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Tomosynthesis and contrast-enhanced digital mammography: recent advances in digital mammography

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Abstract Digital mammography is more and more replacing conventional mammography. Initial concerns about an inferior image quality of digital mammography have been largely overcome and recent studies even show digital mammography to be superior in women with dense breasts, while at the same time reducing radiation exposure. Nevertheless, an important limitation of digital mammography remains: namely, the fact that summation may obscure lesions in dense breast tissue. However, digital mammography offers the option of so-called advanced applications, and two of these, contrast-enhanced mammography and tomosynthesis, are promising candidates for improving the detection of breast lesions otherwise obscured by the summation of dense tissue. Two techniques of contrast-enhanced mammography are available: temporal subtraction of images acquired before and after contrast administration and the so-called dual-energy technique, which means that pairs of low/high-energy images acquired after contrast administration are subtracted. Tomosynthesis on the other hand provides three-dimensional information on the breast. The images are acquired with different angulations of the X-ray tube while the object or detector is static. Various reconstruction algorithms can then be applied to the set of typically nine to 28 source images to reconstruct 1-mm slices with a reduced risk of obscuring pathology. Combinations of both advanced applications have only been investigated in individual experimental studies; more advanced software algorithms and CAD systems are still in their infancy and have only undergone preliminary clinical evaluation.

Keywords Breast · Digital mammography · Advanced applications · Contrast enhanced digital mammography · Tomosynthesis

Introduction

Until a few years ago it was inconceivable that digital mammography would be able to meet the high demands on image quality in breast imaging. The technical advances made in this field have since led to the development of digital mammography systems that are even superior to conventional mammography in some populations as shown in large comparative studies [1–4]. Digital mammography enables rapid imaging and rapid processing of the digital data. As a result, more sophisticated techniques can be employed that would be very difficult or even impossible to use in conjunction with film mammography. The sensitivity of mammography is especially limited in dense breasts, which can lead to superimposition artifacts and thereby obscure lesions; studies have shown that the sensitivity is reduced to 62.9% in dense tissue, compared with 87.0% in breasts with fatty involution [5]. Two promising techniques that may overcome the limitations of digital mammography associated with superimposition of structures are tomosynthesis, a cross-sectional technique, and contrast-enhanced mammography with injection of a contrast agent and image subtraction. The basic mechanism of tomography has been known for a long time (one of the first descriptions is from 1932 [6]), although it was not until 1972 that the term "tomosynthesis" was first used by Grant et al. [7]. The first description of tomosynthesis in combination with full-field digital mammography was published in 1997 [8]. Different vendors have since developed prototypes but experience in patients is still limited [9]. Contrast agents have been investigated in digital mammography since the beginning of the millennium and their successful use has been reported by several investigators, enabled after some hardware modifications [10–16]. The advantages of combining contrast administration with the use of cross-sectional imaging modalities [magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound] suggest that breast imaging might likewise benefit from contrast administration in the future. However, only a few pilot studies have so far investigated the combined use of tomosynthesis and contrast agents [17–19].

Description of the techniques

Various techniques are available to minimize the risk of overlooking breast lesions in women with dense breasts. Two interesting approaches currently used or evaluated are contrast-enhanced mammography and tomosynthesis. Two basic techniques of contrast-enhanced mammography are known: temporal subtraction and dual-energy techniques. As with "conventional" digital mammography, tomosynthesis can be performed using a slot scan technique or a flat panel technique, but as a difference compared with "normal" digital mammography when there are both scanning systems and stationary flat panel systems, all systems now require a mechanical scan motion in order to acquire the images from different angles required for the reconstruction of a tomosynthesis image.

Contrast-enhanced mammography

Contrast agents used

The most widely used intravenous contrast agents in radiology contain iodine to attenuate the X-ray beam. Much experience is available with iodine-based contrast agents, which is why it is natural to also use them for mammography. However, one has to be aware that the energy level of the X-ray beam used in mammography is typically much lower than in conventional radiography and that molybdenum/rhodium/tungsten are used as anode/filter material in order to maximize the soft tissue contrast. Low-energy X-rays are not optimal for the visualization of iodine-based contrast agents [20], which is why most studies conducted so far used higher energies. The reason is that structures taking iodine-based contrast agent are much more attenuating X-rays beyond the K-edge of iodine at 33.2 keV compared with all other structures in the breast. Therefore, most investigations of contrast-enhanced mammography used copper filters to shape the Bremsstrahlung spectrum beyond 33.2 keV and higher X-ray tube high voltage of up to 50 kVp. The higher contrast-to-noise ratio of iodine is achieved at the expense of the visualization of microcalcifications and high-contrast depiction of cancer on unenhanced images (microcalcifications and some low contrast objects are sometimes not visible any more in native high energy images). Some pilot experiments suggest that it is possible in principle to also visualize iodine-based contrast agents with lower energies, but this would be at the expense of an increase in dose delivered to the patient [21]. Such approaches are being pursued because it is desirable to have both the high contrast of mammography, e.g., to visualize microcalcifications, and information on contrast agent dynamics. New contrast media, such as agents based on bismuth for temporal subtraction and based on zirconium for dual-energy techniques (see below), might be of interest in order to perform contrast-enhanced mammography in the low-energy range currently used for unenhanced mammography [15]. This would mean that a contrast agent has to be developed exclusively for mammography, which is expensive and of interest to manufacturers only if there is an existing market for mammographic contrast agents.

Contrast-enhanced mammography: temporal subtraction

For temporal subtraction, first an unenhanced image is acquired, next an iodine-based contrast agent is administered intravenously, and then additional images are acquired (in most published studies, about three to five postcontrast images at intervals of 1 min). Most investigators administered the contrast agent at a concentration of about 1–1.5 ml/kg body weight [11, 13, 14, 16]. As with dynamic contrast-enhanced breast MRI, the precontrast image is then subtracted from the postcontrast image for evaluation of the temporal course of contrast enhancement [22, 23]. Figure 1 shows an example of contrast-enhanced mammography with subtraction images obtained at three time points after contrast administration. Note that the contrast-to-noise ratio of iodine is too poor for direct interpretation of the unsubtracted images. This is a limitation of the temporal subtraction approach because purely visual differentiation of contrast enhancement and artifacts (e.g., due to motion) is more difficult. As a matter of fact, motion artifacts have an important impact in temporal contrast-enhanced mammography because images are typically acquired over several minutes with only minimal compression of the breast. Motion artifacts could be reduced by more pronounced compression of the breast

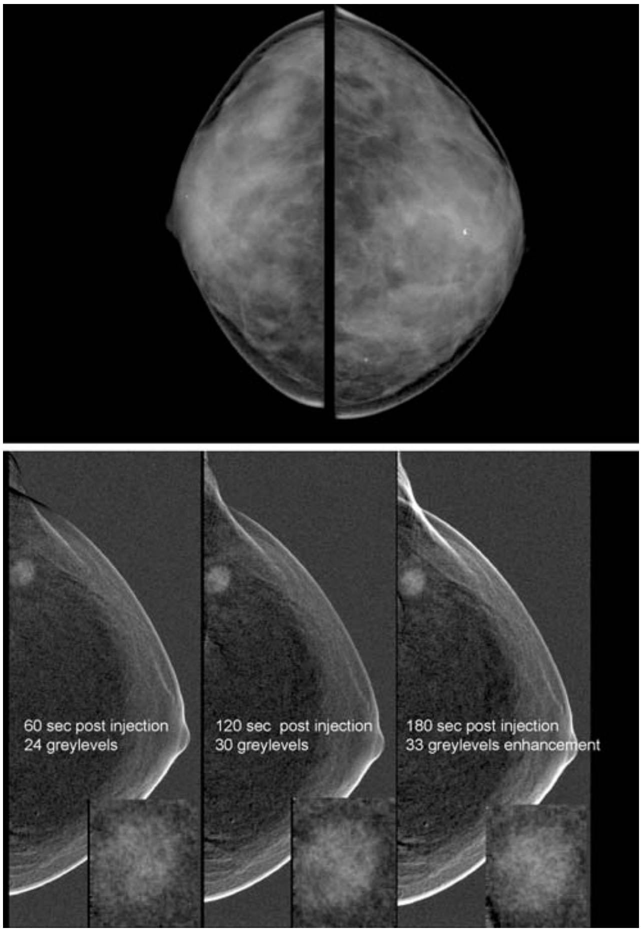

Fig. 1 Example of contrast-enhanced mammography with temporal subtraction: precontrast images (cranio-caudal) and images obtained at three time points after contrast administration (subtractions). Pathology is easier to see on postcontrast images compared with precontrast images (histologically proven carcinoma by ultrasound guidance)

but would lead to patient discomfort if done for several minutes and might also affect contrast enhancement due to limitation of blood flow. The approach of temporal subtraction in mammography was developed on the basis of MR protocols which allow differentiation of benign and malignant lesions on the basis of their enhancement patterns (washout typical of malignant tumors on MRI and delayed enhancement typical of benign lesions). However, the data available so far suggest that the enhancement patterns known from MRI cannot simply be adopted in a 1:1 fashion [11].

Dual energy

Another approach for the visualization of contrast agents in mammography is the dual energy technique. This approach exploits the so-called K-edge of the contrast agent administered. X-ray absorption sharply increases above the K-edge (33.2 keV for iodine). This effect is exploited by intravenous contrast administration and subsequent acquisition of two images, one with an energy above the K-edge of iodine and one below its K-edge. The two images are then subtracted for optimal visualization of the iodine contrast. This approach also requires an energy level far above that of conventional mammography. Again, it has been shown that it is possible to use elements other than iodine with a lower K-edge in the low-energy range of mammography [15].

Of interest for the visualization of contrast agents in the dual energy mode are mammography systems with detectors that can distinguish photons with high energy and photons with low energy within a single image (photon counting systems). These are so-called slot scan systems with slit-shaped detectors that scan the breast with a narrow X-ray beam. Initial experiments with slot scan systems are promising and suggest that they may yield images that are quasi free of motion artifacts. Figure 2 shows an example of a phantom image obtained in the dual-energy mode using a photon counting system.

Tomosynthesis

Unlike conventional tomography, where the X-ray source and detector move in opposite directions, tomosynthesis generally uses a stationary detector while only the X-ray source moves. Radiographs of the breast are obtained from different angles. In this way, objects located at different distances above the detector are shifted against each other in the resulting images. Figure 3 shows a tomosynthesis projected view of a phantom containing a simulated round lesion and microcalcifications at different heights (GE Healthcare tomosynthesis investigational device). The three examples selected illustrate how the two structures are shifted against each other. In a further step, individual slices can be generated (e.g., shift and add algorithm, see next section) from the set of images obtained under different angles (nine to 25 images, depending on the manufacturer). Tomosynthesis is often done with tungsten or rhodium anodes/filters, which are also used increasingly in “normal” digital mammography [24]. Because tomosynthesis is performed from different angles, images are typically obtained without using a grid. This apparent disadvantage can be compensated for to some extent by the higher contrast resolution of digital mammography compared with film mammography [25]. This technique of digital mammography tomosynthesis is performed with flat panel detectors and was described as early as 1997 [8] and is increasingly being used and tested. More recently, multislit scanning systems have also been used for tomosynthesis of the breast. Figure 4 shows a diagram of the function of slit scanning tomosynthesis. A clinical example of slot scan tomosynthesis is presented in Fig. 5.

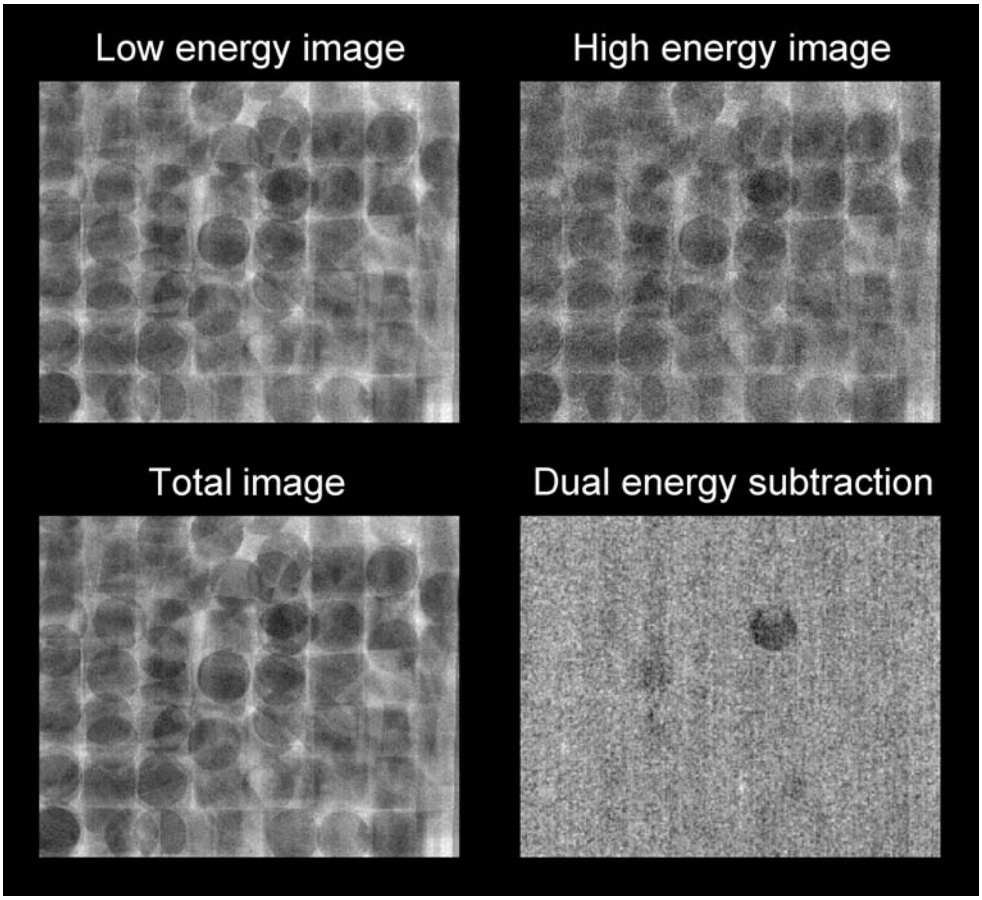

Fig. 2 Dual energy phantom image of an iodine-based contrast agent acquired with a slot scan system. Dark spot in "Dual energy subtraction" represents iodine (kindly provided by Mats Danielsson, Sectra)

The multislit scan technique enables acquisition of multiple projections with a single scan. This is accomplished by moving the entire rotational axis downward below the detector and by movement of the detector and X-ray source in the same direction. Moreover, use of monochromatic X-ray sources has been proposed, which might markedly reduce the radiation dose of slot scan systems. This reduction might be possible because in the polyenergetic spectra used in film mammography, the low-energy photons do not contribute to image generation and only increase the radiation exposure while the higher-energy photons even tend to impair image quality. Therefore, an overall improvement in image quality and a reduced radiation exposure are expected [26–28]. Also, the fact that no grid is used in tomosynthesis is the routine procedure for slot scan systems and has been investigated in several studies [29, 30].

Software: image viewing systems and reconstruction algorithms

Various reconstruction algorithms are available to process the tomosynthesis source data sets [31–33]. As mentioned above, early studies of tomosynthesis [8] used the shift-and-add technique to generate individual slices from the source images obtained at different angles. This is basically very close to a simple "back projection" algorithm. Extensive experience with three-dimensional (3D) reconstruction is available from other 3D imaging techniques such as computed tomography. Today, CT data sets are typically reconstructed using filtered back projection. However, iterative reconstruction of the 3D data sets from individual projections using a system of linear equations was already proposed by Hounsfield in the patent specification from 1972. This approach was acceptable for CT scans obtained with an image matrix of 64 pixels but became too complex for images with higher spatial resolution. Therefore, this approach was abandoned in favor of filtered back projection although it is actually more accurate. Tomosynthesis scanners from various vendors now primarily use algebraic reconstruction algorithms, which were shown to be superior for the Lorad tomosynthesis prototype with nine images [31]; for the GE Healthcare prototype, more advanced algebraic algorithms, such as the simultaneous algebraic reconstruction technique (SART) or maximum likelihood expectation maximization (MLEM), have been experimented with which

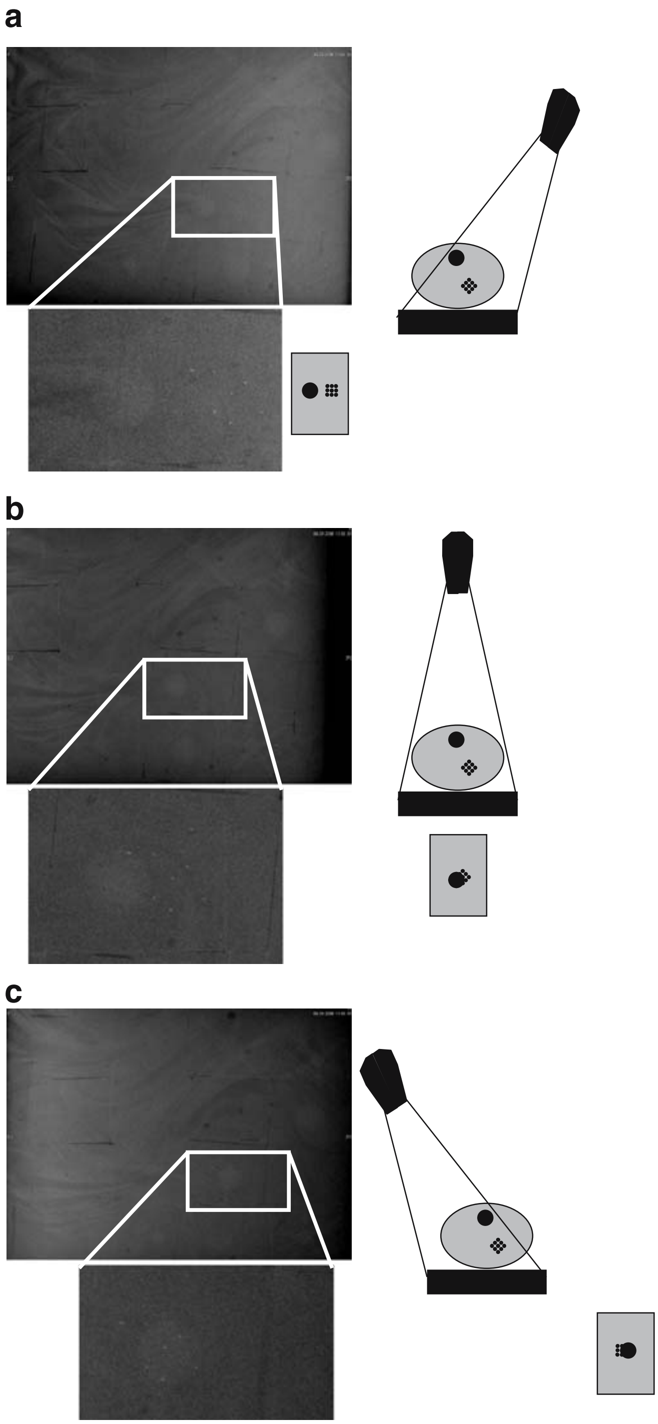

Fig. 3 **a**–**c** Flat panel tomosynthesis images of a phantom acquired from different angles (GE Healthcare, Buc, France)

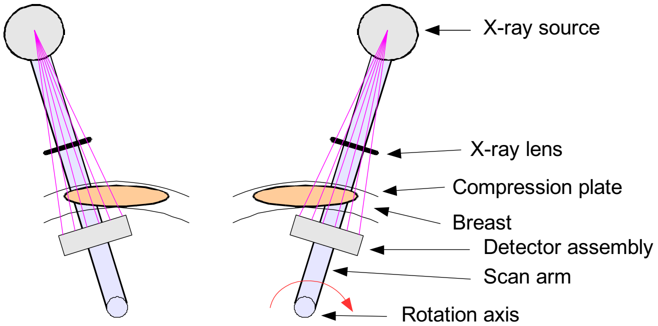

Fig. 4 Diagram of the function of slot scan tomosynthesis

reconstruct the source images at 15 or 21 different viewing angles [34]. An aspect to which only little attention has been paid so far is the fact that further postprocessing of the individual slices may become necessary for optimal interpretation of the images by the radiologist. Single thin slices in multislice CT have a high noise level, which is why they are typically used only to answer specific questions, e.g., regarding the presence of partial volume effects, and not for direct interpretation of the findings. This is why secondary reconstruction of thick slices from thin-slice source data sets has a crucial role in mammography with its high demands regarding image noise (identification of microcalcifications) and contrast resolution. Maximum intensity projections (MIPs) from CT data sets are images with extremely high noise levels but excellent contrast, while simple average algorithms yield images with very little noise but also very low contrast resolution. Figure 6 shows the depiction of simulated microcalcifications and a round lesion in a phantom in the original 1-mm reconstruction (SART algorithm), compared with the depiction on a subsequently reconstructed thick-slice MIP image and average image. Future clinical studies will have to show which construction algorithms are most suitable for processing tomosynthesis data sets.

Prospects: combination of tomosynthesis/contrast administration, CAD systems

Both techniques—tomosynthesis and contrast-enhanced mammography—will be slightly more time-consuming than film mammography, which holds true for both image acquisition and interpretation. This is why it remains to be seen whether either of these new techniques can replace mammography for screening. The new techniques are expected to make image interpretation more accurate because they largely eliminate summation effects that degrade image quality in conventional mammography. Contrast-enhanced mammography is of interest in the non-screening setting. A disadvantage reported by most studies conducted so far is that interfering summation effects must be eliminated by image subtraction, which makes the technique susceptible to artifacts. This limitation might be minimized by combining contrast-enhanced mammography with tomosynthesis. A first study of this combination has yielded promising results [19] but the data published in

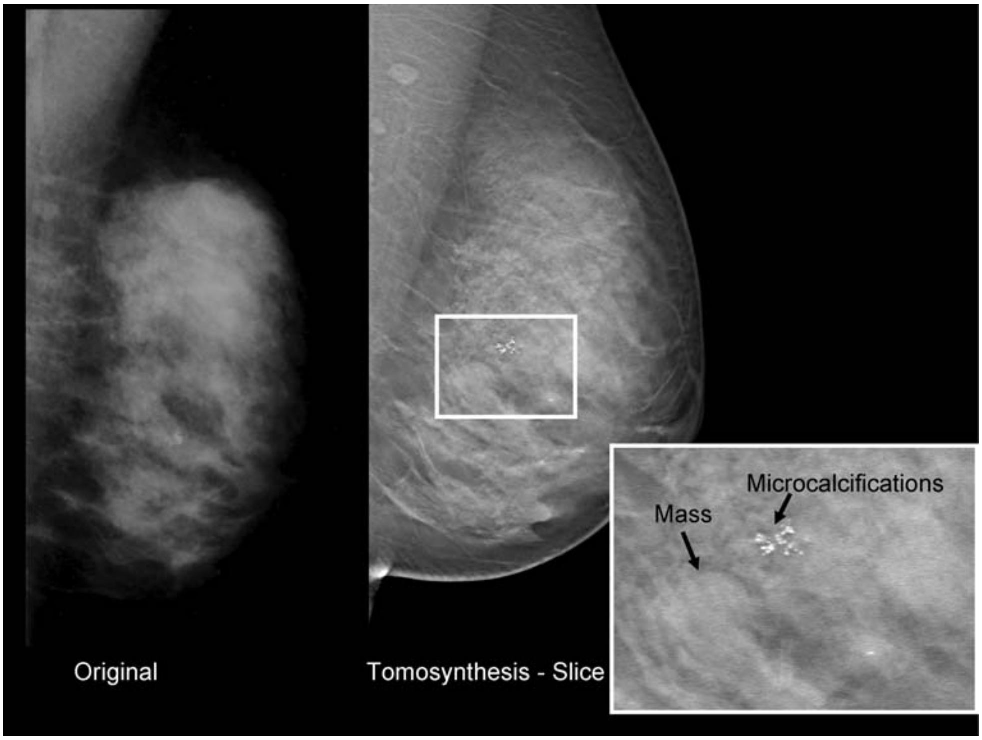

Fig. 5 Example of slot scan tomosynthesis, microcalcifications and mass visible in one tomosynthesis slice (kindly provided by Mats Danielsson, Sectra)

writing is limited to 13 patients so far. In 12 of these patients, the combination of tomosynthesis and contrast administration were in agreement with the histologically proven MRI diagnoses. However, in one of the patients, a papilloma with marked enhancement on MRI failed to show any enhancement using the combined approach. This observation might suggest that the overall contrast-to-noise ratio of iodine in contrast-enhanced mammography is inferior to that of gadolinium in MRI—but further clinical studies are needed for a final appraisal of the clinical relevance of this observation. Based on the experience with earlier studies of contrast-enhanced mammography, contrast-enhanced tomosynthesis in this study was performed using copper filters and high energies as well as a contrast agent concentration of 1 ml/kg body weight and a similar rate of administration.

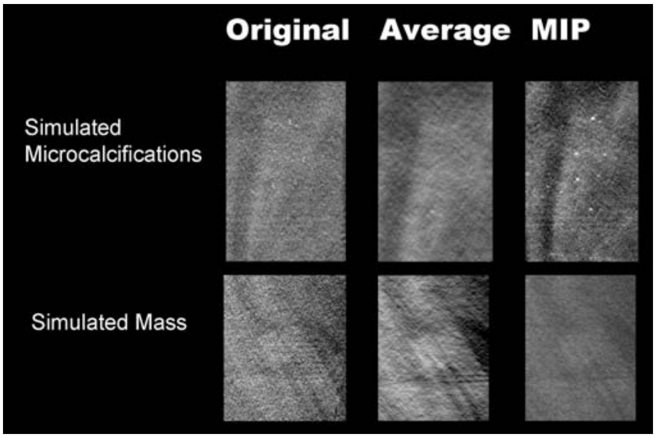

Fig. 6 Thick-slice reconstructions from 1-mm tomosynthesis slices. *Left:* source image; *middle:* average algorithm (reconstruction of a 1-cm slice); *right:* maximum intensity projection (reconstruction of a 1-cm slice)

The software is crucial for both tomosynthesis and contrast-enhanced mammography. It is known from MRI that comfortable evaluation of dynamic enhancement patterns is possible only on workstations. Computer-assisted diagnosis is advantageous in both mammography and MRI. Initial reports on CAD systems for tomosynthesis have been published [35], and some investigators already used dedicated systems for analysis of contrast-enhancement patterns/subtraction images.

In summary, the two methods described here are promising to at least partially overcome the limitations of currently available mammography techniques. However, clinical experience with both tomosynthesis and contrast-enhanced mammography is still limited and further studies are needed to evaluate their role.

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