CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

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STUDY TITLE: Efficacy of Digital Breast Tomosynthesis (DBT) in Addition to Standard 2-Dimensional Mammography in Evaluating Extent of Disease in Newly Diagnosed Breast Cancer Patients

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PROTOCOL SUMMARY

Protocol Number/Title	CASE 6117 Efficacy of digital breast tomosynthesis (DBT) in addition to standard 2- dimensional mammography in evaluating extent of disease in newly diagnosed breast cancer patients
Study Phase	N/A
Brief Background/Rationale	The proposed project aims at impacting a large set of population of women with newly diagnosed breast cancer. One in every eight women is diagnosed with breast cancer in their lifetime (10). The study aims at comparing the role of DBT in addition to standard 2-D mammograms in all new breast cancer patients to assess for improved detection of the extent of the cancer and additional imaging findings that can impact surgical planning and treatment. Given the significance of the study, this may change the standard of care and practice at our institution.
Primary Objective	The primary objective of the study is to measure the frequency with which DBT alters the surgical plan. Only positive findings, like an additional site of cancer or DCIS (findings requiring surgical intervention), will be taken into account when estimating the frequency of changes to surgical management.
Secondary Objective(s)	Secondary Endpoint(s)
Exploratory Objective(s)	1.To measure the frequency and nature of additional findings like atypical pathology (atypical ductal/lobular hyperplasia, papilloma, LCIS) found on DBT. 2.To identify variables on 2D (e.g. dense breasts, architectural distortions, non-calcified masses) that might predict which patients would benefit from DBT. 3.To measure the proportion of patients undergoing additional work-up following the DBT, and the subset of these patients with benign findings (i.e. False Positives).
Sample Size	Enrollment goal - 150 Age - 25-85 years , gender - female
Disease sites/Conditions	Breast Cancer
Interventions	3dimensional tomosynthesis mammogram

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals

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1.0 Introduction

1.1 Background / Rationale

Currently, only MRI is occasionally used to evaluate the extent of disease in some cancer patients, based on age, breast density and pathology subtype of the breast cancer. It is a sensitive, but relatively expensive, time consuming test given the additional work up (second look ultrasounds and biopsies) required for findings noted on the MRI. This adds to both the diagnosis cost and time to treat. It also helps in assessing chemotherapy response and surgical treatment planning.

Our goal is to evaluate the efficacy of DBT in a similar fashion to study its role in cancer extent evaluation, finding additional ipsilateral and contralateral cancers, assess for multicentric and multifocal disease and study the role in post chemotherapy treatment planning. This is an easily accessible, readily available, time efficient, cost-friendly modality which may prove useful in providing additional information in all new breast cancer patients, since MRI is performed only in a select group of patients. This may prove specifically helpful in patients with non-calcified masses and architectural distortion. In a recent study on DBT, cancers that manifested as architectural distortion at diagnosis included a higher percentage of invasive lobular carcinomas (20%) (11). It may also lead to better mass margin assessment, tumor size and presence of satellite lesions. It is also a useful tool in evaluating the contralateral breast, especially since breast MRI is not performed in every new breast cancer patient at our institution.

2.0 Objectives

The primary aim of the study is to study the efficacy and additional role of digital breast tomosynthesis (DBT) for patients with a new diagnosis of breast cancer. In the current clinical practice at our institution, standard 2-dimensional (2-D) mammograms (DM) are performed as standard of care to evaluate the extent of disease in patients with new diagnosis of breast cancer. DBT (colloquially referred to as a 3-dimensional mammogram) is only occasionally performed, at the discretion of the breast radiologist to further evaluate the findings of the 2-D mammogram. Recently published data shows a greater efficacy of DBT with increased cancer detection and a reduced call back rate for screening mammography (1-4). Chudgar et al assessed MR extent of disease for cancers detected on DBT versus DM alone (5). Additional studies evaluated role of DBT in cancer detection and tumor size assessment in comparison to other diagnostic modalities (6-8), specifically Mariscotti et al assessed its role in characterizing invasive lobular cancers (9).

Our hypothesis is that DBT may provide additional information to evaluate the extent of disease, including possible multifocality and multicentricity and additional findings including margin assessment and tumor size that would aid in staging a new breast cancer patient. This would impact surgical planning and improve patient outcomes. DBT is a relatively inexpensive test; in comparison to breast MRI which is the alternative study performed to evaluate extent of disease in selected new breast cancer patients. One of the reasons that a breast radiologist may recommend a breast MRI for a new breast cancer patient is if the patient has dense breast tissue on mammography. Performing DBT in these patients may improve the mammographic information about the extent of disease. Also, all the previously recently published studies were performed using different vendor versions of DBT other than Siemens used at our site.

2.1 Primary Objective

The primary objective of the study is to measure the frequency with which DBT alters the surgical plan to mastectomy versus lumpectomy. Only positive findings, like an additional site of cancer or DCIS (findings requiring surgical intervention), will be taken into account when estimating the frequency of changes to surgical management.

2.2 Secondary Objective(s)

Secondary Objectives include:

1. To measure the frequency and nature of additional findings like atypical pathology (Atypical ductal/ lobular hyperplasia, papilloma, LCIS found on DBT.
2. To identify variables on 2D (e.g. dense breasts, architectural distortions, non-calcified masses) that might predict which patients would benefit from DBT.
3. To measure the proportion of patients undergoing additional work-up following the DBT, and the subset of these patients with benign findings (i.e. False Positives).

3.0 Study Design

A prospective cohort blinded study will be performed on new breast cancer patients detected at our Breast centers at Main campus and Beachwood family health center between May 2017 and August 2019. The patients assigned a BIRADS 5 category at the time of diagnosis and all new diagnosed breast cancer patients, will undergo a separate 2-D plus DBT in addition to the standard 2-D mammogram performed at our institution at Main campus and Beachwood Family health center. The new breast cancer patients will be scheduled for the mammogram after diagnosis at the time of surgical appointment. The radiologist reviewing the tomosynthesis images will be separate and blinded from the radiologist who reviewed the initial 2-D mammogram. The following pertinent data will be collected, including number of additional lesions, size of the lesion, margins of the lesions, percentage of biopsy rates, cancer detection rate, high risk lesion detection rate, lesions resulting in excisional biopsy, lesions changed to mastectomy, time to treat, false positive pathology. The principal investigator and key personnel will periodically review all the new patients on a weekly basis. The first 150 patients acquired during the study time period will be evaluated to assess for their imaging findings and compared to the initial standard diagnostic mammogram workup.

3.2 Number of Subjects

Approximately 150 subjects will be enrolled in this trial.

4.0 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

1. New diagnosis of breast cancer
2. New diagnosis if a previous breast cancer patient with negative surgical margins
3. Age limit: 25-85 years

Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.
1. Male patients
2. High risk benign lesions as the primary pathology diagnosis
3. Patients under 25, over 85

4.1 Inclusion of Women and Minorities
Women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through the Cleveland Clinic and will be provided a study number by contacting the study coordinator listed on the cover page.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

6.0 DATA SAFETY AND TOXICITY COMMITTEE

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

7.0 DATA SAFETY AND MONITORING PLAN

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

8.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

8.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

9.0 REGULATORY CONSIDERATIONS

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

10.0 WRITTEN INFORMED CONSENT

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

11.0 SUBJECT DATA PROTECTION

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

12.0 RETENTION OF RECORDS

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.0 AUDITS AND INSPECTIONS

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

The primary objective of the study is to measure the frequency with which DBT alters the surgical plan. For this objective, the proportion of subjects with a change in surgical plan will be calculated and its 95% Confidence Interval (CI) constructed. Logistic regression models will be used to identify variables on 2D that are predictive of patients who would benefit from DBT. The dependent variable in the models will be change/no change in surgical plan, and the independent variables will be lesion and breast characteristics. Holm's method will be used to control the family-wise type I error rate. McNemar's test will be used to compare the findings on MRI and DBT.

Sample Size Justification:

A 95% CI for the proportion of patients with changes in their surgical plan attributable to DBT can be constructed with width of +/- 8% or tighter with 150 patients.

REFERENCES

1. Caumo F, Bernardi D, Ciatto S, et al. Incremental effect from integrating 3D-mammography (tomosynthesis) with 2D-mammography: increased breast cancer detection evident for screening centres in a population-based trial. Breast 2014;23(1):76–80.
2. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology 2013;267(1):47–56.
3. Skaane P, Bandos AI, Gullien R, et al. Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and tomosynthesis in a

population-based screening programme using independent double reading with arbitration. Eur Radiol 2013;23(8):2061–2071.

4. Rafferty EA, Park JM, Philpotts LE, et al. Assessing radiologist performance using combined digital mammography and breast tomosynthesis compared with digital mammography alone: results of a multicenter, multireader trial. Radiology 2013;266(1):104–113.

5. Chudgar AV, Conant EF, Weinstein SP, et al. Assessment of disease extent on contrast-enhanced MRI in breast cancer detected at digital breast tomosynthesis versus digital mammography alone. Clin Radiol 2016; 71(9):889-95.

6. Mercier J, Kwiatkowski F, Abrial C, et al. The role of tomosynthesis in breast cancer staging in 75 patients. Diag Interv Imaging. 2015; 96(1): 27-35.

7. Mariscotti G, Houssami N, Durando M, et al. Accuracy of mammography, digital breast tomosynthess, ultrasound and MR imaging in preoperative assessment of breast cancer. Anticancer Res 2014; 34(3): 1219-25.

8. Luparia A, Mariscotti G, Durando M, et al. Accuracy of tumor size assessment in the preoperative staging of breast cancer: comparison of digital mamography, tomosynthesis, ultrasound and MRI. Radiol Med 2013; 118(7): 1119-36.

9. Mariscotti G, Durando M, Houssami N, et al. Digital breast tomosynthesis as an adjunct to digital mammography for detecting and characterising invasive lobular cancers: a multi-reader study. Clin Radiol. 2016; 71(9): 889-95.

10. Howlader N, Noone AM, Krapcho M, et. al. (eds). *SEER Cancer Statistics Review, 1975–2009 (Vintage 2009 Populations)*, National Cancer Institute. Bethesda, MD, 2012. Retrieved September 7, 2012.

11. Dang PA, Humphrey KL, Freer PE, Halpern EF, Saksena MA, Rafferty EA. Comparison of lesion detection and characterization in invasive cancers using breast tomosynthesis versus conventional mammography [abstr]. In: Radiological Society of North America Scientific Assembly and Annual Meeting Program. Oak Brook, Ill: Radiological Society of North America, 2013; 156.