Contrast-Enhanced Spectral Mammography: A Radiologic-Pathologic Perspective of a Novel Functional Imaging Modality for Breast Cancer

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ABSTRACT

Contrast-enhanced Spectral Mammography (CESM) is an emerging and promising functional imaging modality that tries to address the paucity of physiologic-based tumor imaging for the detection of breast cancer. This article describes two cases of women with non-dense and dense breasts presenting with clinically palpable breast masses and the depiction of breast cancer utilizing Contrast-enhanced Spectral Mammography.

Key words: Contrast-Enhanced Spectral Mammography (CESM), Digital Breast Tomosynthesis, Magnetic Resonance Imaging, Low energy, Subtracted Image, Full-Field Digital Mammography (FFDM)

INTRODUCTION

Mammography is the only breast imaging modality with a demonstrated ability to reduce mortality.¹ A review by Myers et al., confirmed the findings of several published studies that screening mammography in women aged 40-79 reduces breast cancer mortality rates by 20%-50%, with extent of benefit varying by age, as well as study design (RCT vs. observational).² However, mammography has a population-based sensitivity of only approximately 80%³ which is further corroborated by the findings of Carney et al., that showed that with increasing breast density, the sensitivity of mammography decreases to 62% in women with dense breasts.⁴

Breast density refers to the proportion of glandular and fibrous breast tissue to the amount of fatty tissues in a woman’s breast. It has been shown that women who have high density breasts are 4-5x more likely to get breast cancer than women with low breast density.⁴ ⁵ It is also statistically significantly greater among Asian women than among African American and white women.⁶

Contrast-Enhanced Spectral Mammography (CESM)

Contrast-enhanced Spectral Mammography (CESM) is a novel imaging modality that demonstrates the physiologic uptake of contrast by breast cancer. The depiction of breast cancers using contrast media is based on the biologic principle of the rapid formation of tumoral microvessels that render malignancy-associated vessels more permeable to contrast agent than normal tissue, resulting in tumor enhancement.⁷

It has been proposed by Chang et al., that the use of a standard iodinated CT contrast agent and x-ray imaging might also give functional information with a preferential uptake in breast cancers.⁸ An early study done among 26 subjects in 2003 by Lewin et al., of the University of Colorado utilizing dual-energy contrast-enhanced mammography showed tumor enhancement in 13 of the subjects that had subsequent biopsy-proven invasive cancers.⁹

Contrast-enhanced Spectral Mammography was introduced in Europe in June 2010 and received FDA approval in the United States in June 2015.

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States on October 2011. The first center in the UK to acquire the technology was Nottingham Breast Unit and in the United States, early adopters include Memorial Sloan-Kettering Cancer Center in 2010. In Southeast Asia, the early proponents of CESM are Taiwan and Thailand in 2012.

The advantages of using CESM are that it is similar in diagnostic performance with Magnetic Resonance Imaging. Two studies have shown the similarity of Contrast-enhanced Spectral Mammography to MRI. Jochelson et al., found that CESM and MRI have equal sensitivity (96%) while Fallenberg et al., found CESM to have 100% sensitivity compared with 97% sensitivity for MRI.10,11 This was further corroborated by Lee-Felker et al., who also had similar sensitivity of CESM to MRI (94% vs. 99%) as well as having a significantly higher PPV (Positive Predictive Value) of 93% compared to 60% of MRI.12

It can be used in patients with contraindications to doing MRI such as claustrophobia and/or averse to gadolinium contrast.

Furthermore, a recent study by Patel et al., showed that CESM had a reduced exam time of 7-10 minutes compared to MRI with 30-60 minutes as well as reduced staff time of 25 minutes compared to 60 minutes.13

The disadvantages include its contraindication for use in patients with abnormal renal function or if they have a known reaction to iodine contrast. Furthermore, it is not advised for pregnant or lactating women or those who are diagnosed with hyperthyroidism.

How is it performed?
Before a CESM exam is initiated, a thorough history is elicited from the patient with emphasis on allergy history and previous

Figure 1. A 63-year-old post-menopausal female with a newly palpable right breast mass with no family history of breast cancer. (A, B) Low-energy (LE) Mediolateral Oblique (MLO) and Craniocaudal (CC) views of the right breast, which has a fatty breast composition, showing an irregular mass of high density at the lower inner quadrant. (C, D) Subtracted images (SI) in MLO and CC projections show avid enhancement of the right lower inner quadrant breast mass. No other abnormal enhancing lesions are demonstrated. The background parenchyma also shows no enhancement. (E) Ultrasound correlate of the said mass shows an irregular markedly hypoechoic solid mass. (F) Elastography (which is a measure of tissue stiffness) shows the mass to be significantly hard compared to the adjacent fat and glandular tissues.
or known allergy to iodine contrast media. The creatinine level is obtained at least a week before the scheduled exam. Ideally, for premenopausal women, the timing of the exam should coincide with Days 7-14 of her menses, to reduce background parenchymal enhancement.

An IV is inserted into the forearm or antecubital vein and a power injector at a rate of 3 ml/s infuses iodinated contrast agent. The volume is typically calculated at 1.5-ml/kg bodyweight. The iodine concentration ranges from 300 mg/ml to 370 mg/ml. After infusion of the contrast media, let 2 minutes pass before positioning the patient for the standard mammographic views (Mediolateral Oblique and Graniocaudal views) of each breast. For each projection, two energy pairs – low energy and high energy are generated in a single compression. Severe acute reactions to contrast media occur in 4/10,000 (0.04%) patients. According to a study of Lalji et al., the low-energy CESM images are non-inferior to Full-Field Digital Mammography (FFDM) images with no significant differences in image quality, average glandular dose, and contrast detail. The LE images therefore are equivalent to a standard mammogram. The additional radiation dose from the HE images in CESM was approximately 20% that of routine Full-Field Digital Mammography or the equivalent of 1 additional view.

DISCUSSION

The core principle in functional imaging is based on tumor enhancement secondary to tumor neoangiogenesis. The process of tumor neoangiogenesis plays a central role in the growth and spread of tumors. Tumor cells secrete vascular endothelial growth factor (VEGF), a potent angiogenesis activator that stimulates the formation and proliferation of endothelial cells. The newly grown vessels are immature and differ from normal capillaries. They are tortuous and irregular, resulting in poorly efficient perfusion, they are leaky (especially to macromolecules), and they are independent of the normal mechanisms of regulation of the capillary blood flow. Hemodynamic characteristics of immature neovessels can be conservatively assessed by dynamic contrast-enhanced magnetic resonance imaging or computed tomography. Tissue enhancement depends on arterial input function, kinetics of distribution of blood into the capillary bed, leakage across the capillary walls, and volume of the interstitial space.

In our current setting, the detection of breast cancer mainly utilizes analog film mammography, conventional digital mammography, digital breast Tomosynthesis (DBT/2D+3D Mammography) and breast ultrasound, which are based on morphologic (anatomic) information, as opposed to MRI (Magnetic Resonance Imaging) which gives functional information. MRI, however, is limited in its use in our local setting because of its limited availability and the cost is prohibitive.

The sensitivity of CESM was found to be high (98%), underscoring its potential to rival the diagnostic performance of MRI, but with added advantages of improved accessibility and lower cost. In women with dense breasts, Cheung et al., demonstrated that CESM is superior to mammography in both sensitivity and specificity with improvement from 71.5% to 92.7% and 51.8% to 67.9%, respectively.

Akin to the improvements and technological advances made in the field of Pathology, namely, with the development of novel molecular characterization of breast cancer with cellular markers, functional-based imaging of breast cancer is poised to change the paradigm of current diagnostic practice.

Dual-energy Contrast-enhanced Spectral Mammography may provide added value in determining the microcalcifications that show enhancement with a diagnosis favorable to cancer or a lack thereof as virtually diagnostic for non-malignant or noninvasive subgroup of cancers. Likewise, its ability to identify multifocal or multicentric disease enables it to adequately and simultaneously stage both breasts for better pre-biopsy planning.

Local Experience

The first institute to acquire Contrast-enhanced Spectral Mammography is Health Cube Advanced Medical Imaging Unit in March 2016. It was initially utilized as part of the surveillance monitoring of patients with either mastectomy or post-breast conservation surgery and is currently integrated into the diagnostic workflow in the work-up of patients with clinically suspicious findings, particularly those who have dense breasts.

Figure 2. Histopathologic features of the high-density mass seen in the right breast of the patient discloses invasive ductal carcinoma. (A) Seen are neoplastic ductal structures infiltrating the surrounding structures including the adjacent adipose tissue (H&E, 40x). (B) Other areas prominently show the formation of new blood vessels amidst clusters of tumor cells with associated extensive desmoplasia (H&E, 100x).
Contrast-enhanced spectral mammography stands to be a viable and practical diagnostic imaging modality that can contribute to increased cancer detection rate and improve breast cancer care in our country.

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CONCLUSION

The two cases included in this case series showcase the ability of CESM to image cancer whether in dense or non-dense breasts. The first case illustrates cancer without background parenchymal enhancement in a non-dense breast while the second case shows two (2) foci of cancer in a patient with dense breasts with additional background parenchymal enhancement.

Contrast-enhanced spectral mammography stands to be a viable and practical diagnostic imaging modality that can contribute to increased cancer detection rate and improve breast cancer care in our country.

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REFERENCES

Figure 4. Microscopic appearances of the core biopsy taken from the enhancing left breast mass identified in the patient showing invasive ductal carcinoma. The tumor is very cellular and is composed of neoplastic cells disposed in tongues, cords and groups with attempts to form ducts (A) Note the pronounced desmoplastic reaction, which adds to the density seen radiographically. Some areas of the lesion reveal an abundance of well- and newly-formed blood vessels (B) (H&E, 100x).


