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Independent Study Validating FMTVDM Measurements of Breast Cancer and Transitional Tissue Changes with Confirmation of Gompertz Function & Laird Model

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ABSTRACT

Background: *A quantitative molecular breast imaging (MBI) utility patent, previously validated at experienced MBI centers was independently tested for clinical application at non-experienced centers.*

Methods: *Using the utility patent, forty-four regions of interest were analyzed and compared with the clinical data of 12-women with transitional breast changes.*

Results: *Centers without prior expertise can easily utilize this quantitative method to measure changes in women's breast tissue. These measured changes provide earlier opportunities to treat tumor-induced angiogenesis and follow the changes in tumor growth predicted by Gompertz-Laird-Folkman.*

Conclusions: *Quantitative MBI allows differentiation of tissue types through measurement of enhanced regional blood flow and metabolic differences. These differences not only provide enhanced understanding into the growth processes and limitations of tumor genesis, but open new treatment opportunities to improve patient outcomes.*

Summary Box

What is already known:

1) *Diagnostic and treatment making decisions for cancer are primarily made using qualitative image interpretation.*
2) *There is a transitional process through which tissue must pass to transition from non-cancerous to cancerous tissue.*
3) *This transitional process is associated with changes in tissue metabolism and regional blood flow.*

New findings

1) *The ability to measure these changes in regional blood flow and metabolism does not require extensive training or expertise, but can be accomplished using FMTVDM with current nuclear cameras.*
2) *These measured transitional changes, demonstrate dissimilar growth rates of tissue as expressed by their differences in regional blood flow and metabolism.*
3) *These differences are sigmoidal in character and provide new insight into the growth rates of cancer and precancerous tissue.*

Clinical impact

1) *The ability to measure these changes in regional blood flow and metabolism,*
   a) *Makes possible the ability to diagnose the transitional changes in tissue prior to the actual completion of tissue transition into cancer,*
   b) *Makes it possible to measure the impact of treatment upon these changes in tissue, be it cancerous or the transitional changes toward cancer on an individual patient-specific basis - saving time, money and potentially lives -, and*
   c) *Confirms the changes in tissue growth postulated by Gompertz and Laird.*

Keywords: *FMTVDM, Breast Cancer, Tumor genesis, Transitional Changes, Gompertz Function, Laird Model, Angiogenesis.*

INTRODUCTION

Qualitative imaging for screening and diagnostic purposes have proven to have little value in women with dense breasts and according to the Canadian National Breast Screening Study [1], provided no survival benefit for women in general. Accordingly, efforts to quantify changes in tissue associated with cancer and inflammation, have resulted in the patented development of a method for quantitatively measuring changes in regional blood flow and metabolism, associated with these different types of tissue [2].

A fundamental consequence of cellular change from expected (normal) cells to breast cancer can be measured using quantitatively calibrated nuclear imaging cameras, followed by enhancement of regional blood flow differences resulting from cellular metabolic changes. This change can be quantified to do more than merely determine that someone does or doesn't have breast cancer. Such measurement allows the patient to be placed on the continuum of tissue change [3].

Following more than 1000 women and men already studied using FMTVDM, an independent site was selected, which had no prior experience in molecular breast imaging (MBI). The site utilized the protocol established [2], to determine if FMTVDM could be employed by centers with minimal training. In the process of affirming this, the outcome data revealed the Gompertz function of cellular differentiation and growth.

METHODS

Patient enrollment: Twelve women, all previously identified as having breast irregularities, volunteered to undergo FMTVDM testing, the results of which were compared with the information already known about the extent of breast changes. Each woman signed an informed consent to undergo nuclear imaging per FMTVDM protocol as approved by the diagnostic center. All personal identifying information was redacted to protect patient identification and as such all data available for public access is provided in this manuscript.

FMTVDM: Prior to imaging, the nuclear technologist, who was familiar with cardiac imaging, but unfamiliar with MBI, calibrated the Siemens' Orbiter according to patent instructions.

Patients arrived in the overnight fasting state and were prepared for imaging with placement of an intravenous catheter through which a vasodilator was given, followed by the imaging isotope as previously described [4].

Patient records: Patients provided *inter alia* detailed medical records, including prior biopsy results, mammography results, family history of cancer, any prior false positive or false negative (FPFN) results from prior testing, smoking history, current medications, a diagnosis of dense breasts.

Measurement of Maximal Count Activity: An individual with no prior medical or technical training, received instructions on how to draw regions of interest (ROI) around the acquired breast images and obtain the measured scintillation activity used for diagnosis. The ROIs and results were obtained without knowledge of patient history.

RESULTS

The diagnostic information obtained from these 12-women included 44-regions of interest based upon imaging and patient medical records/information. This included one woman who smoked and another woman taking hormone treatment. Four (one-third) had breast implants and four (one-third) had dense breasts. Only one of the women with dense breasts had breast implants. Four of the women (one-third) had incorrectly been told she had breast cancer, two of which had dense breasts and two who did not.

Table one shows the specific details for each region of interest measured, along with the patient number and breast involved. The maximal count activity (MCA) for the region measured is shown, along with tissue information, the presence or absence of breast implants, dense breasts and false positive (FP) mammography results.

Table1. *Patient data and diagnostic information*

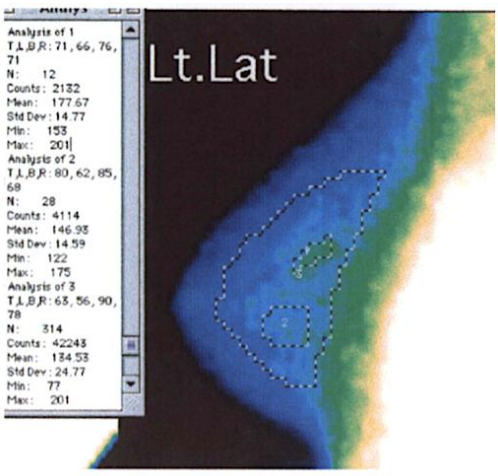
Initial-Breast	MCA	Tissue Data	Other
1-R	54	Lumps	Implants, Not Dense
1-L	74	Lumps	Implants, Not Dense
2-R	91	No CA	Nothing reported
3-L	92	No CA	Breast Implant
4-R	103	None CA Lumps	?, Breast Implant (Right Only)

5-R	142	Breast Lumps-Not CA	No, FP, smoker
2-L	143	No CA	Nothing reported
3-L	144	No CA	Breast Implant
6-L	146	Irregularities	Dense Breasts, Implants
7-R	154	Cysts	Dense Breasts
5-R	156	Breast Lumps-Not CA	No, FP, smoker
3-R	158	No CA	Breast Implant
8-L	158	No CA	Dense Breasts, FP
9-L	160	No CA	Dense Breasts, FP
10-R	163	No CA	FP
11-R	167	No CA	Nothing reported
10-L	171	No CA	FP
4-L	173	Non-CA Lumps	Breast Implant, Taking HT
7-R	178	Cysts	Nothing reported
1-L	180	Lumps	Implants, Not Dense
11-L	184	No CA	Nothing reported
7-L	184	Cysts	Dense Breasts
9-R	185	No CA	Dense Breasts, FP
10-R	186	No CA	FP
2-R	191	No CA	Nothing reported
10-L	194	No CA	FP
8-L	201	No CA	Dense Breasts, FP
9-L	203	No CA	Dense Breasts, FP
5-L	204	Breast Lumps-Not CA	No, FP, smoker
9-R	213	No CA	Dense Breasts, FP
8-R	222	No CA	Dense Breasts, FP
3-L	232	No CA	Breast Implant
8-L	237	No CA	Dense Breasts, FP
3-R	238	No CA	Breast Implant
1-R	245	Lumps	Implants, Not Dense
6-L	259	Irregularities	Dense Breasts, Implants
7-L	264	DCIS	DCIS, Dense Breasts
12-R	270	Not tested yet	?
6-R	290	CA with marker left	Dense Breasts, Implants
4-L	297	Lumps	?
12-R	348	Not tested yet	No Implants, DB-?
12-L	396	Breast Cancer Dx	No Implants, DB-?
6-R	417	CA with marker left	Dense Breasts, Implants
12-L	444	Breast Cancer Dx	No Implants, DB-?

DB = Dense Breasts (Yes, No, ?=Uncertain), FP=incorrect mammogram, HT=Hormone Therapy

An example of images and measurements obtained at a nuclear imaging lab with experience in MBI and the results obtained in this independent laboratory without prior experience are shown in figure 1.

(Top) – Experienced Center



(Bottom) – Inexperienced Center

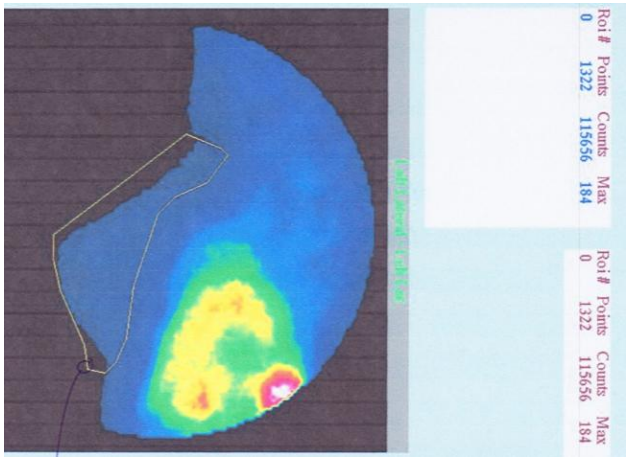


Figure1. *Images and MCA values obtained at both an experienced (top) and inexperienced (bottom) laboratory.*

The resulting measured MCA values are plotted in figure 2 along with the associated changes in tissue. The results reveal a sigmoid function for tissue change across the spectrum from metabolically inert material through expected (normal) breast tissue, through changes in inflammation and tumor development. When the individual components are compared, the changes in MCA measured growth rates resulting from metabolism and regional blood flow, reveal changes in growth rate; including a deceleration in growth rate later in the curve.

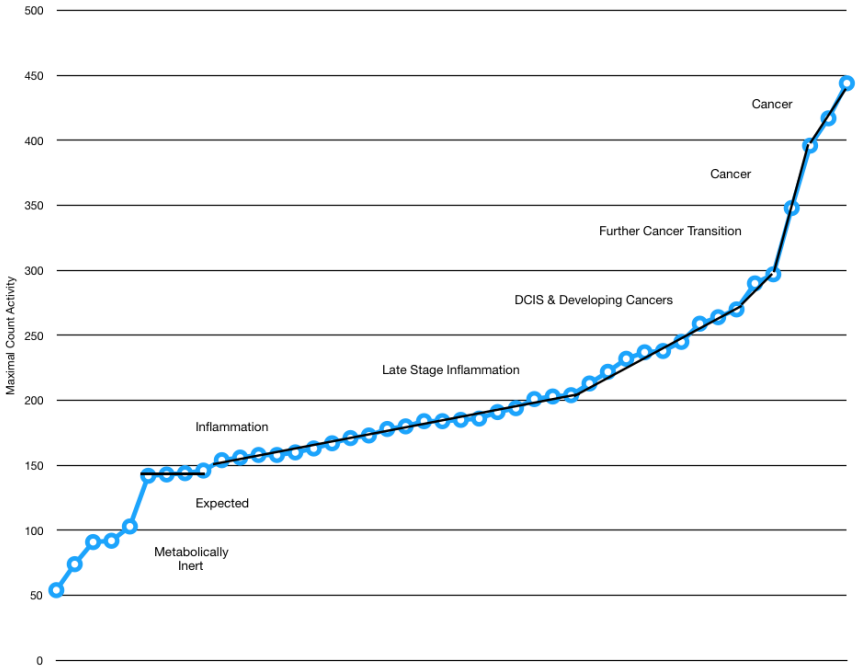


Figure2. *FMTVDM measurements consistent with Gompertz Function and Laird Model*

DISCUSSION

While the sample size was relatively small, it provided more than adequate information to prove the utility of FMTVDM. First, could non-trained individuals perform the necessary components of the patent, to (a) correctly quantitatively calibrate the nuclear camera used, (b) sequentially perform FMTVDM, and (c) utilize the nuclear camera to quantify changes in tissue based upon enhancement techniques differentiating tissue based upon regional blood flow differences and metabolism.

The function of performing a diagnostic test is to discern which individuals require treatment and which do not. To effectively do that, we would argue that a diagnostic test needs to do more than merely distinguish between the two ends of the disease spectrum (normal vs.

cancer). The test needs to be able to differentiate the transitional changes, which occur as the tissue changes from normal to cancer.

To determine if FMTVDM is capable of such differentiation, women were selected with known intermediate (transitional) status. These women did not have normal breasts (free of any abnormalities) as we have classically defined breast tissue. Instead, they had known irregularities in their breast tissue, the types of irregularities, which would typically result in women undergoing testing. These women had irregularities (lumps, cysts) and/or represented women with dense breasts. They also represented women with breast implants, which has become an area of increasing concern, given recent information regarding implants and associated anaplastic large cell lymphoma.

While the appearance of imaging results were not as eloquent as those obtained in centers with MBI training, the calibration of the nuclear cameras and the ability to quantify the tissue based upon drawn ROIs, demonstrated that the utility patent makes possible accurate assessment of breast tissue health independent of human skill or qualitative interpretation – thereby removing the human error element.

In this group of women, multiple ROIs were obtained matching the medical information available provided by the women including tissue, false positive (FP) mammograms, use of hormone therapy, smoking (of which there was only one), and family history. This provided 44 data points to look for transitional changes. Of great interest, was the graphic representation of changes in regional blood flow and metabolism associated with changes in tissue.

While Gompertz, originally described a mathematical model addressing human mortality, Laird later applied this concept to tumor growth models [5]. In this model, both Gompertz and Laird proposed that accelerated tumor growth models would be associated with several phases of development. The first, almost horizontal process would be associated with unrestricted growth. A period of time, where the increase in nutritional support and growth would be relatively unrestrained.

This unrestrained component of growth, we believe would also be associated with a response by the body, recognizing a change, which the immune system would respond to. While it is not obvious that this process would be associated with a clear visual change in the cells themselves, what would be obvious is the body's response to that; viz. an inflammatory process. This period of virtually unlimited growth is seen in the inflammation stage as shown in figure 2.

A later stage of inflammation, associated with an acceleration of tumor growth appears to suggest that sufficient changes have occurred, such that the body's immunologic system appears to have failed to keep the tumor growth in check, with the tumor having developed sufficient metabolic change and enhanced blood flow with nutrients, to increase growth rate [3].

During these inflammatory stages, the prominent microscopy evidence of tissue transitional change, will be the inflammatory process first discussed by Folkman in 1974 [6].

Following these stages of development, the prominent tissue finding will be the inclusion of abnormally appearing cells (mitotic function, lack of growth inhibition, etc.). The continued accelerated growth rate does not continue indefinitely. Ultimately, the blood supply and nutritional support limits the rate of tumor growth and as seen in the later part of figure 1, the change in metabolism and regional blood flow as measured, slows.

Both Gompertz and Laird, described tumor growth as a sigmoid function, which for breast cancer can bee seen in the developmental stages shown in figure 2. The demonstration of this growth process and the ability to measure it, provides not only confirmation of Gompertz and Laird, but opens the possibility of potential treatment options addressing regional blood flow differences resulting from angiogenesis induced by tissue metabolic changes resulting from the interactions between genome and environmental influences [2].

CONCLUSIONS

This investigation demonstrated the ability of the utility patent, FMTVDM, to perform as expected. Absent experience in MBI, individuals without specialized training were able to quantitatively calibrate a nuclear camera and measure regional blood flow and metabolic tissue differences following enhanced tissue differentiation. These measurements demonstrated and confirm the sigmoid change in tissue-tumor growth proposed by both Gompertz in 1825 and Laird in 1964. By measuring these transitional states, we will be

able to accurately differentiate tissue changes earlier and potentially provide new treatment options focusing on angiogenesis and the inflammatory process precipitated by the cellular changes, which occur early in the cycle of tumor growth.

DECLARATIONS

Ethical Approval and Consent to Participate and Consent for Publication:

All participants underwent FMTVDM following a discussion and signing of witnessed institutional informed consent, which included consent for use and publication of results. IRB and IC covered under original licensure agreement.

Availability of Supporting Data

All patient identifier information was redacted. All applicable data is included with manuscript. Additional information is available for recognized institutions upon approval.

Competing Interests

FMTVDM utility patent issued to first author. The first author has no other potential COI. The remaining three authors have no COI.

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