IMPACT OF CONTRAST- ENHANCED SPECTRAL MAMMOGRAPHY & MAMMOGRAPHIC TOMOSYNTHESIS IN DETECTION & STAGING OF BREAST CANCER

Thesis

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List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AI	Allelic imbalance
BI-RADS	Breast Imaging Reporting & Data System
CC	Craniocaudal
CCDs	Charge coupled devices
CEDM	Contrast-Enhanced Digital Mammography
CESM	Contrast Enhanced Spectral Mammography
CR	Complete Radiography
CsI	Cesium-iodide
CT	Computed tomography
DBT	Digital Breast Tomosynthesis
DCIS	Ductal carcinoma in situ
DM	Digital mammography
DQE	Detective quantum efficiency
ECM	Extracellular matrix
FDA	Food & Drug Administration
FFDM	Full Field Digital Mammography
FFPE	Formalin-fixed, paraffin- embedded
IDC	Invasive Ductal Carcinoma
IHC	Immuno histochemistery
ILC	Invasive Lobular Carcinoma
kVp	Kilovoltage peak
LCIS	Lobular carcinoma in situ
LOH	Loss of heterozygosity
mAs	milli Amperage
mGy	milli Gray
MIP	Maximum Intensity Projection
MLO	Mediolateral oblique
Mrad	Million radiation absorbed dose
MRI	Magnetic resonance imaging
MX	Mammography
NCI	National Cancer Institute
NOS	Not otherwise specified
RFS	Relapse free survival
RT-PCR	Reverse transcriptase polymerase chain reaction,
TFT	Thin-film transistors
TNM	Tumour, nodes, metastases

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ABSTRACT

Aim of work:

The purpose is to study the impact of Contrast- Enhanced Spectral Mammography (CESM) versus Digital Breast Tomosynthesis (DBT) in detection &"T" staging of breast cancer.

Materials & methods:

Thirty female patients with pathologically proved breast cancer were enrolled in the study from those attending Radiology department of the National Cancer Institute their age ranging from (26 - 70 years), with a mean age of (50.2 ± 10.6) years, presenting with suspicious breast lesions on conventional sono-mammography.

All abnormal breasts were imaged by 2-views (CC & MLO views) Digital Mammography, Tomosynthesis & Contrast Enhanced Spectral Mammography.

Two readers gave a subjective assessment superiority of the index lesions (mass, focal asymmetry, architectural distortion, calcifications, pattern of enhancement, number of lesions, skin infiltration) and a forced BIRADS score, based on the tumor size as seen on DM, DBT & CESM, without knowledge of the pathology results, then compared to the post surgical specimen tumor size that was used as reference.

Results:

28/30 patients were diagnosed with malignancy; 18/28 cases were, 2 were of benign findings.As regards the size of the lesion (T stage), CEDM showed the highest concordant proportion of cases 24/28 cases (80%) were correctly staged compared to pathology results but also showed the highest percentage of lesion size underestimation 3 cases (10%). DM showed the highest percentage of lesion size overestimation; 9 cases (30%), while DBT showed no lesion size underestimation & 7 cases (23.3%) with lesion size being overly estimated.

As regards extensions of lesions (spiculations), DBT showed highest sensitivity DBT 70.0% (21/ 30) in detection of spiculations while DM was 60.0% (18/30) & CEDM 50% (15/30). As regards multiplicity of lesions a total of (4/ 28) cases in pathology result, both DM & DBT each detected 50% of the positive cases (2/4) with a sensitivity of 50% and a specificity of 96%. While CEDM detected 75% (3/4) of them but with a lower specificity of 88% due to the larger number of false positive results (11.5%). As regards detection of malignant calcifications in lesions a total of (7/28), DM & DBT showed 100% Sensitivity and Specificity in detection of calcifications in lesions compared to pathology with positive & negative predictive values of 100% and an efficacy of 100% while CEDM could not depict presence of calcifications in breast lesions detected by pathology.

When combining 2 or more breast imaging modalities, the results showed significant increase in sensitivities in detection of lesion extensions (spiculations) with a maximum of 76.7 % when combining all three modalities. As regards detection of multiple of lesions no increase in sensitivity (50%) when combining DBT + MX, but combining CEDM to MX or DBT increased in their sensitivities from 50% to 75%. Combining all modalities showed an increase in specificity of CEDM in detection of multiplicity from 88.5% to 95.8% due to the lower number of false positive cases. Combining DM or DBT with CEDM, allowed better depiction of calcifications with Sensitivity & specificity of 100% and with a positive predictive value of 100% and an efficacy of 100 %.

Conclusion:

Our results concluded that DBT showed the highest sensitivity in detecting extensions (spiculations) in a breast lesion, CEDM showed the highest sensitivity in detection of multiplicities. Both DM & DBT showed similar performance in detection of malignant calcifications. Combining two or more breast imaging modalities significantly improves diagnostic quality & helps in better T-staging of malignant breast lesions.

Keyword:- DBT-CEDM-CESM-FFBE-CC

Background:

Mammography is the examination of choice for diagnosis of breast diseases, and its diagnostic reliability is relatively high. Digital mammography was developed to address some of the limitations of screen-film mammography, especially in breasts with dense fibroglandular tissue where the sensitivity of the traditional technology is somewhat limited ***(Kolb et al., 2002).*** Digital systems offer the potential for improved detection because of improved efficiency of absorption of the incident x-ray photons, a linear response over a wide range of incident radiation intensities, and the low system noise ***(Pisano et al., 2000).*** However, on conventional mammograms obtained by the compression method, the normal soft tissue of the breast, tumors, calcium deposits, and other shadows sometimes overlap in such a way as to mask lesions or render the infiltration border unclear the accuracy of mammography is specially limited in dense breasts where surrounding fibroglandular tissue decreases the conspicuity of lesions. Even when tumors are detected, the full extent of disease may not be clearly depicted. Therefore, tumors might not be clearly differentiated from the adjacent mammary structure ***(Bird et al. 1992) & (Rosenberg et al., 1998).***

During the past few years, many methods for imaging angiogenesis in vivo have been developed as studies have shown that higher intratumoral microvessel density is statistically correlated with a greater incidence of metastases, and that intratumoral microvessel density is an independent prognostic indicator for overall and relapse-free survival in early stage invasive breast carcinoma (***Weidner et al., 1991) & (Chu et al., 1995).*** Contrast enhanced breast imaging like both CT and MRI are used for detection of angiogenesis in breast carcinoma. Both techniques improve detection and characterization of breast carcinomas ***(Hagay et al., 1996) &***

(Orel et al., 2001). However, MRI is limited by its specificity, its high cost, and the restricted access of MRI time. Contrast-enhanced digital mammography is a new breast imaging technique using full-field digital mammography in conjunction with the injection of an iodinated non-ionic contrast medium & is able to depict angiogenesis in breast carcinoma ***(Dromain et al., 2006),*** bringing additional clinical & cost benefits to the current standard care ***(Diekmann et al., 2007).***

Breast tomosynthesis is a new tool that can be expected to ameliorate the problems encountered by digital mammography which is tissue overlap especially dense fibroglandualr breasts ***(Kolb et al., 2002).*** Breast tomosynthesis technology is essentially a modification of a digital mammography unit that enables the acquisition of a three-dimensional (3D) volume of thin section data where images are reconstructed in conventional orientations by using reconstruction algorithms similar to those used in computed tomography (CT) ***(Wu et al., 2004) & (Sechopoulos et al., 2007)***.

Promising results from preliminary studies ***(Gur et al., 2009) & (Andersson et al., 2008)*** reveal that DBT has the potential to reduce the callback rate, increasing specificity while also increasing detection rate, and thereby increasing sensitivity, in breast cancer screening.

Aim of Work:

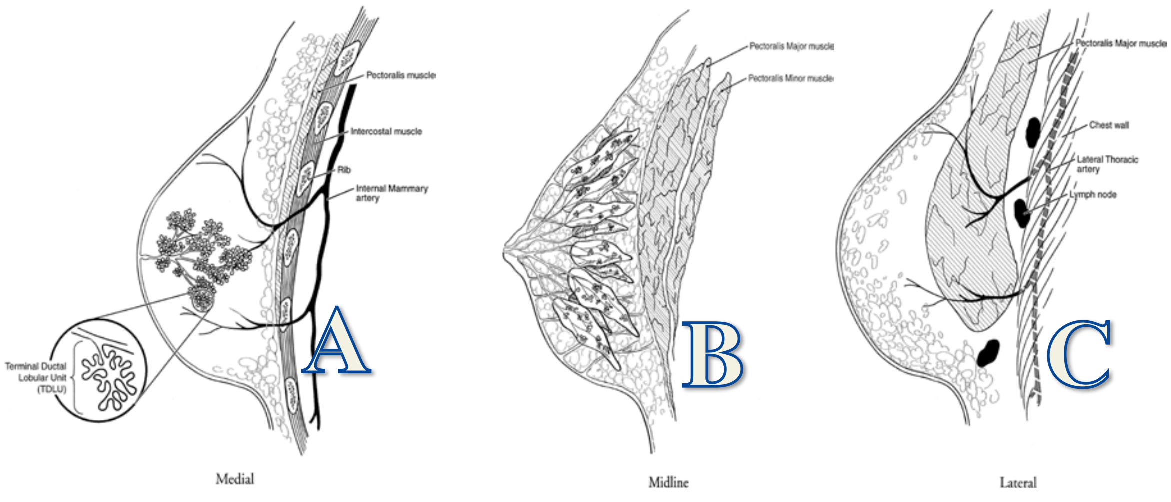
This work presents the initial performance results in studying the impact of Contrast Enhanced Spectral Mammography (CESM) versus Digital Breast Tomosynthesis (DBT) in detection and “T” staging of breast cancer.

CHAPTER 1
Anatomy of the Breast

Normal Breast Anatomy:

The female breast takes variable shapes and dimensions. The average breast measures 10 to 12 cm in diameter and its average thickness centrally is 5 to 7 cm. The contour of the breast varies but is usually dome-like, with a conical configuration in the nulliparous woman and a pendulous contour in the parous woman ***(Osborne, 2000).***

The breast is anterior to the deep pectoral fascia and is normally separate from it by the retromammary space. The breast extends laterally from the lateral edge of the sternum to the mid-axillary line and from the second rib superiorly to the sixth rib inferiorly. An axillary tail (of Spence) extends toward the axilla, or armpit ***(Osborne, 2000).*** *[Fig.1.1]*



<u>Figure 1.1</u>*: *Schematic of sagittal views of the breast

(A) Medially, the internal mammary artery and branches are seen. The terminal duct lobular unit (TDLU), the site of origin of most of metaplastic, hyperplastic, and neoplastic processes of the breast, is demonstrated. (B) At midline, the pectoralis major and minor muscles are usually seen depending on patient anatomy. Each breast contains approximately 15 to 20 lobes. (C) Laterally, the lateral thoracic artery and branches supply the breast. Level 1 lymph nodes are demonstrated posterior to the pectoralis major muscle ***(Morris, 2005).***

Skin and Nipple:

The skin of the breast is thin and contains hair follicles, sweat glands and sebaceous glands. It appears smooth and measures usually 0.5- to 2.0-mm thick, except caudally where it may be slightly thicker due to its usual dependency. Skin should not enhance. Skin scars demonstrate focal skin thickening that does not enhance if mature ***(Morris, 2005).***

The nipple, which is located over the 4^{th} intercostal space in the nonpendulous breast, contains abundant sensory nerve endings. Moreover, sebaceous and apocrine sweat glands are present but no hair follicles. The areola is circular and pigmented, the Morgagny tubercles, located near the periphery are elevations formed by the openings of the ducts of Montgomery glands which are large sebaceous glands capable of secreting milk, and they represent an intermediate stage between sweat and mammary glands ***(Morris, 2005).***

Fascia and chest wall muscles:

The entire breast is enveloped in a duplication of superficial pectoral fascia which is continuous with the superficial abdominal fascia of Camper. Connecting these two fascial layers are fibrous bands (Cooper suspensory ligaments), which represent the “natural” means of support of the breast and provide the shape and consistency of its parenchyma ***(Davis, 2010).***

The undersurface of the breast lies on the deep pectoral fascia covering the pectoralis major and serratus anterior muscles. The pectoralis muscles, though attached to the chest wall, are not considered part of the chest wall. This is an important distinction when it comes to staging the patient. If the chest wall is involved, the patient is Stage IIIB and not generally a surgical candidate. On the other hand, if only the pectoralis muscles are involved, then the patient can have surgery with removal of a portion or all of the muscle(s) to achieve negative margins. Tumor involvement of the pectoralis muscles is suspected when abnormal enhancement is noted, indicating tumor involvement. If tumor infiltrates the muscles, staging of the tumor is not changed although surgical planning may be altered. Abutment of tumor to the muscle with loss of the fat plane does not signify muscle involvement.

Sometimes it may be difficult to differentiate tumor involvement between normal enhancing traversing vessels extending through the pectoralis muscle ***(Morris, 2005).***

Tumor involvement of the pectoralis major muscle generally produces more irregular enhancement. The pectoralis minor muscle, which lies behind the pectoralis major muscle, is not generally involved, unless there is full thickness involvement of the pectoralis major muscle. The true chest wall includes the intercostal and serratus anterior muscles as well as the ribs. In order to diagnose chest wall involvement, abnormal enhancement in these structures is required ***(Morris, 2005).***

Parenchyma and stroma:

The breast tissue comprises parenchyma and stroma, the latter consists of fibrous connective tissue connecting its lobes and adipose tissue in the intervals between the lobes. The parenchyma is divided into 15 to 20 lobes of glandular tissue of the tubule-alveolar type, which converge at the nipple in a radial arrangement. The collecting ducts draining each lobe are 2 mm in diameter, with sub-areolar lactiferous sinuses 5-8 mm in diameter. Each duct drains a lobe made of 20-40 lobules; each lobule consists of 10-100 alveoli or tubule-saccular secretory units ***(Morris, 2005).*** *[Fig. 1.2]*