Contrast enhanced digital mammography (CEDM): From morphological to functional mammography

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Learning objectives

• To learn the basic principle of Contrast Enhanced Digital Mammography (CEDM), for both temporal and dual energy approaches.

• To compare the technical advantages and limitations of these approaches.

• To understand the expected clinical benefits of angiogenesis imaging using X-ray mammography.

Background

The clinical importance of tumor angiogenesis in primary breast cancer is well known. Studies have shown that intratumoral microvessel density is an independent prognostic indicator that correlates with a higher incidence of metastases [1,2].

Several methods for imaging angiogenesis in vivo have been developed in the last few years. First, digital subtraction angiography of the breast has been performed using an X-ray image intensifier system [3,4]. Contrast medium has also been used with both CT and MR techniques to explore angiogenesis in breast carcinoma. Both techniques improve detection and characterization of breast carcinomas [5-9] and contrast-enhanced breast MRI with gadolinium-based agents is currently considered to be the most sensitive imaging technique for breast cancer detection. However, MR imaging is limited by its high cost and the limited access to the imaging equipment in most countries.

The introduction of digital mammography enables development of new clinical applications with the potential to improve breast cancer detection that were not possible with film-screen technology. Contrast-enhanced digital mammography (CEDM) with the injection of iodinated contrast medium is one of these clinical applications. While mammography is a key modality for breast cancer screening and diagnosis, it only provides morphological information about breast structures. In addition, the physics of X-ray image acquisition and superimposition of breast tissue on projected views lead to obscured lesions and limited specificity. CEDM imaging may help to improve the
visibility of suspicious findings and their differentiation thanks to contrast uptake in breast malignant lesions.

We developed two techniques to perform CEDM examinations: temporal CEDM and dual-energy CEDM. Investigational devices based on Senographe 2000D and Senographe DS (GE Healthcare, Chalfont St. Giles, UK) were built enabling clinical investigations of respectively temporal CEDM and dual-energy CEDM (Figure 1).

Images for this section:

**Contrast-Enhanced Digital Mammography (CEDM)**

**Potential Clinical Roles**
- Adjunct to inconclusive diagnostic
- Assessment of extent of disease
- Monitoring response to therapy
- High-risk women screening

**Two Methods Being Researched**
- Temporal subtraction
- Dual-energy subtraction

Fast readout & low noise cesium iodine–amorphous silicon flat-panel detectors make angiogenesis X-ray imaging possible

**Fig. 1:** CEDM: Potential clinical roles and methods
Imaging findings OR Procedure details

IODINE VISUALIZATION & HIGH-ENERGY SPECTRA

Contrast agents are used since many years with both CT and MRI to explore angiogenesis by tracking uptake and washout phases in tissues. Similarly to CT, which is an X-ray imaging technique, we are using iodine as contrast agent for CEDM imaging. It is necessary to adapt the digital mammography system such as the sensitivity of the imaging technique to low concentrations of iodine is maximized. In order to benefit from the extra X-ray attenuation of the iodine compared to soft tissues, we use high-energy spectra with a mean energy beyond 33.2 KeV corresponding to the K-edge of the iodine [6,7]. Voltages ranging between 45 and 49 kVp are typically used in association with a copper (Cu) filter that removes the photons of lowest energy, instead of 26-32 kVp for conventional digital mammography (Figure 2).

TEMPORAL CEDM

Image acquisition & protocol

The temporal subtraction technique produces high-energy digital mammography images before and after contrast medium injection. To enhance visualization of contrast medium in lesions, the pre-contrast image is subtracted from the post-contrast images (Figure 3).

The patient has to be comfortably settled in order to avoid motions during the acquisition of the image sequence. A light breast compression is applied for all mammography images, strong enough to limit motion but limited to avoid reducing the blood flow. The series of images is acquired within a single breast compression. Once the breast has been compressed, the exam begins with the acquisition of a single mask mammogram. A monophasic intra-venous injection is then performed, preferably using a power injector at a high flow rate, and several post-injection images are taken.

The total temporal CEDM examination duration is approximately 15 min and the total X-ray dose delivered to the patient ranges between 1 and 3 mGy, similar to a conventional single view mammogram.

The main interest of temporal CEDM is the access to the kinetics of the contrast uptake. However, only unilateral imaging can reasonably be performed. The pretty long duration of image series acquisition precludes the imaging of the contralateral breast with a
single contrast agent injection. Moreover, possible patient motion due to the light breast compression and the long acquisition time may translate into artifacts in the subtracted images.

**Image display**

Regions of interest can be placed at regions of early enhancement and adjacent breast tissue to analyze the uptake and the washout of the contrast agent. Values of differential enhancement between lesion and normal breast tissue can then be plotted versus time. A functional map may be provided presenting a parameterization of the contrast uptake curves (e.g., time to peak intensity, mean transit time, blood volume) for each pixel of the subtracted images (*Figure 4*).

**Clinical value**

A clinical experimentation has been undergone to assess the clinical accuracy of temporal CEDM as an adjunct to mammography [8].

Mammography (MX) and temporal CEDM images were acquired at 4 sites using Senographe 2000D (GE Healthcare, Chalfont St. Giles, UK), with modified X-ray beam spectrum. Images were obtained before and at least at 3 different time points after administration of iodine-based contrast medium. Five experienced breast radiologists from 4 institutions in Europe and North America defined a reading methodology for CEDM images. A set of mammography studies from 75 patients containing 85 lesions, 17 benign and 68 malignant, was first read without and then jointly with CEDM images. CEDM images were reviewed using a software tool for generation of subtraction images and time density-curves. Probability of cancer, BI-RADS assessment category and level of confidence were recorded. Results were compared using ROC analysis.

The average sensitivity and specificity increased with MX+CEDM from 0.81 to 0.86 and 0.62 to 0.66, respectively. Average number of overlooked malignant lesions decreased from 6 for MX to 4.2 for MX+CEDM. Area under the ROC curve (AUC), using the probability of cancer scale (*Figure 5*) or BI-RADS categories, increased for all readers when temporal CEDM was used in addition to mammography. This increase was statistically significant for 2 out of 5 readers.

While some contrast uptake curves may suggest similar shapes as the ones seen in MRI exams of the breast (*Figure 4*), our experience has shown that the kinetics of CEDM contrast uptake is not a reliable indicator of lesion malignancy. It seems that breast compression and projective images acquisition alter the quantitative assessment
of enhancement parameters [9]. The breast radiologists participating to this clinical experimentation agreed in a consensus meeting that the most relevant information conveyed by temporal CEDM images was the intensity of the contrast uptake and its morphology. For this reason and for the temporal technology limitation already mentioned in Figure 3, we decided to explore the dual-energy CEDM approach.

DUAL-ENERGY CEDM

Image acquisition & protocol

The dual energy technique exploits the energy dependence of the X-ray attenuation through materials of different compositions in the breast, specifically iodine and soft tissues. A pair of low and high-energy images is obtained after the administration of an iodinated contrast medium agent. The two images are then combined [10] to enhance contrast uptake areas (Figure 6).

We designed an investigational device allowing dual energy CEDM acquisitions based on a commercially available digital mammography detector and breast compression system (Senographe DS, GE Healthcare, Chalfont St. Giles, UK). The imaging device was modified to allow the generation of high-energy spectra similar to the ones used for temporal CEDM [6,7] in addition to the low-energy spectra used in conventional mammography (Figure 6).

An iodinated contrast agent is injected preferably using a power injector at a high flow rate. Then the breast is compressed and a pair of low and high-energy images is acquired. With a single contrast administration, it is potentially possible to acquire several pairs of images corresponding to different views (e.g., CC and MLO) and/or both breasts. Image analysis requires the combination of low-energy and high-energy images to generate a CEDM image with contrast uptake information. The low energy images, corresponding to conventional mammograms, bring morphological information of the breast, while the CEDM images bring functional information of the breast (Figure 6).

The duration of examination ranges from 5 to 10min depending on the number of projections. The total X-ray dose delivered to the patient for a pair of low and high-energy images is estimated to be 20% higher than the dose needed for one projection in standard digital mammography for a breast of same thickness and composition. The resulting images are reviewed using reading criteria based on contrast enhancement intensity and morphology.
While dual-energy CEDM provide no or very limited kinetic information on the contrast uptake, this technique potentially enables bilateral examinations of breasts under several incidences with one single injection of iodinated contrast agent. The injection being performed before patient positioning, and each pair of low and high energy images being acquired in only few seconds, dual-energy CEDM presents less motion artifacts compared to temporal CEDM [11].

In order to ground the result of our acquisition parameter optimization with solid scientific foundations, we underwent experiments at the European Synchrotron Radiation Facility (ESRF) in Grenoble (France), using monoenergetic radiations (Figure 7).

Image acquisitions of phantoms with iodine inserts using monoenergetic synchrotron radiation confirmed that, in order to maximize the Signal Difference to Noise Ratio (SDNR) of the iodinated contrast agent, the low energy image needs to be acquired at energies close to the ones used in conventional mammography (around 20keV) and the high energy image needs to be acquired at an energy just above the iodine K-edge [12]. With a mammography X-ray tube, polyenergetic spectra with those mean low and high energies are achievable with KVP ranges respectively 26-32 and 45-49 KVP (Figure 7).

**Image display**

We developed a new dual-energy recombination algorithm that takes the breast thickness and the low and high energy spectra as input parameters, and then, uses an image chain model to simulate the gray levels for varying glandular percentage and iodine thickness. A linear regression is performed on these simulated values to derive the coefficients for the low and high-energy images combination, using a quadratic form [10]. The originality of our algorithm lies in the use of a quadratic combination of the low and high-energy log-signals, instead of the usual linear combination which is only accurate in the monoenergetic case. Actual dual-energy recombination methods have rarely attempted the use of a more refined form than the linear combination of log-signals, and even if a few of them did, the computation of the coefficients for the recombination always required calibration measurements on phantoms. Our approach avoids these inconvenient measurements thanks to an image chain model which is capable of simulating gray levels in the image.

An example of dual-energy recombined image is shown in Figure 8. In order to simulate the presence of lesions with iodine, we used a DSA phantom (Nuclear Associates - DSA phantom, linearity insert), which is composed of a 2.4cm block of PMMA (material equivalent to 50% glandular breast tissue) with embedded inserts of different iodine surfacic concentrations. Slabs of swirl texture phantoms, made of a mix of materials similar to 50% and 0% glandular breast tissue (custom product by CIRS) were added to simulate background anatomical noise. The weighted logarithmic subtraction is only
exact in the case of mono-energetic beams, for which the result is an exact iodine-equivalent image. But for poly-energetic X-rays, the weighted logarithmic subtraction gives only an approximate iodine-equivalent image, with significant residual background clutter, while our approach provide a better background texture removal.

**Clinical value**

We organized a reader study to assess the diagnostic accuracy of dual-energy CEDM as an adjunct to mammography (MX) compared to the diagnostic accuracy of MX alone [13].

107 women with 133 suspicious findings on MX and or ultrasonography (US) underwent CEDM. A pair of CEDM exposures were taken in MLO view at 2 minutes and in CC view at 4 minutes after the injection of 1.5 ml/kg of a iodinated contrast agent. The gold standard was the pathology results in all cases. One reader first evaluated the MX images alone, then the MX+CEDM images. Confidence of presence (5-level scale), probability of malignancy (7-level scale) and BI-RADS assessment were evaluated for each lesion.

Pathology results identified 80 benign and 53 malignant lesions. The sensitivity was 0.94, 0.94, 0.94 for MX+CEDM compared to 0.80, 0.78, 0.85 for MX alone considering respectively probability of cancer (p=0.01), BI-RADS (p<0.01) and confidence of presence (p=0.07). There were no significant differences between specificity for MX and MX+CEDM. The area under the ROC curve was superior for MX+CEDM (p<0.01), using either probability of malignancy or BIRADS (Figure 9). The Negative Predictive Value (NPV) improved from 0.66 to 0.85 when using CEDM as an adjunct to Mammography.

Preliminary results show a significantly higher diagnostic accuracy of two-views dual-energy CEDM versus mammography (MX) alone. CEDM should result in a simple way to enhance the detection of some breast cancers, to improve the characterization of breast lesion and to provide some prognostic factors of breast carcinoma. Few clinical cases are discussed in the following material to illustrate the benefits and the limitation of dual-energy CEDM exams.

**CLINICAL CASES**

**Problem solving**

This patient (Figure 10) had a normal physical exam and a small mass only seen on a mammography CC view (red arrow). The ultrasonography performed by the referring physician was normal. She was categorized in the BI-RADS 3 category. However,
because the radiological finding seen on the CC-view mammogram was suggestive of malignancy, this woman was sent to Institut Gustave Roussy, Villejuif (France) to get a second opinion.

This patient was then included in the dual-energy CEDM clinical protocol. The dual-energy images show a very clear focal contrast uptake on both CC and MLO views (green arrows), confirming the presence of a lesion associated to the suspicious CC-view mammography finding (Figure 10). The dual-energy images allowed to accurately guide a new ultrasonography exam in the Upper Inner Quadrant of the breast. A 5 mm hyperechoic nodule was found that turned to be an adenocarcinoma confirmed by an ultrasound guided cytology.

**Detection of occult lesions in dense breasts**

This 53 years old patient had a follow-up for a fibrocystic mastosis leading to very dense breasts (Figure 11). Two fibroglandular areas were described at physical examination in the upper medial and the retroareolar locations of the right breast. A large suspicious mass was identified on mammograms (red arrow) and confirmed during an ultrasonography exam in the lower inner quadrant of the same breast.

The dual-energy CEDM images showed an obvious contrast uptake for this large mass (Figure 11), but also revealed three small satellite lesions that were invisible on mammograms and very difficult to catch at ultrasound (green arrows). Those three satellite lesions turned out to be an adenocarcinoma for two of them and a invasive ductal carcinoma (IDC) for the third one.

**Assessment of Extent of Disease**

A nipple stiffness of the left breast was described since 1 year for this patient who presented a nipple and areola thickening on mammograms (red arrow). Ultrasonography was normal. A nipple biopsy allowed the identification of an invasive lobular carcinoma (ILC), and a surgery excision of the nipple-areola complex was recommended (Figure 12).

Before going to breast MRI for an assessment of the extent of the disease, this patient underwent a dual-energy CEDM examination. The CEDM images showed non only a contrast uptake in the retroareolar area of the left breast, but also an obvious contrast uptake of the lower inner quadrant of the same breast (green arrows). Those retroareolar and quadrant contrast uptakes were spatially correlated with the contrast uptakes seen
on MRI images (yellow arrows) confirming the extension of the ILC to the lower inner quadrant (Figure 12).

True negatives

Patient with a normal physical examination and a small mass with slightly irregular margins seen on mammograms (Figure 13) in the upper quadrants close to pectoral muscle (red arrows). This finding was rated as BI-RADS 4 and the ultrasonography did not show any abnormality.

On the dual-energy CEDM images, no contrast uptake was visible (Figure 13). We asked the patient to bring back her prior mammograms. It was then possible to confirm the stability of this small nodule over the 4 previous years. A biopsy of the nodule bring only normal parenchyma and an additional 19-months follow-up confirmed that the mass corresponded to normal fibro-glandular tissues. This case is an illustration of a true negative of dual-energy CEDM.

False Positives

This 45 years old patient had a normal physical examination (Figure 14). A nodule was visible on mammograms in the upper outer quadrant of the right breast (red arrows). The dual-energy CEDM images demonstrated contrast uptake of this nodule (green arrows). However, this nodule was stable in size since 1 year and its ultrasound image was not suspicious. A micro-biopsy proved out the lesion to be a fibro-adenoma.

This case is an illustration of false positives of dual-energy CEDM. As with breast MRI, dual-energy CEDM present some false positives we need to be aware of. In our experience, we found fibro-adenomas, micro-cystic adenosis, radial scars and phyllodes tumors to take contrast and therefore being considered as false positives of dual-energy CEDM.
**Contrast-Enhanced Digital Mammography (CEDM)**

**Potential Clinical Roles**
- Adjunct to inconclusive diagnostic
- Assessment of extent of disease
- Monitoring response to therapy
- High-risk women screening

**Two Methods Being Researched**
- Temporal subtraction
- Dual-energy subtraction

Fast readout & low noise cesium iodine-amorphous silicon flat-panel detectors make angiogenesis X-ray imaging possible

**Fig. 1:** CEDM: Potential clinical roles and methods

**Contrast-Enhanced Digital Mammography (CEDM)**

**Iodine visualization**

- Mo target, Cu filter
- High Voltage range between 45 and 49 kVp
- 0.15 - 0.7 mGy per exposure
- Average glandular dose depending on breast thickness (about 1/5 of screening view)

**Fig. 2:** CEDM: Iodine visualization and X-ray spectra
Temporal CEDM

**Temporal subtraction**
- Mask image before injection
- 3-7 exposures after injection
- Dose/image ≈ 1/5x screening MX view

- Kinetic information available
- 1 breast & 1 view / injection
- Breast under compression during 5-7’

**Fig. 3:** Temporal CEDM: Principle, acquisition protocol, benefits and limitations

**Fig. 4:** Temporal CEDM: Visualization of contrast uptake information
Temporal CEDM

Material & method
- MX and Temporal CEDM images acquired at 4 sites
- 5 experienced breast radiologists (4 institutions in Europe and North America)
- 85 lesions (17 benign and 68 malignant)
- MX read without and then jointly with CEDM images

Results
- Average Se : 0.81 (MX) → 0.86 (MX+CEDM)
- Average Sp : 0.62 (MX) → 0.66 (MX+CEDM)
- Average number of overlooked malignant lesions : 6 (MX) → 4.2 (MX+CEDM)
- Area under the ROC Curve values increased for all readers

Conclusion
- Diagnostic accuracy increases by adding CEDM as an adjunct to MX

Fig. 5: Temporal CEDM: Assessment of clinical accuracy

Dual-Energy CEDM

Dual Energy subtraction
- Pair of exposures (low and high kVp)
- Fast readout & low noise CsI-αSi flat-panel detector enabling short-interval image acquisition
- Average glandular dose ≈ 1.2x screening view

- Bilateral 2-views possible with 1 injection
- Post injection = standard MX procedure
- No / limited kinetic information

Fig. 6: Dual-energy CEDM: Principle, acquisition protocol, benefits and limitations
Dual-Energy CEDM

Experimental validation with synchrotron radiation

Knowledge of optimal monoenergetic spectra constitutes a good indicator for the design of optimal spectra produced by standard sources.

We investigated the optimal monoenergetic spectra for CEDM using simulations and experiments with synchrotron radiation.

Fig. 7: Dual-energy CEDM: Experimental validation with synchrotron radiation

Dual-Energy CEDM

Fig. 8: Dual-energy CEDM: Visualization of contrast uptake information
Dual-Energy CEDM

Material & method

- 107 women with 133 suspicious findings on Mammography or US
- 80 benign and 53 malignant
- Injection of 1.5 ml/kg of a iodinated contrast agent
- MLO view at 2 minutes and CC view at 4 minutes after injection
- 1 reader first evaluated the mammography images alone, then the mammography + CEDM images

Results

- Se: 0.78 (Mammography) \rightarrow 0.94 (Mammography+CEDM) with p<0.01
- no significant difference between specificity for mammography and mammography+CEDM
- Area under the ROC Curve superior for mammography+CEDM (p<0.01)

Conclusion

- Preliminary results show a significantly higher diagnostic accuracy of two-views Dual Energy CEDM versus mammography alone.

Fig. 9: Dual-energy CEDM: Assessment of clinical accuracy

Dual-Energy CEDM – Problem solving

Physical examination
Normal

Mammography
Small mass only visible on CC view
- Low confidence of presence
- Global classification BI-RADS 3

Ultrasoundography
Normal
(performed by referring physician)

CEDM image
RMLO - 2 min

Conventional Mammograms

CEDM image
RCC - 4 min

Ultrasound guided cytology:
Adenocarcinoma

Ultrasonography directed on CEDM images:
- Hyperechoic nodule
- 5mm vertical large axis

Fig. 10: Dual-energy CEDM: Problem solving
**Fig. 11:** Dual-energy CEDM: Detection of occult lesions in dense breasts

**Dual-Energy CEDM – Detection of occult lesions in dense breasts**

**Patient history**
- 53 years old
- Follow-up of a fibrocystic mastosis

**Physical examination**
- Retroareolar fibroglandular area (50 mm)
- Upper-medial fibroglandular area (40 mm)

**Mammography**
- Mass in the outer lower quadrant

**Fig. 11:** Dual-energy CEDM: Detection of occult lesions in dense breasts

**Fig. 12:** Dual-energy CEDM: Assessment of extent of disease

**Dual-Energy CEDM – Assessment of extent of disease**

**Physical examination**
- Nipple stiffness since 1 year

**Mammography**
- Nipple and areola thickening

**Ultrasoundography**
- Normal

**Nipple biopsy**
- Invasive lobular carcinoma

**Fig. 12:** Dual-energy CEDM: Assessment of extent of disease
Dual-Energy CEDM – True negatives

Physical examination
Normal

Mammography
Opacity with borders partially well circumscribed BI-RADS 4

Ultrasonography
Normal

![Image of true negatives]

True negative result
Biopsy → normal parenchyma
19 months follow up

Fig. 13: Dual-energy CEDM: True negatives

Dual-Energy CEDM – False positives

Patient history
45 years old

Physical examination
Normal

Mammography
Nodule in the Upper Outer Quadrant of the right breast

Ultrasonography
Normal

![Image of false positives]

True negative result
Biopsy → normal parenchyma
19 months follow up

Fig. 14: Dual-energy CEDM: False positives
Conclusion

The feasibility of CEDM exams has been technically and clinically demonstrated on Senographe platform using a CsI-aSi detector technology. Minor hardware adaptation, optimization of acquisition parameters and specific post-processing software made possible the design of both temporal and dual-energy CEDM investigational devices. Our clinical experiments established the significant higher diagnostic accuracy of both temporal and dual-energy CEDM as adjunct to mammography compared to mammography alone. Both sensitivity and negative predictive value were improved when using dual-energy CEDM in addition to mammography.

Dual-energy CEDM presents the unique ability to bring functional information in bilateral exams of the breast with potentially only one contrast agent injection. It offers an immediate availability in the mammography suite without new appointment and without loss of time. Furthermore, no special training of the technologist is needed for positioning the patient and for the acquisition of images. Dual-energy CEDM examination is well accepted by patients, pleased to have a complete assessment without remaining questionable findings at the end of the day. It is a fast imaging technique that provides a direct correlation with conventional mammograms. In addition, subtracted CEDM images are very easy and fast to interpret by the radiologists and to understand by the oncologist and the surgeons.

Our experience tends to prove that dual-energy CEDM has the potential to become a more available, faster and cost effective exam than MRI for some indications such as problem solving when conventional mammography assessment is equivocal, detection of occult lesions in dense breasts, or evaluation of newly diagnosed breast cancer to assess extent of disease and to evaluate for possible contralateral disease. Additional clinical experimentations would be of interest to investigate the potential of CEDM in the assessment of response to neoadjuvant chemotherapy, in the evaluation of breast cancer recurrence and for the guidance of biopsies or wire localization.

Personal Information

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