White paper

Contrast-Enhanced Mammography

ClearCEM with MAMMOMAT B.brilliant

siemens-healthineers.com/mammography/clearcem

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Contents

1. Introduction

Full-field digital mammography (FFDM) is currently the most used imaging modality for breast cancer screening in Europe [1]. While it delivers high-resolution two-dimensional images of the breast in a short time, tissue superimposition remains a challenge in FFDM. To overcome this limitation, digital breast tomosynthesis (DBT) has been introduced in clinical practice. It provides three-dimensional (3D) information on breast tissue by acquiring data at different angles and computing stacks of slice images with reduced tissue overlap. Both FFDM and DBT are morphological techniques, showing tissue structures rather than physiology. Although these techniques might be sufficient to detect abnormalities in screening women with an average risk of breast cancer [2,3], functional breast imaging techniques can offer a significant diagnostic advantage in a diagnostic setting or screening of women with a higher-than-average risk of breast cancer [4].

For X-ray mammography systems, contrast-enhanced mammography (CEM) is the functional imaging technique that has shown the greatest potential in this respect. CEM is a combination of contrast-enhanced imaging, known from computed tomography (CT), angiography and magnetic resonance imaging (MRI), and dual-energy imaging, known from CT and dual-energy X-ray absorptiometry.

Siemens Healthineers has entered the CEM market with CEM as an option on the MAMMOMAT Revelation in 2019. In 2026, Siemens Healthineers introduced a second-generation CEM reconstruction algorithm, ClearCEM, as an option on the MAMMOMAT B.brilliant.

The first part of this white paper (Chapters 2 and 3) will have an educational character, with a strong focus on CEM imaging principles. The second part (Chapter 4) will focus more on the reading and clinical indications of CEM, and the final part (Chapters 5 and 6) discusses details about ClearCEM, the new CE-marked CEM implementation of Siemens Healthineers.

2. Contrast-enhanced imaging

The use of contrast agents is common practice in radiology, for example in CT [5], MRI [6] and ultrasound [7]. The purpose of injecting a contrast agent is to increase the visibility of vascular structures or to visualize contrast agent uptake in tissues. As contrast enhancement depends on the tissue type, pathological processes might show abnormalities in contrast agent uptake and enable detection of malignancies. And since mammography is based on the attenuation of X-rays, the choice of iodine-based contrast agents, which are also used in CT, is obvious.

2.1 Physiology

After an iodinated contrast agent has been intravenously injected, it will traverse the lungs and the heart (twice) before it enters the systemic circulation. From the aorta, the contrast agent is then distributed throughout the body to the organs and tissues. Although a large part of the contrast agent will stay within the arteries during its first pass through the body, over time the contrast agent will leak out of the capillaries into the extravascular extracellular space, also known as interstitial fluid. Depending on the blood flow, on the volume percent of extravascular extracellular space and on vessel permeability ("leakiness"), a certain amount of contrast agent will accumulate in a tissue and give rise to a signal enhancement during imaging (Figure 1). The entire process of how contrast agents behave inside the human body is called contrast agent kinetics, and can be described by means of tracer kinetic models [8, 9].

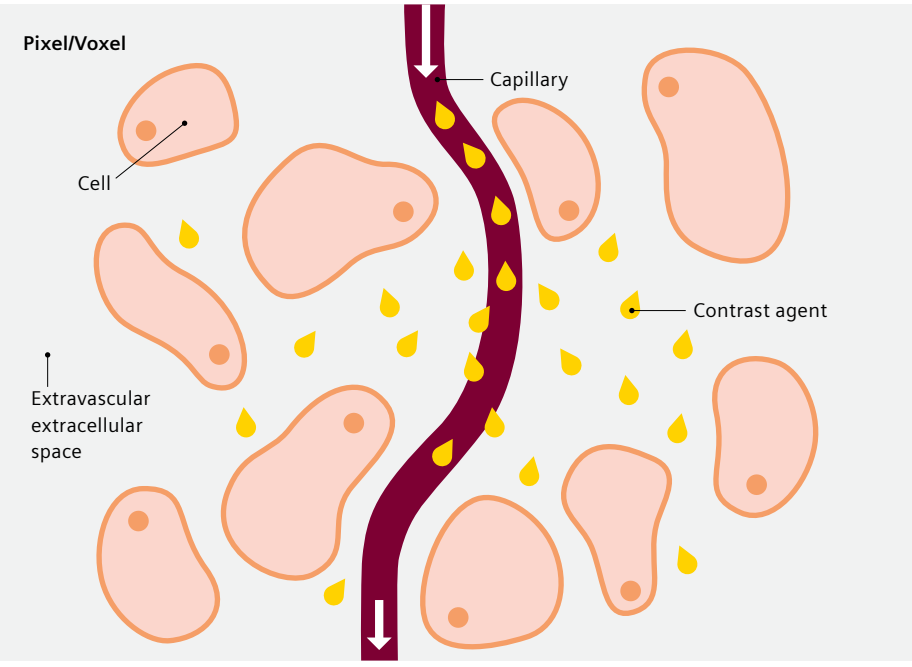


Figure 1: Depending on vessel permeability, blood flow and the amount of extravascular extracellular space, part of the contrast agent will accumulate in a tissue and give rise to a signal enhancement during imaging.

2.2 Contrast enhancement in healthy breast tissue

The human breast consists primarily of two different types of tissue: adipose and fibroglandular tissue. The contrast agent uptake in adipose tissue is typically very low, leading to almost no contrast enhancement over time. Fibroglandular tissue, on the other hand, has a good vascular network and thus is well perfused. However, the blood vessels are not highly permeable, which results in a slow contrast agent uptake, a low amplitude and contrast enhancement typically showing a plateau [10]. Typical contrast-enhancement curves observed in the human breast are shown in Figure 2.

This contrast agent uptake of healthy glandular tissue has been described in scientific literature as background parenchymal enhancement (BPE) and is a well-known phenomenon in MRI and CEM. It is usually present in a bilateral, symmetrical distribution. Asymmetric BPE denotes a greater level of more broad distribution of enhancement in one breast than in the other. This may be seen after radiation therapy, with the radiated breast showing less BPE [11]. If asymmetric BPE is seen without a known cause, according to the ACR BI-RADS CEM lexicon [12], it should be evaluated as it may represent a pathologic process such as diffuse inflammation or diffuse malignancy in the breast with the asymmetrically higher BPE.

BPE is known to fluctuate with breast density and hormone levels (e.g. phase of the menstrual cycle, menopause, hormone therapy) [11]. There are even indications that compression force seems to influence BPE levels in CEM [13]. Noteworthy, it has been demonstrated to be an independent predictor of breast cancer risk [14]. BPE is not necessarily directly related to the amount of fibroglandular tissue and should be described as minimal, mild, moderate or marked enhancement (Figure 3) [12]. A higher BPE can lead to decreased visibility of enhancing lesions, as these stand out less clearly from the background at higher BPE levels on CEM [15] or MRI [16].

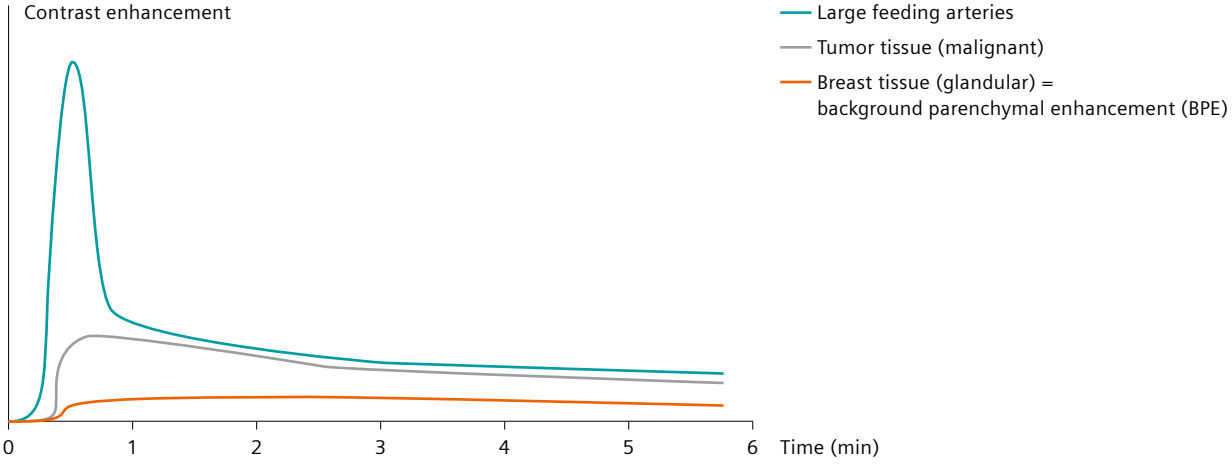


Figure 2: Differences in physiology, predominantly blood flow and vessel permeability, are reflected in the shapes and amplitudes of enhancement curves. Please note: The purpose of this schematic figure is to illustrate different enhancement patterns in general. The contrast signal intensity curve might reach a plateau in some malignant lesions, while it has a rapid uptake followed by a fast decrease (wash-out) in other malignant lesions.

2.3 Contrast enhancement in tumors

For most invasive tumors, the formation of new blood vessels, called angiogenesis, is one of the pathophysiological processes characteristic of tumor growth [17]. Tumor cells initiate the formation of new vasculature from pre-existing vessels, often resulting in an irregular bed of leaky vessels. These abnormalities in tissue perfusion and contrast agent leakage lead to increased visibility of tumors in contrast-enhanced scans. The reason for this is that a lot of contrast agent is taken up by the tumor tissue due to the good blood supply. Furthermore, the leaky vessels allow the contrast agent to move into and out of the tumor tissue rapidly, a process commonly referred to as wash-in and wash-out [10].

2.4 Measuring contrast enhancement: dynamic or static

Distinct dynamic contrast intensity curves are well-described in the literature [18]. These patterns are classified as type I, persistent rise in contrast signal intensity, which suggests a low probability for malignancy; type II, plateau type, which has an intermediate probability for malignancy; and type III, wash-out type of signal intensity, which is indicative of malignancy. Therefore, it would be desirable to perform repeated measurements over time to obtain information about the contrast agent dynamics and to capture the arterial phase of tumor enhancement characterized by a steep upslope and a rapid wash-out as is measured with MRI.

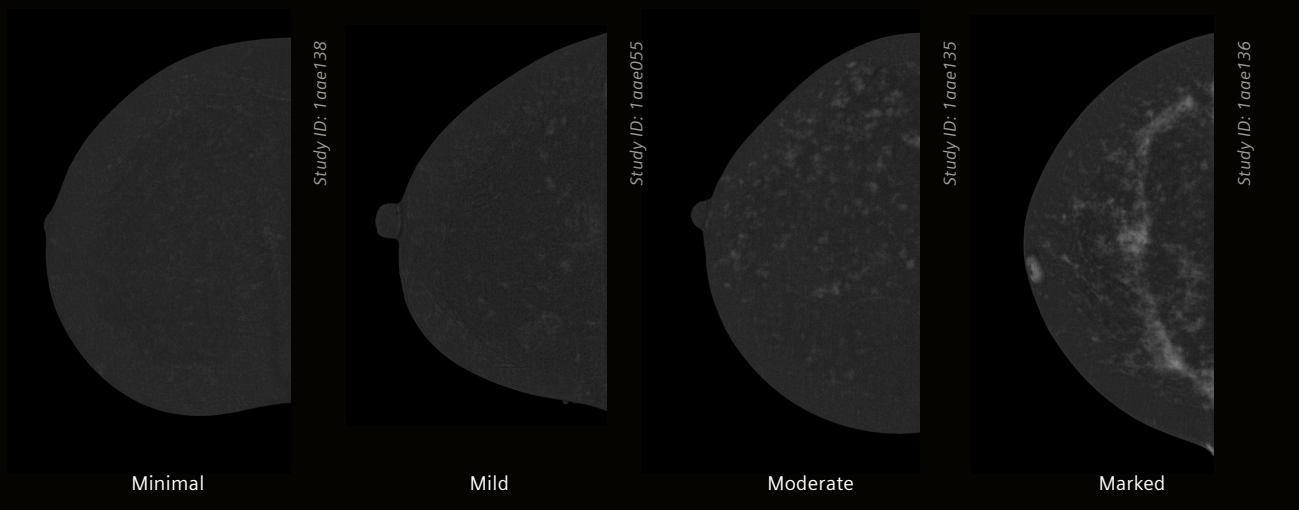


Figure 3: The ACR BI-RADS CEM lexicon recommends reporting BPE as one of the following 4 categories: minimal, mild, moderate or marked enhancement.

This approach with CEM has been tested by subtracting a baseline image prior to injection from the subsequent images, as is known from angiography procedures, for example. However, in clinical studies this so-called temporal subtraction mammography [19] has not been able to consistently demonstrate distinctly different patterns for benign and malignant lesions [20]. Furthermore, the most prominent factors hindering successful implementation of this dynamic acquisition method are the high cumulative radiation dose of repeated acquisitions, the necessity for repeated contrast agent injections for each view and breast, as well as the breast compression that hinders normal blood flow into the breast. So far, clinical studies that investigated static imaging at both early and late phase did not show a significant diagnostic benefit for late phase imaging [21,22].

This has two important implications for the implementation and workflow of CEM. First, the compression-induced restriction of blood flow into the breast means that patient positioning, breast compression and image acquisition should take place after the injection has been completed. As a result, imaging the arterial phase of contrast enhancement is not possible. However, the contrast enhancement is more stable after the arterial peak (Figure 2), allowing for a larger timing window to perform the measurements. Also, differences in contrast agent uptake between malignant lesions and healthy tissue still permit differentiation of malignancies.

Second, differences in contrast agent uptake should be derived from independent measurements at single time points, as no baseline image (acquired prior to the injection) will be available. And since the iodinated contrast agent is not visible in a routine mammogram [23], there is a need for a different approach to extract the iodine signal at a single time point. This is where the dual-energy methodology comes into play, as will be explained in the next chapter.

2.5 Safety

It is advised to monitor patients, especially those receiving iodinated contrast material for the first time, during and after injection for signs of an adverse reaction to the contrast material or an extravasation event, after which the intravenous line can be safely removed. As with all intravenous contrast agent injections, allergic reactions may occur, but can be minimized by following regular safety guidelines for iodinated contrast agents [24,25] as well as local standard operating procedures.

3. Dual-energy imaging

In FFDM, images are generated by measuring the attenuation of X-rays that have passed through the breast. Because of the working principle of X-ray tubes, the photons in the X-ray beam do not all have the same energy; they have different energies, resulting in an X-ray spectrum (Figure 4). The shape of an X-ray spectrum depends on:

- the peak voltage of the X-ray tube (kV);
- the anode material; and
- the filtering of the X-ray beam.

The peak voltage determines the highest photon energy in the X-ray spectrum, whereas the anode material influences the distribution of energies present in the spectrum. It is important to filter the X-ray beam before it reaches the patient, to reduce the number of low-energy (LE) photons. These would merely lead to higher radiation doses but would not contribute to the image. With additional filtering, specific photon energies can be filtered out of the beam, to increase or decrease the average energy of the X-ray spectrum (see paragraph 3.3).

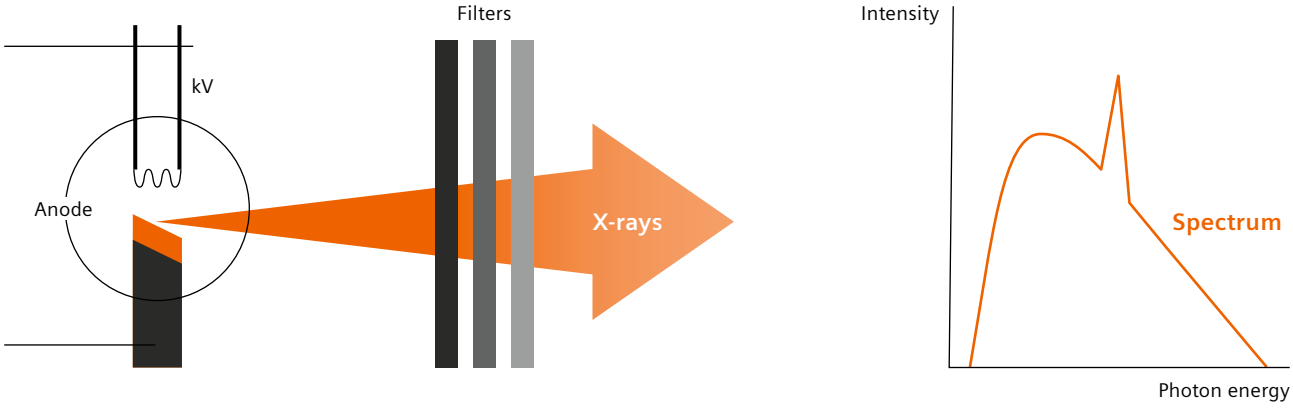


Figure 4: The shape of an X-ray spectrum depends on the peak voltage of the X-ray tube (kV), the anode material and the filtering of the X-ray beam.

3.1 Attenuation of X-rays

In X-ray based imaging modalities, the contrasts in the final image originate from differences in X-ray absorption inside a scanned object. X-ray absorption in turn depends on both the physical density and chemical composition of the object. The effect of chemical composition on X-ray absorption can be described by means of the mass attenuation coefficient, which is material-specific and depends on the photon energy. This energy dependence is illustrated in Figure 5, which shows the mass attenuation coefficients for several types of tissue as a function of photon energy [26]. The higher the mass attenuation coefficient of a material is, the more photons are absorbed. Since breast tissue is a mixture of adipose and soft tissue (fibroglandular or tumor tissue), the curve for breast tissue (black line in Figure 5) lies between the curves for adipose and soft tissue.

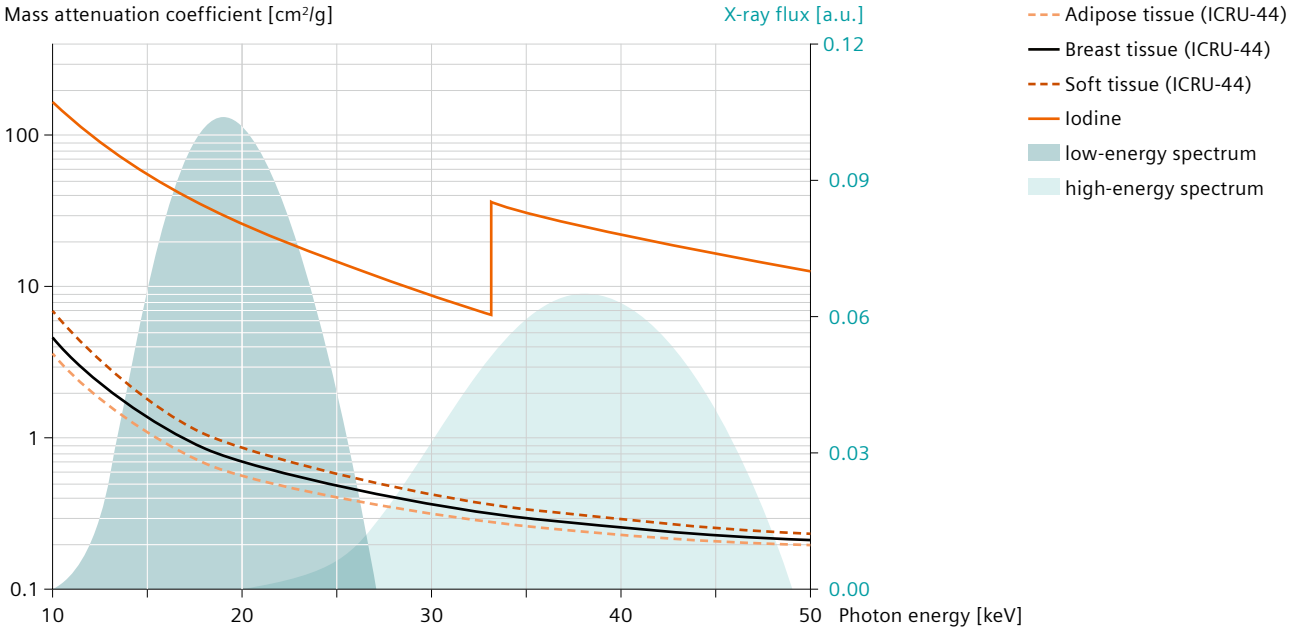


Figure 5: Mass attenuation coefficients for several types of tissue [26]. The higher the mass attenuation coefficient of a material is, the more photons are absorbed. The K-edge of the iodine atom leads to a sudden increase in the mass attenuation coefficient at 33.2 keV.

3.2 Why dual-energy imaging?

Whereas standard mammography is performed using one X-ray spectrum ("single-energy"), the term "dual-energy" refers to imaging a tissue by acquiring two images each with a different spectrum. Its advantage is that two materials can be discriminated by processing the two images if the difference in their mass attenuation coefficient is significantly different for the two X-ray spectra. Since both tumor tissue and healthy fibroglandular tissue are soft tissues, the mass attenuation coefficient is similar for each photon energy (dashed dark orange line in Figure 5) and cannot immediately be differentiated by means of dual-energy imaging. However, as explained in Chapter 2, differences in iodine uptake between healthy fibroglandular and tumor tissue exist. As the mass attenuation coefficient between soft tissue and iodine is significantly different (Figure 5), a processed image can be calculated in which contrast agent uptake is being indicative for tumor tissue.

Especially in dense breasts, where the iodine contrast might be hidden under or confused with high-intensity fibroglandular tissue in a normal, single-energy mammogram, dual-energy acquisitions can have a definite advantage. Despite the much higher mass attenuation coefficient of iodine compared to soft tissue, the iodinated contrast agent cannot be seen in normal FFDM images (single-energy), although present in the tissue [23]. This is due to its very low concentration, resulting in only very slightly increased pixel intensities.

Therefore, contrast-enhanced dual-energy mammography is a result of:

- differences in the mass attenuation coefficient between breast tissue and iodine; and
- differences in contrast agent uptake between tumor and fibroglandular tissue.

3.3 Choice of X-ray spectra

Two different X-ray spectra must be selected when performing dual-energy mammography; one for each acquisition. Finding a good combination of X-ray spectra that leads to optimal iodine contrast in the processed dual-energy image is a complex task and will unquestionably involve a trade-off, since many factors need to be considered.

The mass attenuation coefficient of iodine shows a characteristic step at 33.2 keV, the so-called K-edge (Figure 5). This is an important peak, since for photon energies just below 33.2 keV, the attenuation will be much lower compared to photon energies just above this K-edge. Since the attenuation of breast tissue is almost the same below and above 33.2 keV, an iodine uptake will result in a different attenuation for an acquisition with a mean photon energy below or above the K-edge of iodine. For an optimal iodine contrast in the processed dual-energy mammography image both spectra should be separated, one directly below the K-edge of iodine and one above.

For the LE spectrum (dark petrol-colored spectrum in Figure 5), filter materials with less attenuation are recommended as they are used for mammography with a peak voltage below or slightly above the K-edge of iodine. For the high-energy (HE) spectrum (light petrol-colored spectrum in Figure 5), the use of additional filtering with high-Z (high atomic number) materials is also beneficial. By increasing the filter thickness, the average photon energy can be increased, and the spectrum will become harder. However, a thicker filter will also absorb more X-rays and therefore necessitates a higher tube output to obtain the same radiation dose in the tissue. So, the maximum filter thickness is always dependent on the maximum output of the X-ray tube and should be tailored to its heat capacity.

3.4 Image processing

CEM is the generally used term for contrast-enhanced dual-energy mammography. As CEM is implemented on a standard mammography system, the LE and HE exposures must be acquired successively, resulting in a time difference between the two acquisitions. For this reason, image acquisition is performed during the venous phase, where the changes in contrast enhancement over time are only minor. Because of the time difference between the successive acquisitions, patient motion may occur even though the breast is compressed. In such cases, image registration could be of help before further processing of the raw LE and HE images [27]. In CEM two images will be displayed to the radiologist. The first one, similar to a standard FFDM, is processed from a raw LE image. The second one is calculated by a weighted logarithmic subtraction of the raw LE image from the raw HE image (see paragraph 5.3). This image is further post-processed to calculated the "recombined" image that highlights areas of iodine uptake while simultaneously suppressing normal fibroglandular breast tissue (Figure 6).

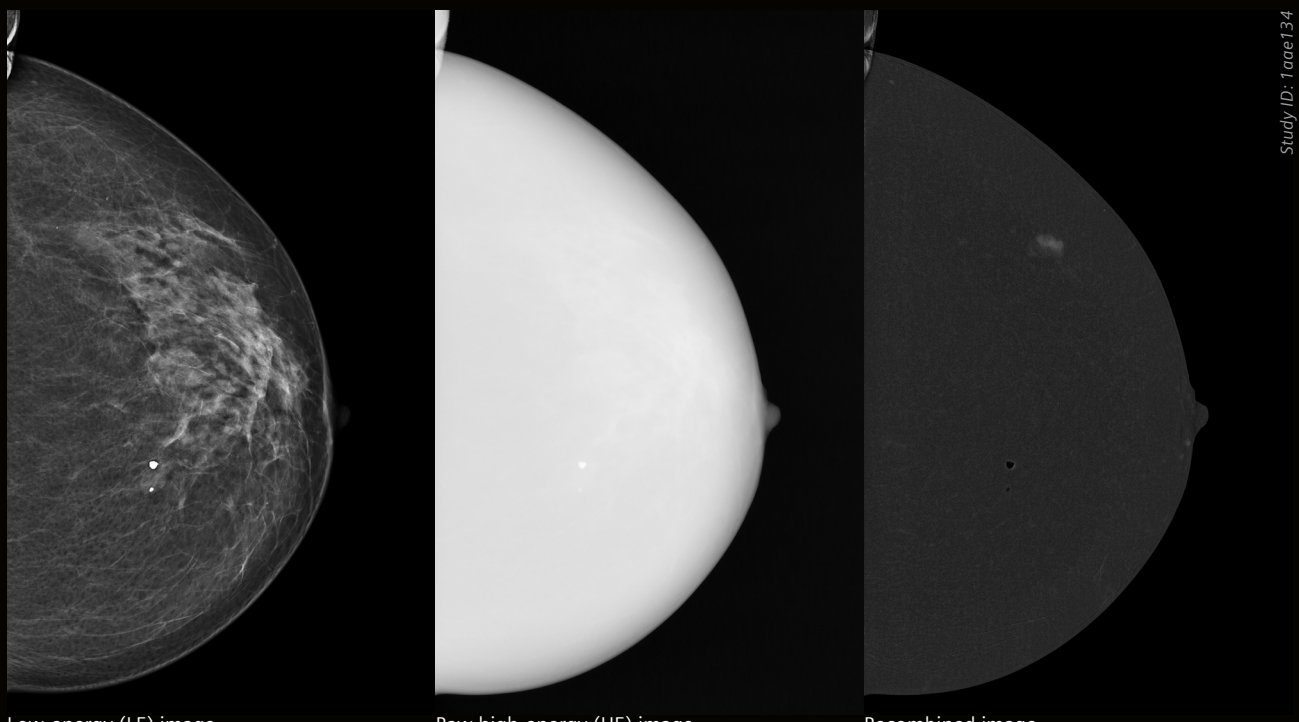


Figure 6: Clinical example of a female who underwent a CEM examination. The post-processed LE image (left) shows a breast with fibroglandular dense tissue. After the weighted logarithmic subtraction of the raw LE from the HE image (middle) and post-processing (see paragraph 5.3), the recombined image (right) reveals a small area of iodine contrast agent uptake without masking by the fibroglandular tissue. Histological analysis confirmed an invasive ductal carcinoma grade 2.

4. CEM reading and clinical indications

CEM has increasingly been established as a valuable tool in breast imaging. The CEM supplement of the ACR BI-RADS published in 2022 contributed significantly to integrating CEM as an essential component in clinical practice. A common lexicon simplifies and standardizes communication between specialists, resulting in moderate to substantial inter-reader agreement in reporting [28].

Following the recommendation stated in the CEM supplement of the ACR BI-RADS [12], it is important to include the interpretation of both the LE and the recombined image when evaluating a lesion. The raw HE image alone is not incorporated in the reading. As the recombined image primarily shows iodine uptake and not morphological structures, the LE image can be used for assessing morphologic abnormalities inside the breast. Studies have shown that ductal carcinoma *in situ* and invasive carcinoma can present as calcifications on LE images without abnormal enhancement on recombined images [29-31]. Therefore, if any suspicious calcifications are present on LE images with no enhancement or minimal lesion conspicuity on recombined images, further investigation is necessary [12]. Vice versa, the LE images may help to identify artefacts or BPE and rule out suspicion of a lesion in areas with unexpected enhancement in the recombined images. Siemens Healthineers' reading workstation MAMMOVISTA B.smart offers dedicated layouts for CEM examinations and enables toggling between the LE and recombined images.

To date, breast MRI is the gold standard functional imaging technique for women requiring diagnostic workup. The scientific literature delivers mixed results in studies comparing the diagnostic performance of breast MRI with CEM. Pooled data from meta-analyses indicate a slightly higher overall diagnostic performance of breast MRI compared to CEM [32-34]. The results of these meta-analyses, however, should still be interpreted with caution due to differences in study setup, small study sizes and limited subgroup data of the included studies. Importantly, MRI also has some disadvantages compared to CEM, potentially making the latter an attractive cost-effective alternative to MRI (Table 1).

Advantages of breast MRI or CEM	Breast MRI	CEM
Imaging both breasts simultaneously	x	
Extended field of view (including chest wall and axilla)	x	
No radiation dose	x	
No breast compression	x	
Dynamic imaging possible	x	
3D information	x	
Better availability		x
Lower costs		x
Shorter exam time		x
Imaging of calcifications		x
Imaging of patients with metal implants, claustrophobia, or those unable to lay in prone position		x

Table 1: Advantages of breast MRI or CEM

CEM and breast MRI both image the same physiological process – tumor neoangiogenesis – by using intravenous contrast agents to highlight hypervascularized tissue. Therefore, many indications for breast MRI also apply for CEM. Clinical indications of CEM that are reported in scientific literature are:

- Problem-solving after inconclusive findings on conventional imaging [35-37]
- Evaluation of symptomatic patients [38]
- Preoperative assessment of disease extent [32]
- Neoadjuvant therapy response monitoring and evaluation [39,40]
- Post-treatment breast cancer surveillance [41]
- Screening women with dense breasts [42] and/or intermediate to high risk for breast cancer [43]

5. ClearCEM

After the introduction of the MAMMOMAT B.brilliant system, Siemens Healthineers has implemented its second generation CEM reconstruction algorithm (ClearCEM). ClearCEM builds on the previous CEM algorithm, with new components in the postprocessing pipeline to make the background more uniform while improving lesion conspicuity in the recombined images [44].

5.1 Clinical workflow

The clinical workflow for a ClearCEM examination (Figure 7) starts with the injection of the iodinated contrast agent by means of a power injector. Injection protocols differ among institutions, but typically the iodine concentration of the contrast material varies from 300 mg/mL to 370 mg/mL. A total volume of 1.5 mL/kg of body weight (with a maximum of 150 mL) with an injection rate of 2-3 mL/sec is often used, followed by a saline flush [45]. At the time of injection, the breast is not (yet) compressed, to allow for normal tissue perfusion and unhindered inflow of the contrast agent into the breast. The dosage of the contrast agent is typically weight-dependent and varies between institutions and countries due to different iodine agents.

After a waiting time of approximately 2 minutes, the woman is positioned at the MAMMOMAT B.brilliant and the breast is compressed. Then, an LE and an HE image are acquired successively. Subsequently, a recombined image of that view, is calculated. These steps are then repeated for each additional view, without the need to perform a new contrast agent injection.

The recommended time window for performing multiple views with a single contrast agent injection is up to 10 minutes [12], although the views should be acquired without any unnecessary delays. The order in which the views are acquired seems to be of little clinical significance and does not appear to affect image quality [46,47]. However, many institutions adopted an imaging protocol that starts with a view of the affected breast to increase the likelihood of detecting malignant lesions with a fast contrast wash-out. Care should be taken

1) when handling the contrast agent to avoid contamination of the detector or the skin with pure contrast agent [48].
2) when positioning the breast to avoid inconsistent breast thickness, e.g. due to skin folds occurring predominately in the axillary region or inframammary fold, which can cause artefacts in the recombined images [48] that appear as bright areas and may lead to false-positive findings.

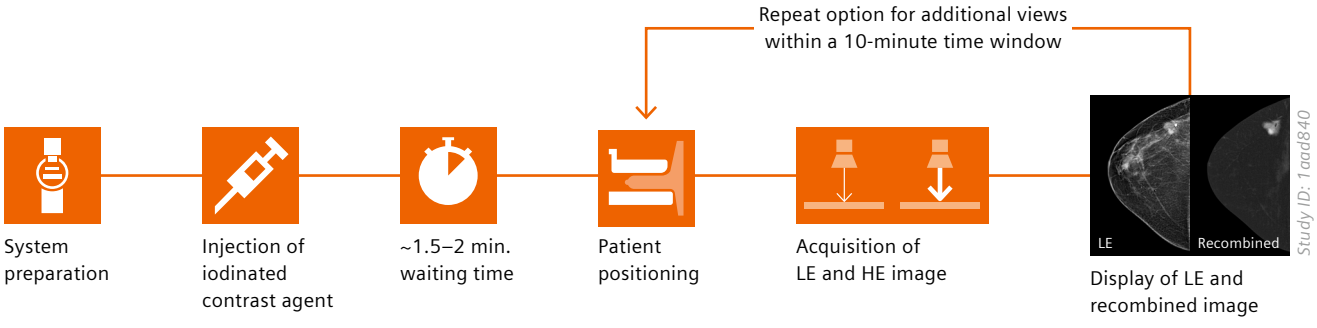


Figure 7: Simplified workflow illustration. The workflow may vary depending on the method used, patient situation and institutional preferences.

5.2 Image acquisition

The LE image is acquired first, all acquisition parameters being identical to those of a normal FFDM acquisition with a tungsten (W) anode target with a 1.0 mm aluminum (Al) filter and a tube voltage between 24 and 32 kV under automated exposure control. The LE acquisition kV range mimics FFDM acquisition parameter settings, so that a comparable image quality and dose as for standard FFDM is achieved. As previously explained (Chapter 3), the contrast agent uptake, although present in the tissue, is practically invisible in the LE image [23]. Subsequently, the HE image is acquired at 49 kV with the unique 1.3 mm titanium filter. The total acquisition time, start of LE exposure until end of HE exposure, depends on the breast thickness and density as measured by the automatic exposure control. Figure 8 demonstrates how the ClearCEM total acquisition time varies for different breast thicknesses.

The average glandular dose (AGD) of the LE acquisition equals that of a normal FFDM acquisition, whereas the additional dose of the HE acquisition is on average ~50% of the LE dose. Figure 9 demonstrates how the total AGD, LE plus HE dose, of ClearCEM varies for different breast thicknesses.

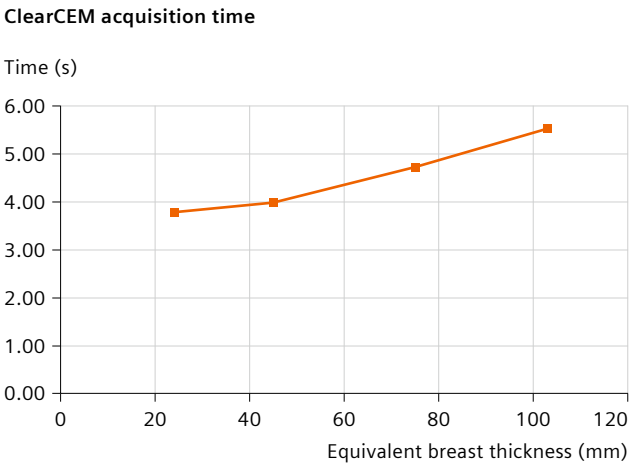


Figure 8: ClearCEM's total acquisition time, start of LE exposure until end of HE exposure, measured by imaging PMMA blocks under automated exposure control.

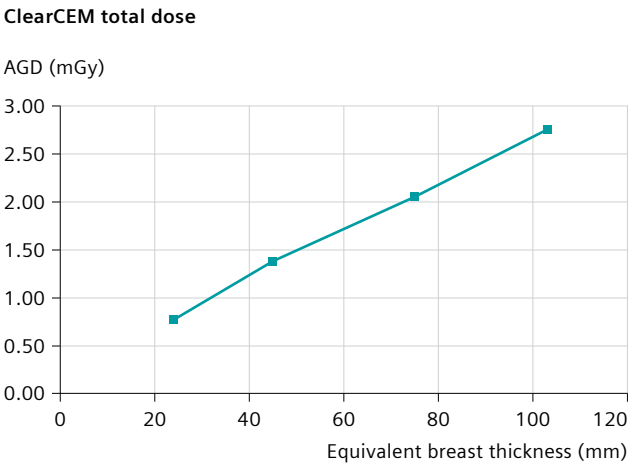


Figure 9: ClearCEM's total AGD, LE plus HE dose calculated according to the Dance method [49], measured by imaging PMMA blocks under automated exposure control.

5.3 Image post-processing

First, a new scatter correction algorithm removes scattered X-ray photons from the raw LE and HE images. Second, non-rigid image registration is performed between the raw LE and HE images to compensate for presence of patient motion [27]. Next, a weighted subtraction of the logarithmic HE and LE images is performed to calculate the raw recombined image:

*raw recombined image = ln(HE) – w * ln(LE) [eq. 1],*

where ln is the natural logarithm and w the weighting factor. The raw recombined image shows the iodine signal mixed with the influence of breast thickness. Further postprocessing with the help of a new thickness map estimation removes image artifacts where the compressed breast thickness is no longer constant, especially at the borders of the breast (Figure 10).

The effects of these new components is a more uniform background and higher contrast lesion conspicuity [44]. The final postprocessed recombined image is presented to the reader for interpretation and reporting. Figure 11 and 12 show two case examples of detected breast cancers with ClearCEM.

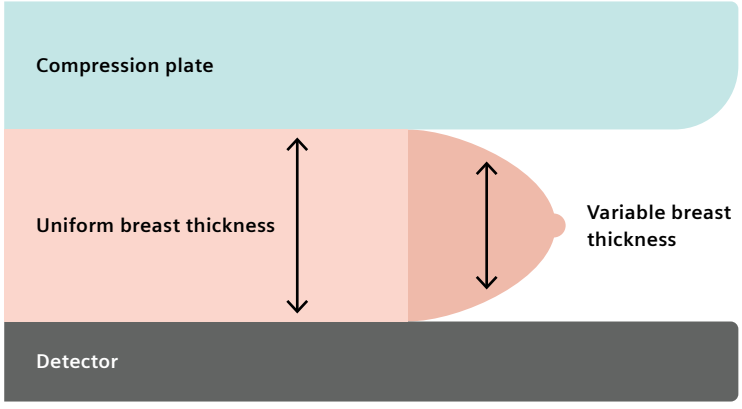


Figure 10: The recombined image post-processing suppresses artifacts at the borders of the breast, where the breast has a variable thickness.

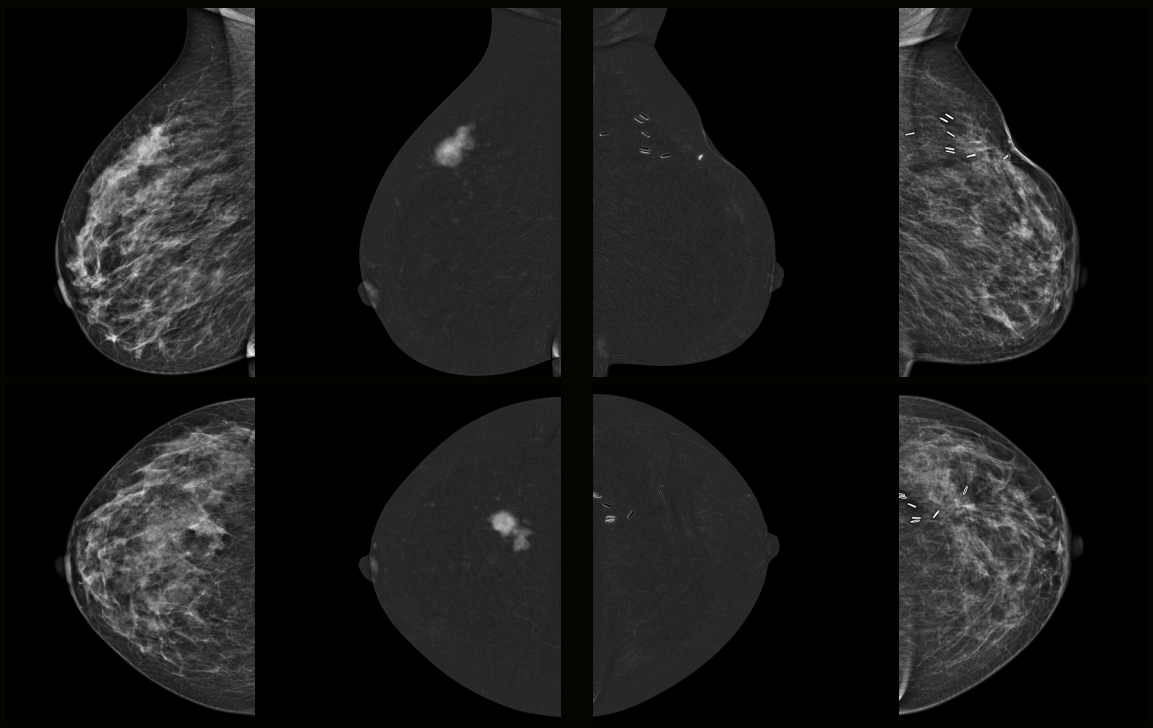


Figure 11: Patient with a history of left breast-conserving surgery. Follow-up imaging with ClearCEM showed an area of mass-enhancement in the right breast with mild BPE. Histological analysis confirmed a hormone receptor-positive, HER2-negative invasive ductal carcinoma grade 3.

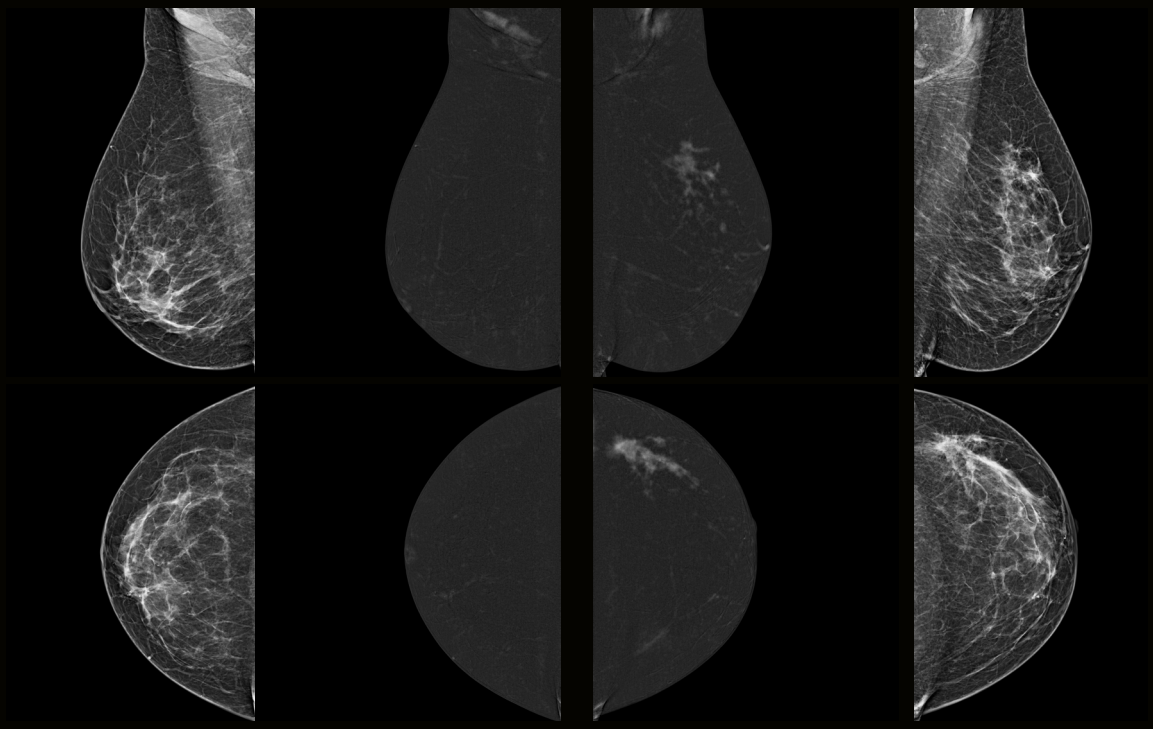


Figure 12: ClearCEM imaging showed an irregular mass with enhancement on the recombined images in the left breast with mild BPE. Histological analysis confirmed a hormone receptor-positive, HER2-negative invasive lobular carcinoma grade 2.

6. Combination of ClearCEM as a scout with DBT-biopsy

The ClearCEM technique can also be combined with other technologies such as DBT-guided biopsy. MAMMOMAT B.brilliant enables the acquisition of a 2D ClearCEM scout view in the DBT-guided (or stereotactic) biopsy workflow (Figure 13). First, the ClearCEM scout (LE and recombined images) is acquired followed by the DBT target acquisition. The target is set on the DBT image and visualized at the same x,y-coordinates in the ClearCEM scout images as a reference. Once the target is set, further imaging is similar to a standard DBT-guided biopsy procedure with the possibility of pre- and/or post-fired DBT images. The biopsy procedure requires a horizontal (i.e. lateral) needle holder in combination with the closed, non-fenestrated biopsy paddle. The main advantage of the closed paddle is to ensure uniform breast thickness and prevent artefacts in the recombined image due to differences in breast thickness, as breast tissue may bulge out of the paddle opening. The clinical utility of this procedure is for cases where contrast uptake information in addition to anatomical landmarks seen in FFDM and/or DBT may facilitate the radiologist in determining the biopsy target.

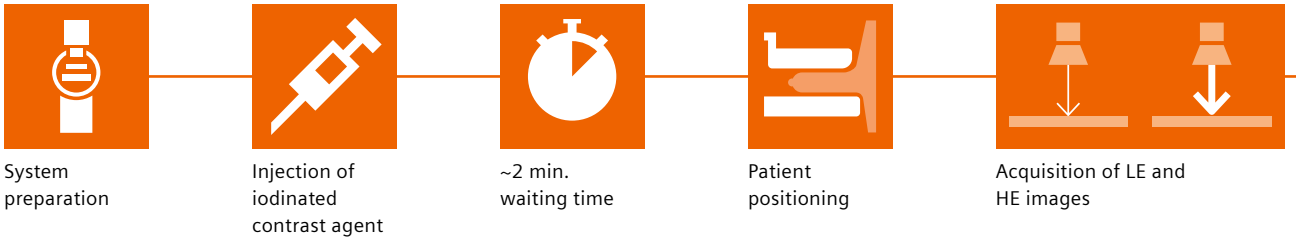
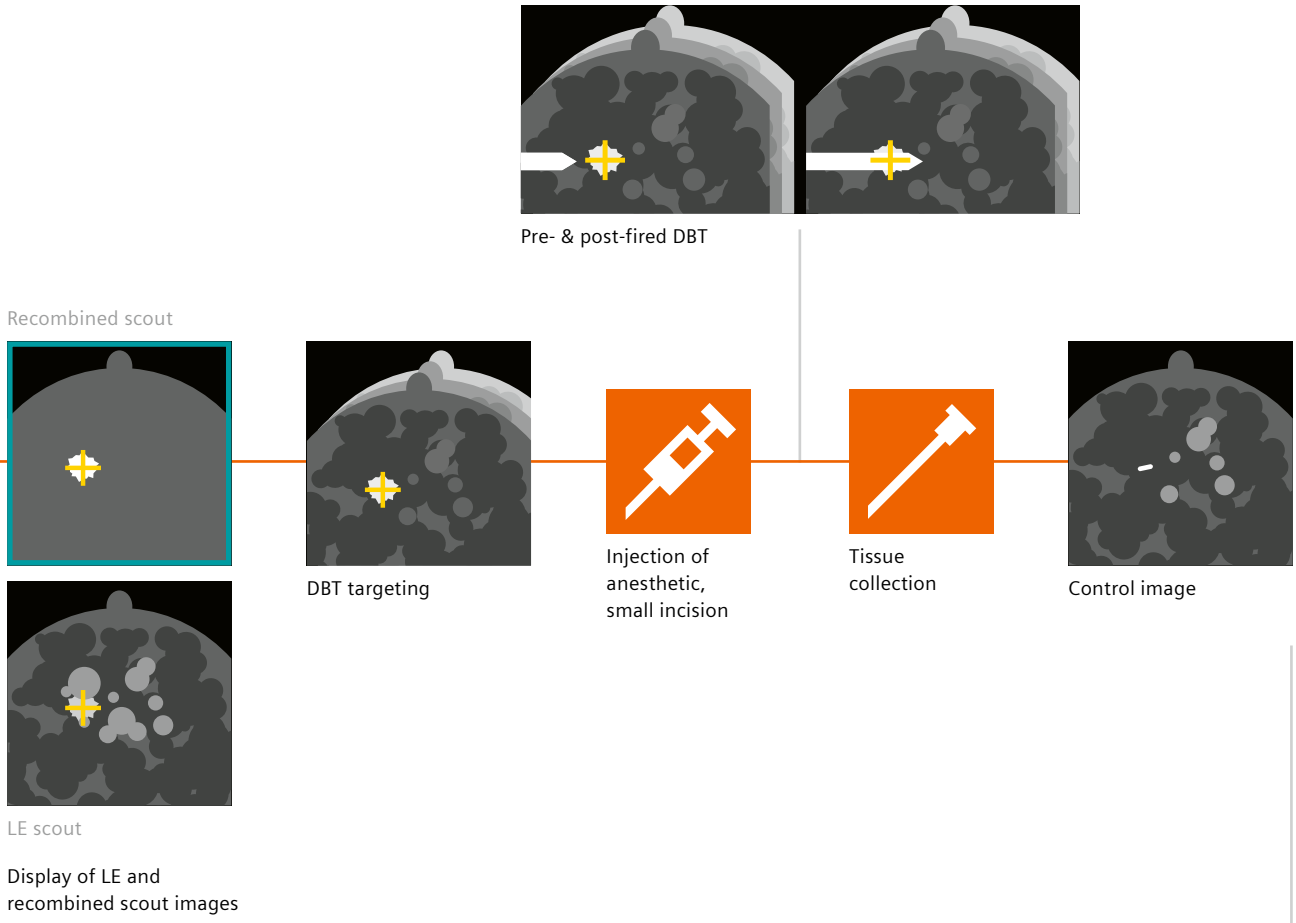


Figure 13: Simplified ClearCEM biopsy workflow illustration for MAMMOMAT B.brilliant with software version VA11.

7. Summary

ClearCEM on MAMMOMAT B.brilliant delivers functional diagnostic information with a high lesion conspicuity [44] in addition to the morphological information by FFDM, and may be a viable alternative to contrast-enhanced breast MRI. It offers certain advantages over MRI, including reduced cost and shorter procedure times.



8. Abbreviations

2D / 3D	two-dimensional / three-dimensional
ACR	American College of Radiology
AGD	average glandular dose
BPE	background parenchymal enhancement
CEM	contrast-enhanced mammography
ClearCEM	Siemens Healthineers marketing name for CEM with software version VA11
CT	computed tomography
DBT	digital breast tomosynthesis
FFDM	full-field digital mammography
HE	high-energy
LE	low-energy
MRI	magnetic resonance imaging
PMMA	Polymethylmethacrylate

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In this white paper, the term Contrast Enhanced Mammography (CEM) refers to the methodology in general.

ClearCEM refers to the product implementation of Siemens Healthineers for MAMMOMAT B.brilliant with software version VA11.

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