

Research Article

FMTVDM*-BEST[®] (B.E.S.T.[®]) Breast Cancer Imaging Test (BBCIT[®]): An Enhanced Quantitative Method for Performing Molecular Breast Imaging (MBI)

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Abstract

Background: Molecular breast imaging (MBI) uses nuclear isotopes to “qualitatively” look at the delivery and uptake by breast tissue. Clinicians then make interpretations based upon these images. Such qualitative image interpretation has limited the applicability of MBI. MBI “quantitative” imaging using enhancement of regional blood flow differences (RBFs) augmenting isotope delivery and uptake differentiating these RBFs and metabolic differences [Breast Enhanced Scintigraphy Test (B.E.S.T.) Imaging] has been shown to enhance diagnostic measurement of cancer and pre-cancerous tissue.

Methods: In an effort to develop a “quantitative” method to differentiate breast calcium, normal breast tissue, and inflammatory changes of the breast, pre-cancers and breast cancer, this study set out to answer three fundamental questions. First, what are the fundamental differences between these four tissue types? Second, is there a method, which can briefly “enhance” these differences? Finally, can these differences be accurately “quantified?” Following the development of this method [FMTVDM-BEST[®] (B.E.S.T.[®]) Breast Cancer Imaging Test] B.E.S.T.[®] Breast Cancer Imaging Test (BBCIT[®]) was used to image 195 people and to compare these results with mammography and tissue pathology.

Results: In the first part, of this study, 10 women were compared using both MIRALUMA (currently employed MBI) and BBCIT[®]. No statistical difference was seen between MIRALUMA and BBCIT[®] and women with “normal” breast tissue. Women with inflammatory breast changes showed a statistically significant ($P < .05$) increase in isotope measuring RBFs and metabolism using BBCIT[®]. This difference was even more significant ($P < .005$) in women with breast cancer where there are even greater RBFs and metabolism.

In part two of the study 195 people were studied using BBCIT[®]. The results were compared with biopsy specimens. BBCIT[®] demonstrated an exponential increase in tracer uptake as tissue transitioned from calcium deposits to normal breast tissue to inflammatory changes of the breast to precancerous tissue changes with the greatest measured activity occurring in breast cancer proper. When maximal count activity (MCA) was compared between these tissue types, there was a statistically significant ($P < 0.001$) difference between normal breast tissue and inflammatory changes of the breast (ICB), between ICB and pre-cancerous atypia (A), and between A and cancer (CA).

Conclusion: Enhanced delivery and uptake of isotope was statistically significantly increased using BBCIT[®] compared with the currently employed MIRALUMA Molecular Breast Imaging (MBI) approach, which is a non-enhanced qualitative method. This statistically enhanced delivery and uptake of isotope, once “quantified,” (BBCIT[®]) allows for the “quantitative” differentiation of breast tissue, including earlier detection of changes in breast cancer and the ability to “quantitatively” measure if treatment of breast cancer, pre-cancers and inflammatory breast changes is or isn’t working.

Keywords: FMTVDM[®]; B.E.S.T. Imaging[®]; Breast cancer; Breast inflammation; Theranostics; Quantification; AI

Abbreviations

FMTVDM: The Fleming Method for Tissue and Vascular Differentiation and Metabolism

Introduction

The detection of breast cancer is traditionally based upon the finding an anatomic and/or physiologic abnormality. Anatomic detection is made by breast self-examination by the patient or the physician, mammography (radiographic detection), ultrasound evaluation of a lump/mass, mammography, computed tomography (CT) and/or magnetic resonance imaging (MRI). These methods all depend upon the detectability of an anatomic mass large enough to be detected based upon the physical limits imposed by the test being employed. These tests are all qualitative with “inattention blindness”, reader bias and problems with sensitivity (the ability to find disease when present) and specificity (the ability to exclude disease when absent). They provide yes, the disease is present or no the disease is

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absent responses to a disease process, which is a continuum (Figure 1) these tests are not diagnostic and require tissue confirmation.

Physiologic detection of breast cancer is made either by using positron emission tomography (PET) imaging with or without CT/MRI (anatomic) or single photon emission computed tomography/planar (SPECT/planar) imaging again with or without CT/MRI; referred to as Molecular Breast (MBI) Imaging. Qualitative MBI imaging, like the anatomic methods described have the same limitations, introducing errors in both sensitivity and specificity and failing to provide a method for measuring transitional tissue changes (Figure 1).

Technetium (Tc-99m; Tc) based isotopes, primarily Sestamibi and Tetrofosmin, have been used with MBI [1,2] primarily as an adjunct to mammography. The delivery and uptake of these isotopes are dependent upon (1) the delivery of the isotope to the cancer; regional blood flow differences (RBFs) within breast tissue and (2) the presence of living tissue with active mitochondria; metabolism. More than 90% of Sestamibi is taken up [3] by mitochondria in an energy-dependent manner. This uptake increases with the number of mitochondria present [4-6] and the functional activity [7] of these mitochondria. Inflammatory cells [8] take up Sestamibi to a greater extent than normal cells but to a lesser extent than cancer cells. The same appears to be true for Tetrofosmin. This uptake demonstrates the ability of viable cells to maintain a transmembrane energy potential gradient [9,10] and has been used in cardiac imaging to demonstrate ischemic, infarcted [11-14] and viable myocardium. As such, it has also been used to determine Adriamycin-induced [15] cardiotoxicity following chemotherapy.

In addition to the mitochondrial activity, the amount of Sestamibi taken up at the cellular level is also dependent upon its delivery to the region of the body being imaged; the delivery of which occurs via the bloodstream; i.e. the tissue regional blood flow (RBF). This regional blood flow is different (RBF) depending upon the tissue itself. Regions of inflammation and cancers, which produce angiogenic factors [16-18] consequently have a greater vascularity (RBF), increasing the delivery of Sestamibi to those tissues compared with tissues of lesser vascularity; hence, a shift, which can be enhanced (infra).

Like breast cancer, the ability to find coronary artery disease (CAD) is dependent upon the same anatomic (angiography, intra-vascular ultrasound) and/or physiologic (SPECT or PET) imaging tests. The importance of changing RBFs to increase the ability to unmask CAD has previously been described [19-24] as has the importance of enhancing those RBFs [25,26].

Recognizing that MIRALUMA neither quantifies nor enhances RBFs, the first part of this study “quantitatively” compares the resting (non-enhanced) MIRALUMA results with “quantitatively enhanced RBFs” B.E.S.T. Imaging. In the second part of the study, using this “enhanced quantitative” B.E.S.T. Breast Cancer Imaging Test (BBCIT[®]) method, another 195 individuals were studied using BBCIT[®] comparing the results to tissue biopsy specimens.

Methods

Subject Enrollment

Two hundred five individuals (201 women, 4 men) between the ages of 27-88 were studied, including 181 Caucasians, 5 Hispanics, 17 African Americans, and 2 people of Mediterranean origin.

During the first part of the study, 10 women with either an abnormal mammography or a detectable lump on physical examination were studied comparing their tissue pathology with MIRALUMA MBI and BBCIT[®] results.

During part two of the study, 191 women and 4 men (with detectable breast lumps) were studied comparing results of tissue biopsy with BBCIT[®]. Of these participants, 58 women were seeking additional information regarding personal breast disease concerns and 133 had breast lumps and/or abnormal mammograms. Women were excluded from these initial studies if they were taking hormone replacement therapy, were pregnant, or were breastfeeding. IRB approval is not required for molecular breast imaging (MBI).

The quantification employed for BBCIT[®] does not change the patient risk of imaging or produce a risk beyond qualitative imaging performed in cardiac patients, which does not require IRB approval; only patient consent. All subjects signed institutional consent forms prior to undergoing MBI.

Imaging Protocols

MBI (AKA MIRALUMA): Subjects were asked to fast overnight in preparation for the study. Approximately 15-20 minutes prior to the study a 20-gauge intravenous catheter was placed in the right arm or in the left arm if the right breast was the breast in question. As shown in Figure 2 (upper panel), 25 to 30 mCi (925 to 1110 MBq) of technetium-99m Hexakis 2-methoxyisobutylisocyanide (Sestamibi) was administered intravenously at the 4-minute mark, with image acquisition beginning 6 minutes later at the 10-minute mark. The patient was placed in the prone position on top of a 6-inch foam pad designed to enhance the comfort of the patient while improving lateral breast imaging.

Each side of the 6-inch pad has breast inserts held in place by Velcro that were independently removed to allow each breast to be positioned through the openings for better imaging without breast compression. As shown in Figure 2, image acquisition was started 10-minutes into the study; 6-minutes following isotope injection. All lateral images were acquired with the patient in prone position; the anterior (BrAS) image was acquired with the patient sitting.

Breast image acquisition and reconstruction were performed using a Siemens orbiter SPECT camera with 75 photomultiplier tubes using a 64 x 64 matrix using a low-energy, high-resolution collimator providing 3.4 mm resolution. The images were acquired with the SPECT camera in stationary (planar) position. Cardiac redistribution of Sestamibi (Figure 3) is seen when the 5-minute image was compared with 60-minute cardiac imaging results.

Initial “qualitative” MBI results were first displayed in black-and-white (Figure 4A) format. These were then converted to a blue-green display followed by quantification of isotope RBFs and metabolism (Figure 4B). The greatest regional blood flow and metabolism is then determined. While Figure 4B is an example of an individual following B.E.S.T. Imaging (BBCIT[®]) the same method was used for MIRALUMA MBI subjects.

B.E.S.T. imaging (BBCIT[®]) MBI: Individuals underwent identical preparations for imaging and quantification as they did for the MIRALUMA MBI. The only difference being that prior to “quantification” individuals received a “stressing” agent (Figure 2) to enhance RBFs and delivery of isotope based upon tissue RBFs and metabolism.

Quantification of MIRALUMA and B.E.S.T. imaging (BBCIT)[®] MBI results: MCA Following image reconstruction and display of each breast image, regions-of-interest (ROIs) were obtained and the ROI with greatest MCA was determined. All readings and determination of MCAs were made without knowledge of clinical, mammographic, or pathologic information.

Tissue specimens: Histopathologic information was obtained for all but 58 of the individuals studied. Tissue samples were obtained using one or a combination of ductoscopy, fine needle aspiration, or open biopsy per surgeon decision and were interpreted by board certified pathologists without knowledge of the imaging results. Tissue samples were interpreted as normal, inflammatory (evidence of leukocytes), atypia (with increasing order of cellular change progressing from hyperplasia to metaplasia/atypia to ductal carcinoma in situ) and Breast cancer.

Statistical Analysis

The histopathologic assessment of tissue specimens were compared with the “quantitatively” measured maximum count activity (MCA) in addition to other parameters not reported here. Descriptive statistics of measured MCAs included mean \pm standard deviations and confidence intervals (CIs) for the mean. Group differences were confirmed using 2-tailed t-tests to determine statistically significant differences between MIRALUMA MBI and B.E.S.T. Imaging (BBCIT)[®] MBI defined as P values \leq 0.05. Graphic representation of the means and raw data comparisons for the histopathologic categories are shown.

Results

During the first part of the study, ten women were studied comparing the MCAs obtained using both MIRALUMA and B.E.S.T. Imaging (BBCIT)[®] MBI with tissue results. Four women had normal breast tissue without noted abnormalities, 4 had inflammatory changes, and 2 had breast cancer. Table 1 and Figure 5 shows no statistical difference between the two “normal” groups, with MIRALUMA having MCAs of 107.5 ± 21.9 and B.E.S.T. [®] having MCAs of 125.5 ± 31.5 .

In women with breast inflammation, MIRALUMA had a statistically lower ($P < 0.05$) MCA of 184.0 ± 19.2 compared to that seen with B.E.S.T. [®] Imaging where the MCA was 228.8 ± 24.0 . The differences between MIRALUMA and B.E.S.T. [®].

Imaging were even greater ($P < 0.005$) for women with breast cancer, where “quantification” revealed MCAs of 282.5 ± 14.8 and 442.0 ± 5.7 respectively.

In part two of the study, 195 people including 4 men and 191 women, were studied. No differences in outcomes were found based upon age, race, or sex.

The “quantification” of B.E.S.T. Imaging (BBCIT)[®] MBI demonstrates a transitional increase in RBFs and metabolism from normal to cancerous tissue as measured and graphically depicted in Figure 6. The “quantified” differences in mean \pm standard deviations based upon tissue types are shown in Table 2.

The “measured” B.E.S.T. Imaging (BBCIT)[®] MBI for individuals with normal breast tissue ($n = 88$) ranged from 80 to 202, with an average value of 145.0 ± 29.1 . The 95% CI for normal breast tissue was 139 to 151. Individuals with inflammatory changes ($n = 77$) had MCAs ranging from 130 to 298, with an average of 218.0 ± 40.3 and

a 95% CI of 209 to 227. There were 15 individuals with cellular atypia who’s MCAs ranged from 209 to 333, with an average value of 307.7 ± 29.3 . The 95% CI for people with atypia was 292 to 323. Patients with breast cancer ($n = 15$) had a 95% CI of 399 to 491, with an average MCA of 445.3 ± 83.3 and a range in values from 270 to 594. Breast cancers in this study ranged from 4 mm to 2 cm in diameter, with the average size being 8 to 10 mm.

Figure 7 shows the further graphic distribution of tissue results with the inclusion of precancerous cellular atypia. When analyzed for differences between these four types of tissue, there was a statistically significant difference between each successive tissue type, including (1) normal and inflammatory tissue ($p < 0.001$ level), (2) inflammatory tissue and cellular atypia ($p < 0.001$ level), and between (3) cellular atypia and cancer ($p < 0.001$ level).

Discussion

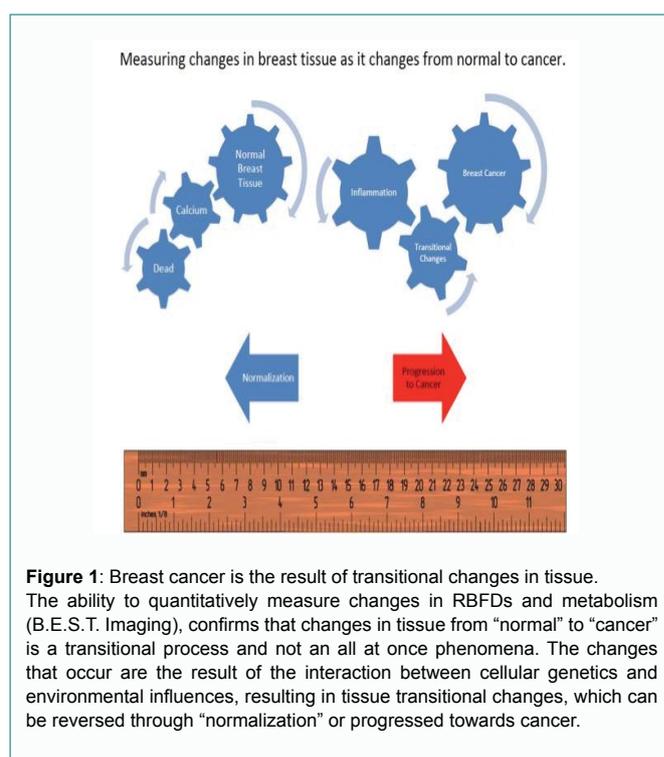
MIRALUMA was introduced with the potential to improve diagnostic detection of breast cancer. My friend Dr. Iraj Khalkhali who introduced MIRALUMA and I was first met during the SNM conference in Toronto in 2001 [27] where Dr. Dooley and I first presented the B.E.S.T. Imaging method I was developing. Iraj’s first words to me after the presentation were “my god I knew there was a way, I just didn’t know how.” Dr. Khalkhali had introduced the era of MBI. What he hadn’t introduced was the critically needed ability

Table 1: Quantification of MIRALUMA and B.E.S.T. imaging (BBCIT)[®] MBI.

	Normal Breast Tissue	Inflammatory Breast Changes	Breast Cancer
MIRALUMA	107.5 ± 21.9	184.0 ± 19.2	282.5 ± 14.8
B.E.S.T. [®]	125.5 ± 31.5	228.8 ± 24.0	442.0 ± 5.7
P level	$p > 0.05$	$p \leq 0.05$	$p \leq 0.005$

Table 2: B.E.S.T. Imaging (BBCIT)[®] MBI tissue differentiation.

	Normal Breast Tissue	Inflammatory Breast Changes	Cellular Atypia	Breast Cancer
MCA	145.0 ± 29.1	218.0 ± 40.3	307.7 ± 29.3	445.3 ± 83.3



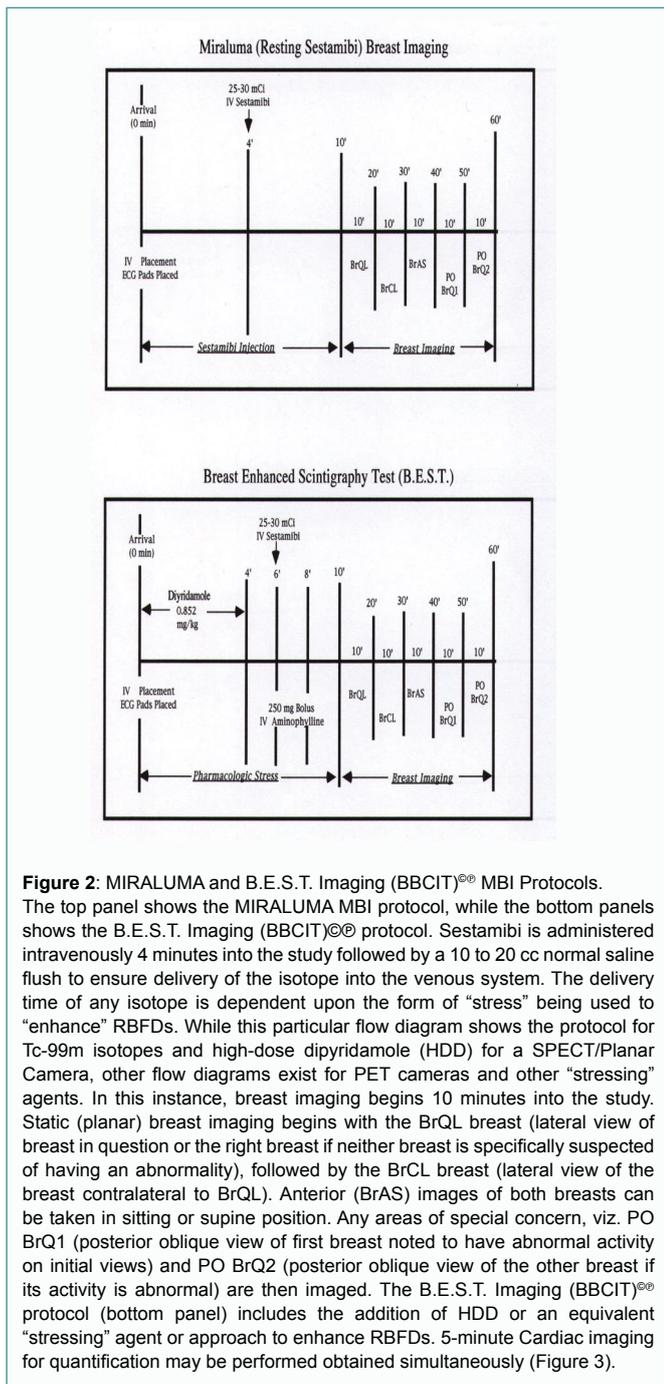


Figure 2: MIRALUMA and B.E.S.T. Imaging (BBCIT)[®] MBI Protocols. The top panel shows the MIRALUMA MBI protocol, while the bottom panels shows the B.E.S.T. Imaging (BBCIT)[®] protocol. Sestamibi is administered intravenously 4 minutes into the study followed by a 10 to 20 cc normal saline flush to ensure delivery of the isotope into the venous system. The delivery time of any isotope is dependent upon the form of “stress” being used to “enhance” RBFs. While this particular flow diagram shows the protocol for Tc-99m isotopes and high-dose dipyridamole (HDD) for a SPECT/Planar Camera, other flow diagrams exist for PET cameras and other “stressing” agents. In this instance, breast imaging begins 10 minutes into the study. Static (planar) breast imaging begins with the BrQL breast (lateral view of breast in question or the right breast if neither breast is specifically suspected of having an abnormality), followed by the BrCL breast (lateral view of the breast contralateral to BrQL). Anterior (BrAS) images of both breasts can be taken in sitting or supine position. Any areas of special concern, viz. PO BrQ1 (posterior oblique view of first breast noted to have abnormal activity on initial views) and PO BrQ2 (posterior oblique view of the other breast if its activity is abnormal) are then imaged. The B.E.S.T. Imaging (BBCIT)[®] protocol (bottom panel) includes the addition of HDD or an equivalent “stressing” agent or approach to enhance RBFs. 5-minute Cardiac imaging for quantification may be performed simultaneously (Figure 3).

to “enhance” the metabolic and RBFs present in different tissue types AND the ability to “quantitatively” measure those differences (FMTVDM; B.E.S.T. Imaging[®]) to make it clinically useful.

During part one of the study we compared MIRALUMA with B.E.S.T. Imaging (BBCIT)[®] MBI (aka B.E.S.T. Imaging[®]). Women who had normal breast tissue showed almost identical results using either method, indicating that once “quantified” using FMTVDM[®] there were no significant RBFs or metabolic changes to unmask using B.E.S.T. Imaging in individuals with “normal” tissue.

However, once tissue changes from being “normal” to tissue, which demonstrate changes in metabolism and regional blood flow, the ability of FMTVDM; B.E.S.T. Imaging to enhance and measure

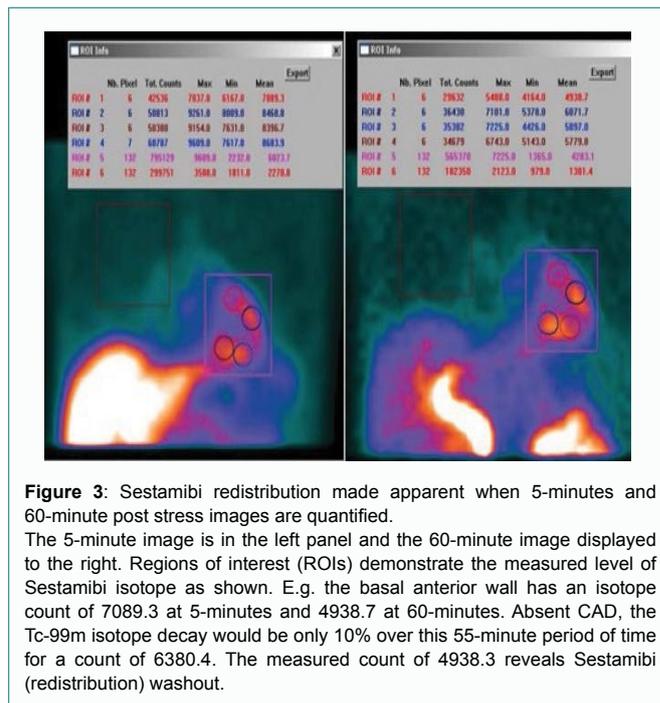


Figure 3: Sestamibi redistribution made apparent when 5-minutes and 60-minute post stress images are quantified. The 5-minute image is in the left panel and the 60-minute image displayed to the right. Regions of interest (ROIs) demonstrate the measured level of Sestamibi isotope as shown. E.g. the basal anterior wall has an isotope count of 7089.3 at 5-minutes and 4938.7 at 60-minutes. Absent CAD, the Tc-99m isotope decay would be only 10% over this 55-minute period of time for a count of 6380.4. The measured count of 4938.3 reveals Sestamibi (redistribution) washout.

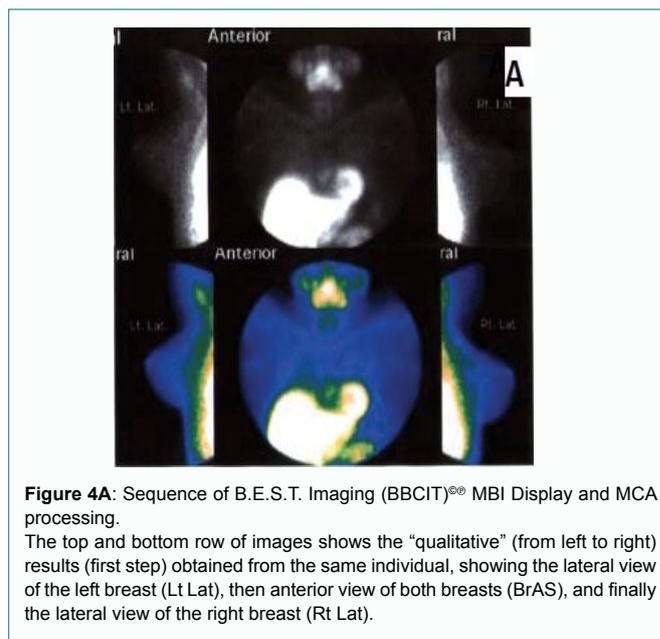


Figure 4A: Sequence of B.E.S.T. Imaging (BBCIT)[®] MBI Display and MCA processing. The top and bottom row of images shows the “qualitative” (from left to right) results (first step) obtained from the same individual, showing the lateral view of the left breast (Lt Lat), then anterior view of both breasts (BrAS), and finally the lateral view of the right breast (Rt Lat).

those differences becomes dramatic and clinically significant as demonstrated here.

This ability of B.E.S.T. Imaging (BBCIT)[®] MBI (aka B.E.S.T. Imaging[®]) to enhance delivery of isotope for uptake, imaging and quantification, increases exponentially with transitional changes in tissue and their associated changes in RBFs and metabolism.

During part two of the study, B.E.S.T. Imaging quantitatively defined differences in tissue based upon these metabolic and RBFs, differences which are statistically significantly different between the various tissue types. Figure 6 shows that the process of tissue differentiation itself follows an exponential increase in both RBFs and metabolism as measured by B.E.S.T. Imaging[®]; an increase which is most pronounced with cellular atypia and cancer [28,29]. This increase is expected given the increased vascularity (angiogenesis) promoted by

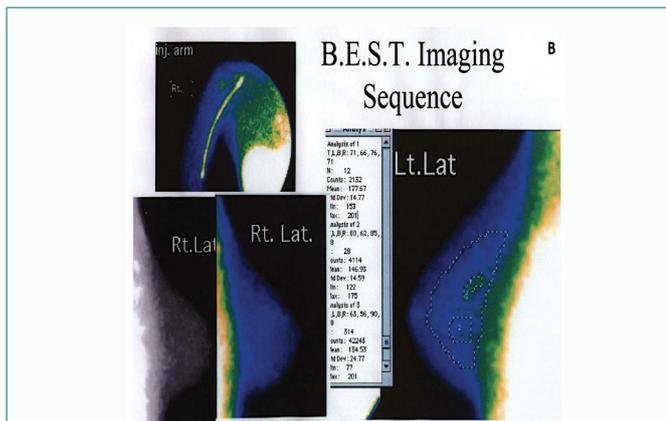


Figure 4B: Sequence of B.E.S.T. Imaging (BBCIT)® MBI Display and MCA processing (cont).

The initial injection of the isotope can be seen in the upper left panel. Immediately below this are the “qualitative” component obtained for the right breast in the lateral position, showing first the black and white display and subsequent blue-green display. In the far right image, “quantification” of the image is performed. Three specific regions of interest (ROIs) are shown and MCA measurements are shown. Region 1 represents a smaller ROI in the upper-middle breast, with an MCA of 201. This ROI is linear and surrounds a milk duct. The second ROI, immediately below the first has an MCA of 175. The third and final ROI includes the entire breast, incorporating both the first and second ROIs. Consequently, the MCA of the third ROI includes the first region with the greatest MCA of 201.

cancer growth factors as well as the increased mitochondrial activity present in cancer cells.

One cancer with an MCA measurement of 270 clearly fell within the MCA range for “inflammatory” tissue further emphasizing the importance of looking at cancer as a transitional disease progressing from normal tissue. It may also reflect the overall immunologic response of the body to the early changes occurring during the development of cancer. On further inspection of this individual, the lymph nodes were negative and the tumor had little evidence of angiogenesis. It was surgically removed, with no additional radiation therapy or chemotherapy recommended to the patient by her oncology team.

The importance of the immunologic/inflammatory responses to disease in the human body present in both heart disease [30] and cancer cannot be overemphasized as the body is responding to changes, which it is trying to control. The cellular participants in these immunologic processes in tumors include inter alia natural killer cells, cytokines, and interleukins.

Just as individuals do not go from having zero heart disease to needing a bypass operation, so too as in also there is a natural progression from normal breast tissue through transitional changes to breast cancer, resulting from a variety of factors, which influence breast tissue. B.E.S.T.® enhancement and measurement of any isotope, be it one that uses SPECT/planar or PET imaging, makes it possible to measure these changes in tissue and monitor those changes over time, whether they be the result of natural transition or in response to treatment itself.

Although not all regions of inflammatory changes are destined to become cancer, these regions may represent regions at greater risk of becoming a cancer, subsequently needing closer monitoring to determine whether they are progressing towards or away from the development of a cancer. Clearly, the sooner a cancer is detected, the

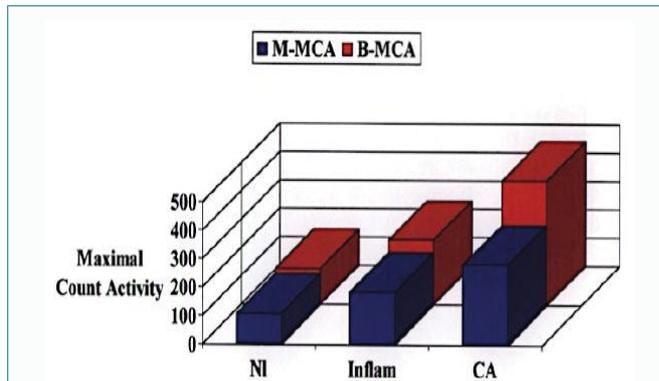


Figure 5: The results of 10-women studied using both MIRALUMA and B.E.S.T.

Imaging (BBCIT)® MBI Protocols.

A comparison of the “quantification” of 10-individuals studied using MIRALUMA (M-MCA in blue) and B.E.S.T. (B-MCA in red) Imaging (BBCIT)® MBI. The “quantified” results were almost identical for those with normal breast tissue, where there are essentially no RBFDs to be enhanced. Individuals with inflammatory changes in breast tissue showed statistically significantly greater delivery and uptake of isotope using B.E.S.T.® Imaging. These differences became even greater in individuals with breast cancer. These mean ± standard deviation MCAs, shown in Table 1 are statistically significant.

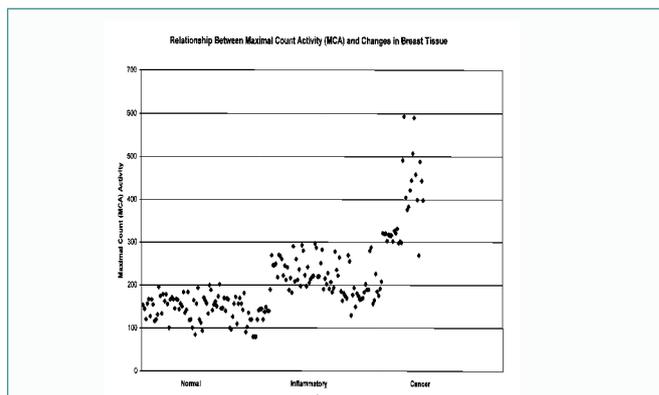


Figure 6: Graphic representation of the results of maximal count activity (MCA) in individuals with normal, inflammatory tissue, and breast cancer following B.E.S.T.® MBI.

B.E.S.T. Imaging (BBCIT)® MBI MCAs are plotted against tissue results for normal, inflammation, and breast cancer. These differences display a transitional (Figure 1) continuum as RBFDs and metabolic changes increase progressing from normal to breast cancer.

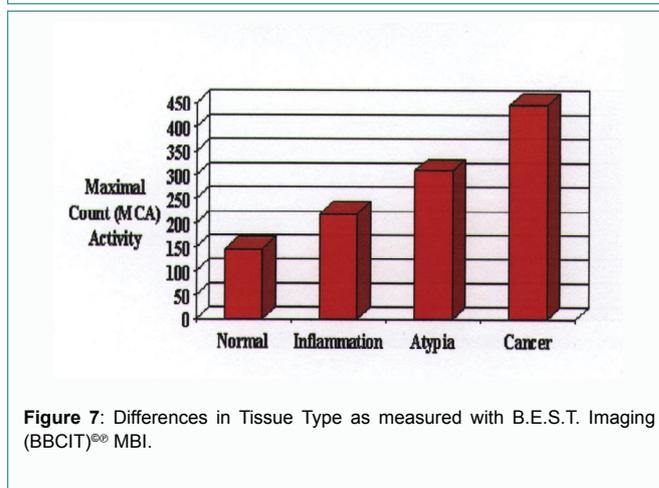


Figure 7: Differences in Tissue Type as measured with B.E.S.T. Imaging (BBCIT)® MBI.

greater the likelihood of successful treatment. The ability to measure differences in tissue also means that the results of treatment can be monitored with successful treatment reducing B.E.S.T.® Imaging measurements while treatment failure would result in increased B.E.S.T.® Imaging measurements; saving time, money and potentially lives.

In addition to the quantified B.E.S.T.® Imaging results, the enhanced delivery of isotope provides an advantage for the “qualitative” interpretation of what is seen by the diagnostician. This enhanced delivery of isotope can only improve the “qualitative” appearance of what is seen, adding additional useful information for interpretation. For example, ductal carcinoma in situ appears more tubular in character, following the path of the milk ducts (Figure 4A and 4B), whereas breast cancers appear more spherical or dendritic in character. This too is entirely consistent with what would be expected and with what is seen with B.E.S.T.® Imaging.

Pre or early cancerous changes like ductal carcinoma in-situ (DCIS) cells and tissue still demonstrate some of their original cellular qualities (e.g., contact inhibition), resulting in more linear growth along the milk ducts. However, once these cells have changed further, they no longer obey contact inhibition and subsequently grow into surrounding tissue, producing the more spherical or dendritic appearance within breast tissue. These changes in appearance may therefore provide further useful information when evaluating the quantitative changes measured using B.E.S.T.® Imaging.

Conclusion

Prior efforts to detect breast cancers using MIRALUMA MBI have been limited due to the inability of MIRALUMA to either enhance the delivery of isotope using RBFs and metabolism OR to measure these differences. B.E.S.T.® Imaging can both enhance the delivery of isotope by taking advantage of these metabolic and RBFs AND measure those differences allowing us to differentiate tissue types based upon those measurements.

Just as there are no absolute cut off values for having too high a LDL cholesterol level, so to on the continuum of tissue transition from “normal” to “cancer” there are no absolute cut offs as these transitions occur. The results show ranges for each of these tissue types and the direct ability to measure and monitor the progression or regressions of these transitional changes occurring with tissue; including for B.E.S.T.® Imaging, Breast Tissue.

B.E.S.T.® Imaging provides the FIRST and ONLY patented method for measuring these changes in RBFs and metabolism seen in tissue, using either SPECT/Planar or PET Imaging, increasing our ability to detect and monitor treatment of not only Breast Cancer but of precancerous changes where an even greater potential for treatment is possible.

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