\%$ (≥ 6 mm)	$-8.5 \pm 15.6\%$ (≥ 6 mm)	$-0.2 \pm 12.5\%$ (≥ 6 mm)	$-11.4 \pm 9.9\%$ (≥ 6 mm)
	6	$4.0 \pm 13.9\%$ (≥ 6 mm)	$-5.8 \pm 10.8\%$ (≥ 8 mm)	$-17.1 \pm 13.3\%$ (≥ 8 mm)	$-3.8 \pm 10.7\%$ (≥ 8 mm)	$-1.4 \pm 12.9\%$ (≥ 8 mm)
	8	$1.7 \pm 14.2\%$ (≥ 6 mm)	$-12.9 \pm 13.4\%$ (≥ 8 mm)	$-30.2 \pm 16.1\%$ (≥ 10 mm)	$1.9 \pm 8.3\%$ (≥ 8 mm)	$1.7 \pm 12.1\%$ (≥ 10 mm)
	10	$-0.9 \pm 16.1\%$ (≥ 8 mm)	$-15.6 \pm 17.6\%$ (≥ 10 mm)	$-23.7 \pm 7.4\%$ (≥ 10 mm)	$-4.1 \pm 9.9\%$ (≥ 10 mm)	$0.6 \pm 15.6\%$ (≥ 10 mm)

TABLE IV. Effect of pixel size on the measured diameter, depth, and T/B ratio for Monte Carlo simulated images of tumors with a T/B ratio of 40:1 and a depth of 1 cm from the lower detector in a 6 cm-thick breast. Pixel size was (a) 1.6×1.6 mm² and (b) 3.2×3.2 mm².

(a) 1.6×1.6 mm ² pixels						
True tumor diameter (mm)	Measured diameter (mm)	Depth using true diameter (mm)	Depth using measured diameter (cm)	T/B ratio using true diameter	T/B ratio using measured diameter	
20	20.2	1.06	1.06	40.0	38.8	
16	15.6	1.06	1.05	39.9	42.9	
12	11.8	0.98	0.97	40.0	42.0	
10	10.3	1.06	1.07	39.9	36.7	
8	8.3	0.99	1.01	39.7	35.7	
6	6.2	0.99	1.00	40.9	37.1	
(b) 3.2×3.2 mm ² pixels						
True tumor diameter (mm)	Measured diameter (mm)	Depth using true diameter (mm)	Depth using measured diameter (cm)	T/B ratio using true diameter	T/B ratio using measured diameter	
20	19.5	1.06	1.05	39.9	42.9	
16	15.7	1.06	1.05	39.9	42.1	
12	11.4	0.98	0.96	40.0	46.3	
10	9.7	1.05	1.04	39.8	43.5	
8	7.6	0.98	0.98	39.5	45.8	
6	7.5	0.98	1.10	41.0	21.7	

the true tumor diameter was used, the accuracy of the T/B ratio measurement improved as the major:minor axis ratio was increased, which is likely caused by the underestimation in the major axis diameter and thus an underestimation of the tumor volume for the ellipsoidal tumors. As given in Eq. (4), the T/B ratio is inversely proportional to the tumor volume and therefore, when the volume is underestimated, the T/B ratio will increase.

III.F. Application to a patient image

The quantification methods were applied to the clinical dual-head MBI images shown in Fig. 8. In this patient, the breast tumor was excised and the pathology results demonstrated a grade II (of III) invasive lobular carcinoma with a

measured size of $14 \times 13 \times 9$ mm. The tumor diameter measured using ultrasound was 10 mm. Application of the tumor diameter measurement methods for MBI resulted in a measured diameter of 10.8 mm in the CC view and 11.7 mm in the MLO view.

Mammography and ultrasound imaging determined that the tumor was located in the medial lower inner quadrant of the left breast, at the 9 o'clock position, approximately 6 cm from the nipple. With MBI, the compressed breast thickness of this patient was 6 cm in the CC view and 5.5 cm in the MLO view. The measured tumor depth on the MBI images was 1 cm in the CC view and 3.7 cm in the MLO view, relative to the lower detector. These measurements place the tumor in the lower inner quadrant. The measured T/B ratio of this midgrade, lobular cancer was 15.7:1 using the opposing CC views and 12.2:1 using the opposing MLO views.

TABLE V. Error in the measured diameter, depth, and T/B ratio for Monte Carlo simulated images of ellipsoidal tumors with major axis:minor axis ratios of 1.4, 2.0, and 2.4. The T/B ratio was 20:1 and the depth was 3 cm from the lower detector in a 6 cm-thick breast.

	Error in measured diameters, depths, and T/B ratios for ellipsoidal tumors Average $\pm$ SD (for true minor axis diameters ≥ 8 mm)		
	Ellipsoid 1 major: minor=1.4	Ellipsoid 2 major: minor=2.0	Ellipsoid 3 major: minor=2.4
Minor axis diameter (mm)	0.3 ± 0.9	-0.2 ± 0.6	0.2 ± 0.5
Major axis diameter (mm)	0.0 ± 0.9	-1.5 ± 1.4	-2.0 ± 1.8
Depth using true tumor diameter (mm)	0.0 ± 0.6	-0.6 ± 1.5	0.2 ± 0.8
Depth using measured tumor diameter (mm)	0.0 ± 0.6	-0.6 ± 1.5	0.2 ± 0.8
T/B ratio using true tumor diameter (% error)	$-3.6 \pm 1.6\%$	$-4.5 \pm 1.3\%$	$-4.7 \pm 1.4\%$
T/B ratio using measured tumor diameter (% error)	$-6.8 \pm 16.3\%$	$4.0 \pm 12.7\%$	$-0.9 \pm 7.7\%$

FIG. 7. Effect of a 1 mm underestimation or overestimation of tumor diameter on the T/B ratio. Both measured error and calculated error [from Eq. (5)] are shown for tumors at a depth of 2 cm in a 6-cm thick breast.

IV. DISCUSSION

This study showed that opposing images from a novel dual-head dedicated gamma camera design can effectively be used to measure the lesion size, depth, and relative uptake of a radiotracer in molecular breast imaging. The major potential uses for these lesion quantification methods include (1) providing appropriate knowledge to the clinician that will aid in performing a nuclear medicine-guided biopsy and (2) application to patient studies in order to correlate the degree of uptake to malignancy and tumor grade and establish a threshold for discriminating between benign and malignant lesions. In addition, this quantitative tool will be useful to assess the

efficacy of neoadjuvant therapy on tumor function and size in breast cancer patients and in future comparative studies of alternative radiotracers for breast imaging.

For MBI studies conducted in our laboratory, subsequent biopsy of the lesion is typically performed with needle biopsy under the guidance of ultrasound or with stereotactic x-ray mammography. Our current protocols dictate that patients with additional suspicious lesions imaged with MBI but not seen with mammography or ultrasound will undergo additional diagnostic mammography, ultrasound, or magnetic resonance imaging (MRI) exams as necessary in order to visualize and biopsy the lesion. However, cases can occur in which the lesion seen on MBI still remains occult on other modalities such as mammography and ultrasound and a MRI-guided biopsy is not always possible (in patients who are claustrophobic or with cardiac pacemakers, for example) or cost effective.

Previous studies have examined the use of combined stereotactic biopsy devices using gamma cameras and a radioactive localization needle^{17,18} or combined with x-ray mammography to perform a biopsy.^{19,20} Coover *et al.* also reported on the use of a biopsy technique for dedicated breast imaging employing radioactive markers.²¹ Quantification methods for MBI as reported here that aid in localizing the lesion by determining its depth to the collimator combined with the use of a radioactive localization needle would provide sufficient information to perform a biopsy of the site under the guidance of a MBI image while the breast remains in its compressed imaging position. Performing a biopsy using depth information could be performed with a dual-head MBI system in which the detectors can move independently from compression paddles containing holes for inserting biopsy needles. This way, the breast compression can be maintained and either gamma camera can be moved out of the way in order to perform a biopsy through the thinnest part of the compressed breast.

Using dual-head quantification methods developed in this study, it was found that the diameter, depth, and T/B ratio can be accurately determined for a range of small breast tumors with T/B concentration ratios between 10:1 and 40:1 and for compressed breast thicknesses between 4 and 10 cm, which correspond to uptake ratios and breast thicknesses observed in our patient studies. This level of quantitative lesion analysis was never before possible with planar images from a single view. Previous scintimammography studies have attempted to quantify lesion uptake by using ROI analysis on the single-head planar breast image in order to correlate uptake with factors such as tumor size, histology, and grade.²²⁻²⁵ However, due to the loss in spatial resolution with distance from the collimator face and the attenuation of the gamma radiation by breast tissue, the apparent size and uptake of a lesion changes with distance from the detector. Therefore, because simple ROI methods do not account for lesion size, distance of the lesion from the detector, or breast thickness, these uptake ratio measurements from a single view are inaccurate and are a poor reflection of the true ratio of uptake in the tumor versus normal breast tissue. Besides the methods presented here for ROI analysis with dual head

FIG. 8. Example images from a clinical dual-head MBI study of the left breast showing upper and lower detector CC and MLO views.

MBI, accurate quantification methods have also been developed by Williams *et al.* using a dual modality x-ray mammography and gamma camera system.²⁶ This technique, however, relies on the detection of the lesion with mammography, which is not always possible, especially in women with dense breast parenchyma.

With single head images alone, both the tumor size and uptake are merely subjective estimates obtained from visual inspection by the radiologist. Two previous studies using a subjective scale to rank tumor uptake have shown positive correlations between the degree of uptake and tumor size and have also suggested that invasive ductal carcinomas have higher uptake than invasive lobular carcinomas.^{9,27} The use of two opposing views for interpretation aids the radiologist in making a better estimate of size and uptake and allows more accurate quantification methods as presented here.

This study showed that accurate measurement of the tumor diameter is critical for the accurate measurement of the T/B ratio. The accuracy of the diameter measurement could likely be improved by using more than four intensity profiles through the tumor. In this study, spherical tumors were used. For nonspherical lesions, profiles could be performed in multiple directions using both the CC and MLO breast views to obtain a three-dimensional estimate of tumor size. This method may more accurately describe the tumor volume for use in the T/B ratio calculation.

The application of these techniques to a patient image example simply demonstrates the feasibility of using such methods to aid in lesion quantification in the clinical setting. The tumor diameter measurements obtained with MBI were compared to those obtained at surgical excision and with ultrasound in order to offer some degree of validation of this measurement in patients. While the measured MBI diameter closely agrees with the pathology and ultrasound measurements in the example, the diameter of functional radiotracer uptake in the tumor may not always be consistent with that measured by anatomical imaging techniques such as ultrasound. Furthermore, future work will be necessary to develop a method for validating the measured tumor depth and T/B ratio in patients. It should also be noted that in this initial study, radiotracer uptake in the tumors was homogeneous and any effects of self-attenuation of the tumors were assumed to be negligible. These two factors will likely require greater attention when applying the methods presented here to patient images.

This initial analysis reported on the development of lesion quantification methods for a specific dual-head dedicated gamma camera with 1.6 mm CZT elements and high sensitivity collimator. Although the equations derived here are for this particular system, similar methods could be used to develop equations for other camera systems. It was shown that the methods to determine the diameter can be affected by changes in the pixel size if the pixel size is large relative to the tumor size for the system to adequately resolve the tumor. Changes in collimation will also change the resolution of the detector system, which alters the apparent size of the

tumor with distance. Therefore, the algorithms developed here will need to be modified for use with other systems and collimators.

It is not necessary to have a dual-head gamma camera system to employ these quantification methods, but it is necessary to visualize the lesion in two opposing breast views. Use of the dual-head system provides simultaneously acquired, registered opposing views of the breast, which saves imaging time in addition to increasing the sensitivity of MBI techniques.¹⁰ Typical acquisition times of 10 min/view allow the collection of simultaneous CC and inverse CC views, and simultaneous MLO and inverse MLO views of one breast in approximately 20 min or 40 min for a bilateral study.

V. CONCLUSION

In this study, methods were developed to use the opposing views from a dedicated dual-head gamma camera to measure the lesion size, depth, and T/B ratio in planar molecular breast imaging. Validation of the methods performed on Monte Carlo and phantom simulations showed that the size, depth, and T/B ratio can accurately be measured for a range of small breast tumors with T/B ratios between 10:1 and 40:1 in breasts with compressed thicknesses between 4 and 10 cm. Future applications of this work include providing information about lesion location in patients for performing a biopsy of site and the development of a threshold for the T/B ratio that can distinguish benign from malignant disease.

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