Dual-Energy Contrast-Enhanced Spectral Mammography: expanding the Frontiers on Suspicious Breast Microcalcifications on Conventional Mammography

Dual-energy contrast-enhanced spectral mammography (DE-CESM) opens a new vision towards the diagnosis of suspicious microcalcifications of breasts, due to an easy and reliable correlation between conventional and contrast-enhanced subtracted mammograms. The additional information given by enhancement allows a better prediction of the outcomes of histology, as well as highlighting the cancer extent for better pre-operative planning.

INTRODUCTION TO DE-CESM

Dual-Energy Contrast-Enhanced Spectral Mammography (DE-CESM) is a state-of-art technique using intermittent exposures of low- and high-energy after a bolus injection of iodinized contrast medium in the same session of examination. By using emitting energies that are limited to below and above the k-edge of iodine (33.2 keV), we can obtain two different attenuations of low- and high-energy mammograms during a single compressed position of breast. Subsequent recombination of the images will automatically generate a contrast-enhanced subtracted mammogram (CESM) using a masking technique to reveal the presence of iodine uptake. After contrast medium injection, the acquisition of images in CC and MLO views of bilateral breasts should be completed within 2 minutes to 7 minutes, which is the time limit before an enhancement equilibrium is reached between cancer and normal glandular breast tissues. Thus, all of the standard mammographic views will have both conventional low-energy mammogram and an additional CESM for assessment.

BENEFIT OF CESM

It has been well-known that the degree of background breast fibroglandular density on a mammogram can have an impact on the rate of cancer detection and diagnosis accuracy. The additional CESM can potentially enhance an occult cancer, especially in patients with denser breasts. Similar to enhanced breast magnetic resonance imaging (MRI), the degree of tumor enhancement depends on the presence of tumor neoangiogenesis. The presence of enhancement may be a clue to the malignant potential of the tumor.

Compared to conventional mammogram alone, many blinded interobserver studies have documented that DE-CESM can improve cancer diagnosis, including sensitivity, specificity, positive predictive value, negative predictive value and accuracy [1-4]. The sensitivity and clinical performance were increased by 15% and 17% respectively when comparing to mammogram; and 7% and 4% as to mammogram plus sonogram [4].

“... many blinded interobserver studies have documented that DE-CESM can improve cancer diagnosis, including sensitivity, specificity, positive predictive value, negative predictive value and accuracy...”

Our blinded interobserver study with 4 colleagues also resulted similar improvement of DE-CESM for cancer diagnosis as compared to low-energy conventional mammograms in dense breasts, as well as showing a steady easy learning curve and high consistency among the readers [3].

DIAGNOSIS OF SUSPICIOUS MICROCALCIFICATIONS WITHOUT ASSOCIATED MASS

Calcifications are common findings on mammograms in screening or clinical setting; however, concerned microcalcifications are a frequent feature for minimal early breast cancer, particularly in ductal carcinoma in
situ (DCIS) [5]. About 20% to 25% of screened microcalcifications were potentially diagnosed to cancers [6]. Despite the high detection rate of microcalcifications on mammography, it is very difficult to differentiate benign from premalignant or malignant lesions when there is no associated mass. Considering the morphologic appearances or distributions of microcalcifications, suspicious microcalcifications have, depending on their ACR-BIRADS categories (4a, 4b or 4c), a wide range of cancer probabilities from to 13%, 36% and 79% respectively [7]. Tomosynthesis is a new tool which facilitates the evaluation of obscured lesions by recovering the superimposition of breast tissue, but its benefit in diagnosing suspicious breast microcalcifications is limited and controversial. Even though more on obvious microcalcifications can be observed, tomosynthesis does not provide adequate additional information on the malignant potential of the suspicious lesions from conventional mammogram.

ENHANCEMENT EVALUATION ON MICROCALCIFICATIONS

As microcalcifications do not enhance, contrast medium administration explores a larger frontier, which is the associated surrounding parenchyma, as the degree of enhancement reflects the severity of neoangiogenesis. Although malignant tumors usually possess a higher degree of neoangiogenesis than benign tumors, the degree of neoangiogenesis is not uniform among malignant lesions. It is more pronounced in IDC, but not always present in DCIS or lobular cancers. The aggressive lesions are usually accompanied with high vessel densities, thus resulting on a strong and more rapid enhancement. On the other hand, many malignant lesions, such as preinvasive or in situ cancers, have low vessel densities. Although it is commonly believed that a certain degree of neoangiogenesis is the foundation stone for invasive processing, DCIS showed a variable degree of vascularization [8]. Apart from neoangiogenesis, other factors can also influence the amount of extravascular leakage of contrast medium to interstitial spaces inside or around the tumor, including vascular permeability, interstitial volume and biochemical structures. Hence, the presence of enhancement is not exclusive for malignancy. Nevertheless, the application of enhancement opens a new possibility towards differentiating the causes of microcalcifications.

COMPARISON WITH ENHANCED BREAST MRI

FIGURE 1A. A 49-year-old female with suspicious malignant microcalcifications from mammographic screening was referred for further evaluation. The low-energy conventional mammogram (mediolateral oblique view) showed regional pleomorphic microcalcifications in right breast.

FIGURE 1B. CESM revealed an 8-cm large lobular enhanced mass in the upper region of the right breast.
Enhanced breast MRI is very sensitive in detecting invasive breast cancers (94% - 100%) [9], but less sensitive with in-situ cancer (45% - 100%) [8]. Several primitive studies have emphasized the value of enhanced MRI not only for diagnosis of invasive breast cancer, also to delineate DCIS with neangiogenic enhancement in the stroma around the periductal tumor bed as a marker of potential extension [10, 11]. However, because microcalcifications cannot be observed on MRI, the correlation of detected microcalcifications in conventional mammogram and their respective locations on breast MRI remains difficult. On the other hand, DE-CESM can easily correlate the exact location of enhancement to microcalcifications on conventional mammogram. From our retrospective analysis, we concluded that DE-CESM could provide additional information of the enhancement on microcalcifications without associated mass [12]. Our result was slightly better than the previous report from enhanced MRI [13], as shown in Table 1. In our series, all the invasive breast cancers and 86.7 % of DCIS could be enhanced, except for 2 unenhanced low grade DCIS. The false positive or false negative rates of enhancement thus remained to 23% and 6%, respectively. For the different concern levels of suspicious microcalcifications, the true positive rates of enhancement were higher on intermediate (93.7%) and high (100%) concern levels as opposed to low level (50%). Furthermore, the true negative rate of enhancement was high (> 90%) for all levels of concern microcalcifications.

In addition to achieving a more accurate diagnosis, CSEM can further assist surgeons with better pre-surgical treatment planning strategies. Accurate pre-surgical measurement of cancer size or extent is important. This is particularly true for the patients having microcalcifications without associated mass. Among this particular group of patients, the exact cancer extent is often unclear from both conventional mammogram or breast sonography. The extent of enhancement from CSEM can highlight the territory of cancer involvement secondary to neovascular formation. A previous study reported that both conventional mammography and enhanced MRI can overestimate the cancer size of malignant microcalcifications without associated masses. The mean differences of conventional mammography and enhanced MRI to pathological examinations were 3.9 mm and 7.3 mm, respectively [13]. In our series, DE-CESM was analyzed as having better agreement of cancer size to microscopic size than mammography by Bland-Altman plot, respectively with average size differences of 0.5 mm and 4.2 mm. [12].

CONCLUSION
DE-CESM provides comprehensive images of conventional and contrast-enhanced subtracted mammograms in the same session of compressed position. The clinical application of CESM should be considered in cases of indeterminate microcalcifications of breast, as CESM can facilitate an improved diagnosis of malignancy and a better delineation of cancer extent for optimizing pre-surgical planning, particularly in patients without associated mass.

REFERENCES

[Table: Comparison of Diagnosis: DE-CESM versus Enhanced MRI]

<table>
<thead>
<tr>
<th></th>
<th>DE-CESM</th>
<th>Enhanced MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>90.9</td>
<td>80</td>
</tr>
<tr>
<td>Specificity</td>
<td>83.8</td>
<td>79</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>76.9</td>
<td>86</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>93.9</td>
<td>71</td>
</tr>
<tr>
<td>Accuracy</td>
<td>86.4</td>
<td>80</td>
</tr>
</tbody>
</table>

TABLE 1.: Comparison of Diagnosis: DE-CESM versus Enhanced MRI.