UPDATE IN RADIOLOGY

Dual-energy contrast-enhanced mammography

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Abstract The degree of vascularization in breast lesions is related to their malignancy. For this reason, functional diagnostic imaging techniques have become important in recent years. Dual-energy contrast-enhanced mammography is a new, apparently promising technique in breast cancer that provides information about the degree of vascularization of the lesion in addition to the morphological information provided by conventional mammography. This article describes the state of the art for dual-energy contrast-enhanced mammography. Based on 15 months' clinical experience, we illustrate this review with clinical cases that allow us to discuss the advantages and limitations of this technique.

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PALABRAS CLAVE
Mamografía con realce de contraste mediante técnica de energía dual

Resumen Es bien conocido que el grado de vascularización de las lesiones mamarias se relaciona con su malignidad. Por ello, las técnicas de diagnóstico por imagen que estudian funcionalmente las lesiones han cobrado mucha relevancia en los últimos años. La mamografía con medio de contraste y energía dual es una técnica de reciente aparición, aparentemente prometedora en el cáncer de mama, que informa del grado de vascularización de la lesión...
Introduction

It is well known that tumor cells are metabolically very active and require a great deal of nutrients which in their growth causes a process known as angiogenesis. Its clinical importance has been established for breast cancer since it is an independent prognostic factor highly associated with the incidence of metastasis. Since they are very rapidly forming micro-vessels, porosity is high and when injecting IV contrast media, they spread the interstitial liquid of tumor mass they enhance. This is why since the 1980s different modalities have been born whose goal is to explore tumor angiogenesis by using contrast media like breast angiography, CT and magnetic resonance (MR). The MR is the most widely used modality and the most important one clinical-wise since it is the most sensitive image diagnostic modality for the detection and study of breast cancer. However, the MR has several drawbacks mainly due to its high cost and also to its limitation in claustrophobic excessively obese patients or with a certain type of extra-breast prostheses, pacemakers or foreign bodies among others. This is why numerous patients cannot have access to it. With the arrival of the new millennium digital radiology has gained momentum and it is full of advantages. One of the main ones is that it allows us to post-process images with computer applications aimed at improving diagnosis. One of these computer apps is iodinated contrast enhanced digital mammography. Several studies have proven that it is a cheaper alternative than MR. It is also an alternative to conventional mammography in order to avoid unnecessary biopsies also and adjunct modality to conventional mammography and ultrasound in order to improve the diagnosis of malignant lesions, and even better than MR for diagnosis. However, this modality is still recent and no author has clearly established what role it plays in the diagnostic algorithm of breast disease. During these years this technique has been developing parallel in two modalities. The first one, more like conventional angiography, is called temporal contrast-enhanced mammography (TCEM). The other one, based on image-acquisition at different energies, is called contrast-enhanced spectral mammography (CESM) (also called dual energy mammography). In both cases we must inject the patient an IV iodinated contrast media through an automatic injector to secure constant flow. During these first ten years of life several studies showing that both modalities are promising have been done since they improve both the specificity and sensibility to diagnose breast lesions. Nonetheless results indicate that TCEM has some important technical limitations still not worked out while the clinical performance of CESM can be improved. In this article we mainly deal with the dual energy modality but in the following segment we will discuss the main features, advantages and limitations of TCEM.

Temporal contrast-enhanced mammography

The main feature of this modality is that other than enhancing the images of those contrast media uptaking-lesions, it also gets information on the temporary pattern of uptake and further iodinated contrast clearance. This is why it is the most similar of the two to the MRI. Although there is some controversy about it, the information delivered by the uptake curves of breast lesions can be very relevant since it seems that the more slowly uptaking-lesions are usually benign while a fast pattern in the uptake is associated with a greater degree of malignancy. To be able to use this pattern through digital mammography different images are taken in various moments. In the first place one image before injecting the contrast media with the compressed breast (“mask”) needs to be taken. Then while compressing the breast the contrast media is injected and sequential images are acquired (usually one image per minute) during a different time frame (4–10 min) depending on the pattern we want to explore (uptake or uptake + clearance). To improve the view of the lesions the “mask” is subtracted from the images acquired through the contrast agent. One of the main limitations is that patients cannot tolerate so much time of compression (up to 15 min), so there are usually numerous movement artifacts that makes images unable to be fully overlapping. This is why we need specific software to compensate all distortions caused by movement. Another important limitation is that with this modality we can study one breast and with one view only and that limits the confirmation of lesions previously diagnosed clinically or radiologically. If we want to study both breasts as we usually do through conventional mammography both the times and contrast doses will multiply by the number of views we want. This is why even though the dose of radiation needed to obtain each individual image is similar to that of routine mammographies (1–3 mGy), the total dose will depend on the number of images obtained. Several studies done so far show that when artifact-free images are obtained the TCEM is way more sensitive and specific than conventional mammographies to diagnose cancer. However, the main theoretical advantage of this modality with respect to CESM—that is the study of the uptake/clearance pattern
Table 1 Comparison of the features of TCEM and CESM.

<table>
<thead>
<tr>
<th></th>
<th>TCEM</th>
<th>CESM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study</td>
<td>15 min</td>
<td>7 min</td>
</tr>
<tr>
<td>Compression</td>
<td>From the beginning</td>
<td>2 min after the administration of contrast</td>
</tr>
<tr>
<td>Mask</td>
<td>Necessary</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Study range</td>
<td>One breast-one view</td>
<td>Two breasts-two views ea</td>
</tr>
<tr>
<td>Patient tolerance</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Reported information</td>
<td>We acquire the contrasted image and clearance and uptake curves</td>
<td>We acquire the routine mammographic diagnosis and the contrasted image. No acquisition of clearance/uptake curves</td>
</tr>
<tr>
<td>Prior diagnostic suspicion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Radiation received</td>
<td>Equivalent to that of conventional mammography based on the views obtained</td>
<td>20–50% greater than that of conventional mammography</td>
</tr>
<tr>
<td>Artifacts</td>
<td>Many (movement)</td>
<td>Few</td>
</tr>
</tbody>
</table>

CESM: contrast-enhanced spectral mammography (or dual energy); TCEM: temporal contrast-enhanced mammography.

does not seem as closely associated as MRI with malignancies/benignities of lesions.

As a matter of fact in one recent investigation the gradual uptake of contrast was very common in 20 malignant lesions studied (80%). This was attributed to the fact that breast compression probably altered the pattern of local circulation of the breast during the study. For all these reasons at least up to now CESM is being more widely accepted than TCEM in radiology units since its diagnostic power is similar and it is faster, easier to do and is way more tolerated. In Table 1 we show a comparison between the features of both modalities of digital contrast enhanced-mammographies. In Table 2 we show a summary of the main investigational studies used to evaluate the clinical performance of digital contrast enhanced-mammographies (both TCEM and CESM).

Contrast-enhanced spectral mammography

Features

This modality is based on the attenuation of radiation when it goes through different materials, in this case iodine and soft tissues. Hence, after injecting iodinated contrast the usual mammographic views are done with the difference being that two consecutives images are acquired for each view: one of low energy and the other one of high energy. The criteria used to select the range of kVp and mAs for each image are defined in Ref. 17. For the high energy-image adapting the digital mammography is required since we need a breast compression system modified to allow the use of an additional filter.

Low energy-images are obtained through technical exposure similar to that of conventional mammographies (26–31 kVp). This is how even iodine cannot be seen; it is already present since the kilovoltage is well below the iodine energy K-absorption edge (33.2 kVp). Immediately after this the second image of the breast is automatically acquired with a 45–49 kVp kilovoltage that because it is above the iodine energy K-absorption edge it obtains information from the lesion on contrast uptake. For low energy exposure anodus, molibdenus (Mo) or rodius (Rh) filters should be used and for high energy exposure aluminum or copper filters which allow the absorption of soft unnecessary radiation and preservation of photons around the iodine absorption energy. Postprocessing allows us to obtain one combined image where contrast uptake-areas are enhanced and the normal tissue areas suppressed. Up to now one

Table 2 Summary of the main studies done for the assessment of clinical performance of contrast-enhanced digital mammography.

<table>
<thead>
<tr>
<th>Authors and reference</th>
<th>Year</th>
<th>Patients</th>
<th>Type of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jong et al.</td>
<td>2003</td>
<td>22</td>
<td>12 benign, 10 malignant</td>
</tr>
<tr>
<td>Dromain et al.</td>
<td>2006</td>
<td>20</td>
<td>All malignant</td>
</tr>
<tr>
<td>Diekmann et al.</td>
<td>2011</td>
<td>70</td>
<td>50 benign, 30 malignant</td>
</tr>
<tr>
<td><strong>CESM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewin et al.</td>
<td>2003</td>
<td>26</td>
<td>12 benign, 10 malignant</td>
</tr>
<tr>
<td>Dromain et al.</td>
<td>2011</td>
<td>120</td>
<td>62 benign, 80 malignant</td>
</tr>
<tr>
<td>Dromain et al.</td>
<td>2012</td>
<td>110</td>
<td>54 benign, 84 malignant</td>
</tr>
<tr>
<td>Jochelson et al.</td>
<td>2013</td>
<td>52</td>
<td>All malignant</td>
</tr>
<tr>
<td>Fallenberg et al.</td>
<td>2013</td>
<td>80</td>
<td>All malignant</td>
</tr>
</tbody>
</table>

CESM: contrast-enhanced spectral mammography (or dual energy); TCEM: temporal contrast-enhanced mammography.
computer program is available for commercial purposes to combine different images (Senobright®, General Electric Healthcare™, Buckinghamshire, United Kingdom) that limit the implementation of this modality to many radiology units.

In sum, in around 7 min a combination of low and high energy-images is acquired through breast and views (cranial caudal and media-lateral-oblique views). This is how in the same process we acquire both the conventional image of mammography (obtained at low energy) (Fig. 1) and the combined image (after applying the subtraction algorithm) which will allow us to view uptake areas only (Fig. 1B). In the CESM the movement artifact is not a problem and the patient can tolerate it very well (Table 1) while both breasts can be studied in the same proceeding and with one contrast injection only. However, the CESM does not allow us to study the uptake and clearance pattern and it is estimated that the overall average radiation dose is 20–54% greater than the dose of one routine view of a digital mammography. The main clinical studies have compared the diagnosis of malignant breast lesions through CESM and conventional digital mammography alone and in combination with breast ultrasound. These studies showed that CESM was superior for the diagnosis of malignant lesions (93% and 78%), and also superior for the diagnosis of additional malignant lesions (sensibility) without increasing the number of false positives (specificity). According to these studies both the sensibility and specificity of CESM for the diagnosis of malignant lesions would be equivalent to that of conventional mammographies and ultrasounds combined. As a matter of fact with one experienced radiologist the diagnostic capacity of CESM can be up to 40% greater than conventional mammographies and ultrasounds combined. CESM and MRI can be considered equivalent for the detection of primary tumors while for the detecting of additional lesions MRI are superior. However, the number of false positives of MRI was greater (greater specificity of CESM) and the predictive value for carcinomas was significantly greater with CESM (97% and 85%). Also, CESM can be better than MRI to estimate the size and stratify tumors. In Table 3 we show the main pros and cons of CESM today.

**Examination protocol**

The necessary material is an automatic contrast injection pump, one digital mammography kit equipped with a breast compression system with aluminum or copper filters and a working station with the application Senobright® (General Electric Healthcare™, Buckinghamshire, United Kingdom). When it comes to human resources we need one nurse for the IV injection and monitoring during the whole process and one expert technician in radiodiagnostics who has experience in mammographies. The physical presence of a radiologist is not necessary. The informed consent from the patient is necessary so that we know if she has prior known allergies to contrast agents or renal disease counter-indicated by the study and we will proceed as in other radiological modalities using IV iodinated contrast. It will

<table>
<thead>
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<th>Table 3</th>
<th>Main pros and cons of CESM.</th>
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<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>Fast (7 min)</td>
<td>Greater dose of radiation than conventional mammography (20–50%)</td>
</tr>
<tr>
<td>Easy to do</td>
<td>Fasting required (it needs to be planned)</td>
</tr>
<tr>
<td>Easy to read</td>
<td>Non eligible for patients allergic to iodine without premedication</td>
</tr>
<tr>
<td>Cost-effective (compared to MRI), though it results in 20% more expenses than conventional mammographies</td>
<td>Non eligible for patients with renal failure</td>
</tr>
<tr>
<td>Well tolerated by all patients</td>
<td>Some cases of allergic reactions have been reported</td>
</tr>
<tr>
<td>It results in the acquisition—in the same process of the routine study and contrast image</td>
<td>Today one company owns the patent of the needed software only</td>
</tr>
<tr>
<td>It studies both breasts in the same process</td>
<td>Lesser degree of diagnostic performance in breast prostheses</td>
</tr>
<tr>
<td>Eligible for patients carrying pacemakers and metallic materials</td>
<td>Non eligible to study silicones</td>
</tr>
<tr>
<td>Eligible in claustrophobic patients</td>
<td>Few clinical studies today</td>
</tr>
</tbody>
</table>

CESM: contrast-enhanced spectral mammography (or dual energy).
Figure 2  CESM exam protocol. Two minutes after injecting the IV contrast media low and high energy images are acquired following this order: (a) medial-lateral oblique view—non-suspicious breast; (b) cranial-caudal view—non-suspicious breast; (c) cranial-caudal view—suspicious breast; (d) medial-lateral oblique view—suspicious breast.

also explain what dose of radiation can the patient receive being patients who might be pregnant totally discarded. In Fig. 2 we can see the steps to follow during a CESM study. Once the patient is seated and preferably relaxed iodinated contrast is administered (1.5 mg/kg iv, at 3 ml/s). Two minutes after the injection the acquisition of images begins following a process involving a fewer mammograph manipulations for the patient’s convenience. In our unit we

Figure 3  (A) Palpable lesion in the superior external quadrant of her left breast corresponding to a suspicious solid lesion in the ultrasound. (B) Low energy-CESM and (C) combined in which a lesion with uptake in the irregular thick ring can be seen—suspicious for malignancy. Final outcome: colloid carcinoma. In the breast we can see one percutaneous marker since CESM was done once the patient was diagnosed.
are starting to study the suspicious breast through and in this order mediolateral oblique and cranial-caudal views. Then the abnormal breast in inverse order is studied. Even though order does not seem to influence the final result of the study,\textsuperscript{9,14} it is recommended that once the protocol to be followed has been established such protocol will not be altered. The acquisition of all images is done in 5 min tops.

In our service we began with CESM back in January 2013 and ever since then we have studied 136 patients (average age 49.1 years; age range 32–83 years). Most patients were studied due to previous suspicion (67%), routine mammographic monitoring (22%) and due the impossibility of doing MRI (7%), and also to monitor the response to neoadjuvant therapy (4%). With this modality we have studied 187 lesions in total (114 malignant and 73 benign).

Main clinical applications

- \textit{Diagnosis of palpable lesions}. Given CESM also includes one image equivalent to conventional mammography it has the same clinical applications with the additional advantage that the combined image can make the diagnostic power be similar to that of the combined used of mammography + ultrasound\textsuperscript{11,12} (Fig. 3).

- \textit{Diagnosis of lesions lowly suspicious for malignancy}. When signs at the conventional mammography or ultrasound are not conclusive the European Society of Breast Imaging claims that due to its high negative predictive value MRI allow us to almost completely discard breast cancer.\textsuperscript{19} Studies done so far have proven that the performance of CESM is similar to that of MRI in these cases,\textsuperscript{19} yet the series of patients are still relatively small (Fig. 4).

- \textit{Complementary study of recently diagnosed-malignant lesions}. When breast cancer is clinical or radiologically diagnosed the CESM can be very useful to find multicentric, multifocal, and contralateral lesions that can usually be seen in combined images but that are not so evident in conventional mammographies. Similarly CESM can help in the ultrasound of multiple lesions to decide which ones require biopsy\textsuperscript{13} (Fig. 5).

- \textit{Assessment of the response to neoadjuvant chemotherapy and post-operative follow-up}. CESM is potentially a good substitute for MRI in the assessment of the response to neoadjuvant chemotherapy,\textsuperscript{1,13} yet we still need solid studies to prove it scientifically (Fig. 6). On the other hand, the CESM is also a potentially useful modality to distinguish between post-operative breast remodeling

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.jpg}
\caption{Patient with suspicious focal asymmetry in the superior external quadrant of the right breast in the low energy-image (A) without uptake in the combined image (B).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.jpg}
\caption{Patient with extensive comedocarcinoma-like subtype intraductal carcinoma. (A) Low energy image and (B) combined image CESM is performed. Multifocal affection that CESM allowed to delineate with greater accuracy through ultrasound-directed biopsy.}
\end{figure}
and cancer relapse since it allows us to distinguish between the fibrotic tissue—not highly vascularized and tumor neoforming whose contrast uptake-enhancement is equivalent to that of MRI.14

- **Patients not eligible for MRI studies.** CESM is a good substitute for MRI when this modality is relative or absolutely counter-indicated or in the presence of physical limitations.20

**Main limitations of the contrast-enhanced spectral mammography**

- **False negatives.** Yet, despite the fact that in the clinical studies done so far the percentage of false negatives has been really low, some of them have been associated with poorly vascularized tumors. It also has some diagnostic limitations in deep or axillary tumors and even though clinical performance is better than that of conventional mammography in these cases, the ultrasound is also recommended as an adjunctive modality.14

Its limitations with malignant microcalcifications with no underlying mass11,12 have also been reported. As a matter of fact our false negatives have been associated with this; they can be seen in low energy images but not in the combined image. In these cases the result of biopsy was malignancy (Fig. 7). Even though some studies of this sort have precluded them,11,12 we have studied them because the low

**Figure 6** Patient with neoadjuvant therapy of infiltrating ductal carcinoma. CESM combined image (A) before and (B) after finishing chemotherapy. Complete remission. MRI and CESM can be overlapped. No enhancement.

**Figure 7** Patient with malignant micro-calcifications in the inferior internal quadrant of her right breast also showing several nodes in the large area of micro-calcifications. (A) Low energy-image and (B) combined in which only the area that coincides with the underlying mass is enhanced. The intermediate area without any findings in the ultrasound does not show uptake. Final outcome: infiltrating intraductal carcinoma.

**Figure 8** Seventy-year-old patient with intraductal carcinoma in her left breast diagnosed with a lesion suspicious for malignancy in the contralateral breast (retroareolar region of her right breast) eventually resulting into fibroadenoma.
energy image gives us information and sometimes the combined image shows uptake areas.\textsuperscript{19} This shows that longer series of patients are still necessary to be able to categorically say that this is an absolute limitation.

- \textit{False positives.} In our patients we also found an intense uptake pattern in the case of two benign lesions (fibroadenomes) (Fig. 8) of an overall 114 lesions (1.7\%), a number that is lower to that of our MRI studies. Similar percentages have been published by other authors.\textsuperscript{14} However, there are not enough publications yet to be able to conclusively determine the real percentage of CESM false positives.

- \textit{Other limitations.} In our own experience siliconomes through direct injection in the breast of liquid silicone is one important limitation (Fig. 9A). Even though the effect of these implants is not reviewed in the reference in our unit, we see them often. Due to the features of this material the CESM combined image used with diagnostic purposes is completely useless. Nevertheless, other image diagnostic modalities are not useful in these cases either. On the other hand, patients with silicone surgical implants are usually tagged as not eligible for CESM diagnosis (verbal communication from General Electric Healthcare\textsuperscript{15}). In the 8 patients studied in our unit we
could only diagnose cancer through CESM in 50% of all cases (Fig. 9B).

Another limitation is the interpretation of ganglions and adenopathies since most do not have specific features to distinguish benignity from malignancy. However, this also happens with breast MRIs.21

Lastly, probably due to the limited experience with this modality and also the limited literature about it we still often find uptake patters in combined images that are not easy to explain and interpret and that can be justified by the patient’s moment of hormonal cycle and breast pattern (Fig. 10). No doubt we need longer series of patients and more cases in order to be able to assess correctly the clinical performance of this modality in the overall spectrum of breast disease.

Conclusions

CESM is at the same time a routine mammographic study and the contrasted image capable of finding angiogenesis. It is faster, easier to do and uses reproducible modality that is also easier to interpret. It is well tolerated by patients and its overlappable signs are similar to those of the MRI with the advantages that it is cheaper and it can be performed in patients in which MRIs are counter-indicated. It also allows us to do a correct diagnosis of multifocal, multicentric and bilateral affectionation and a precise monitoring of the response to neoadjuvant chemotherapeutic therapy. Since both breasts with the same dose of contrast and proceeding are studied it can be recommended as first line diagnostic image—above all in high-risk patients. In any case it is interesting as a complementary test to mammographies and ultrasounds in all patients. However, experience is still limited and we need further studies with larger series of patients to be able to establish correctly both the clinical performance and the sensibility and specificity of this new modality.

Ethical responsibilities

Protection of people and animals. Authors confirm that no experiments have been performed on human beings or animals.

Data confidentiality. Authors confirm that the protocols of their centers have been followed on matters concerning the publishing of data from patients. They also confirm that all patients included in this study have been given enough information and handed over their written informed consent for their participation in this study.

Right to privacy and informed consent. Authors confirm that they have obtained the written informed prior consent from patients and/or subjects appearing in this article. This document is in the possession of the corresponding author.

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6. Statistical analysis: N/A
7. Reference search: MMTA, VVB, OPL.
8. Writing: MMTA, OPL.
9. Manuscript critical review with intellectually relevant contributions: MMTA, OPL, MRR, SAH, VVB.
10. Final version approval: MMTA, OPL, MRR, SAH, VVB.

Conflict of interests

The authors reported that they have no conflict of interests.

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References

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