



Research paper

Contrast-enhanced spectral mammography as work-up tool in patients recalled from breast cancer screening has low risks and might hold clinical benefits



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ABSTRACT

Objective: Contrast-enhanced spectral mammography (CESM) is a reliable problem solving tool in the work-up of women recalled from breast cancer screening. We evaluated additional findings caused by CESM alone and outweighed them against the disadvantages of this technique.

Methods: From December 2012 to December 2015, all women recalled from screening who underwent CESM were considered for this study. Radiation exposure and number of adverse contrast reactions were analysed. An experienced breast radiologist reviewed all exams and identified cases with lesions detected by CESM alone and scored their conspicuity. From these cases, data on breast density and final diagnosis were collected. For malignant cases, tumour grade and receptor characteristics were also collected.

Results: During this study, 839 women underwent CESM after a screening recall, in which five minor adverse contrast reactions were observed. Median radiation dose per exam was 6.0 mGy (0.9–23.4 mGy). Seventy CESM-only lesions were detected in 65 patients. Of these 70 lesions, 54.3% proved to be malignant, most commonly invasive ductal carcinomas. The remaining CESM-only lesions were benign, predominantly fibroadenomas. No complications were observed during biopsy of these lesions. Retrospectively, the majority of the lesions were either occult or a ‘minimal sign’ on low-energy CESM images or the screening mammogram.

Conclusion: Using CESM as a work-up tool for women recalled from screening carries low risk for the patient, while additionally detected tumour foci might hold important clinical implications which need to be further studied in large, randomized controlled trials.

1. Introduction

Contrast-enhanced spectral mammography (CESM) has shown to be consistently superior to full field digital mammography (FFDM) [1,2]. Previous studies concluded that CESM is a reliable problem-solving tool in patients recalled from a national breast cancer screening program [3,4]. In these studies, the use of CESM as a work-up tool in recalled women resulted in an increase in all diagnostic performance parameters, mainly specificity and positive predictive value [3].

However, these results reflected CESM’s performance on a patient-to-patient level. Several risks and benefits associated with CESM use were not considered in these parameters, such as the detection of occult breast cancers or the identification of multifocal tumours where

unifocal tumours were suggested by the initial recall. Disadvantages of CESM include an increase in radiation dose [5], the use of iodine-based contrast agents (which might cause adverse anaphylactic reactions) and additional false positive findings induced by CESM alone.

In this study, we aimed to analyse the risk and benefits of using CESM in patients recalled from screening. We evaluated the additional findings that were found by CESM only compared to the original screening FFDM. Furthermore, we studied the number of CESM-induced false positive findings and the number of CESM-detected breast cancers that were either mammographically occult or visible only in retrospect as a ‘minimal sign’. These observations were weighted against the number of adverse contrast agent reactions and the total radiation dose used in a complete CESM exam.

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2. Materials and methods

2.1. Study design

In the Netherlands, women between 50 and 75 years are invited to participate in the national breast cancer screening program in which they undergo FFDM biennially [6]. If a breast abnormality is detected by two independent certified screening radiologists (three in cases of discrepancies), women are recalled to an assessment clinic for further imaging. In our institute, CESM is the primary imaging tool for the diagnostic work-up of these patients regardless of the type of mammographic abnormality that was recalled.

All women who underwent CESM in the period December 2012 to December 2015 were considered for this retrospective analysis. Included were women that underwent CESM as part of their work-up after a screening recall. Excluded were patients with breast implants and who underwent CESM for an alternate indication (such as breast MRI alternative) or response monitoring in patients who received neoadjuvant chemotherapy. Due to its retrospective study design, the acquisition of informed consent was waived by our local ethics committee (METC decision number 16-4-099).

For all cases in the final analysis, the incidence of adverse contrast reactions (including its grade of severity) and total radiation exposure used in each CESM exam was collected. For the cases containing additional CESM-only lesions breast density and final diagnosis of the findings was collected. In malignant cases, tumour grading and receptor status was also collected.

2.2. Imaging protocol and radiation exposure measurements

All examinations were performed on two identical CESM-compatible mammography systems (Senographe Essential with Senobright* upgrade, GE Healthcare, Chalfont, United Kingdom). The CESM imaging protocol was described previously [8,9]. In short, a non-ionic monomeric, low-osmolar contrast agent was administered intravenously (iopromide, Ultravist 300; Bayer Healthcare, Germany) two minutes before the first image acquisition. A dose of 1.5 mL/kg body weight was automatically administered with a flow rate of 3 mL/s followed by a saline flush. Standard mediolateral oblique (MLO) and craniocaudal (CC) views were obtained with additional views being requested by the radiologist if deemed necessary. Images and data, such as radiation exposure-related data, were stored in a dedicated PACS (IMPAX version 6.5, AGFA Healthcare, Mortsels, Belgium).

The occurrence of adverse contrast reactions in patients were collected from the radiology report and/or patient files. Based on these reports, the adverse reactions were categorized according to the European Society of Urogenital Radiology (ESUR) guidelines as mild (*i.e.* itching, nausea, urticarial, mild vomiting), moderate (*i.e.* marked urticaria, vasovagal attack, facial/laryngeal edema, bronchospasm, severe vomiting) or severe (*i.e.* hypotensive shock, respiratory arrest, cardiac arrest, convulsion) [7,10].

Radiation exposure was determined by calculating the average glandular dose (AGD), as it is the radiation absorbed by the glandular tissue that is related to health detriment. The AGD was determined following the European guidelines [11], which use the Dance model [12,13] according to methods described previously [14]. In short, for both mammography systems tube output and half value layer (HVL) was measured for low and high energy spectra separately.

For the low energy spectra, a dosimeter calibrated for the target/filter combinations observed in the clinical images (Piranha; RTI Electronis, Molndall, Sweden) was used. For the high energy spectra, a dedicated 1.5 mL ionization chamber was used (PS-033), combined with a Capintec 192A electrometer (Capintec Inc, Ramsey, NJ). The high energy tube output was determined by the difference of two measurements: 1) low and high energy cumulative measures and 2) low energy measures using a setting of CESM exposure parameters in FFDM

mode. The remaining technical parameters required for AGD calculation, *i.e.* kV, target, filter, current-time product and compressed breast thickness (CBT), were obtained for each exposure from the images DICOM header. In case of unilateral examination of the breast due to a previous mastectomy, the given radiation dose for contralateral side was set on 0 mGy. The life attributable risk (LAR) was calculated using the LAR-values reported in the BEIR VII report [15]. The LAR calculations were based on the AGD of one full exam for the ages of 40, 60 and 80 years.

For all included patients, one breast radiologist (certified by the Dutch Reference Centre for Screening and with more than five years of CESM reading experience) reviewed the images on a dedicated mammography workstation (IDI MammoWorkstation 4.7.0, GE Healthcare, Chalfont St Giles, UK) which was customized with mammography-approved monitors (Barco Coronis 5MP Mammo, Barco, Kortrijk, Belgium). The correspondence letter of the screening institute, in which the recalled lesion(s) was (were) annotated, was made available prior to image review. Based on this knowledge but blinded for final diagnosis, the radiologist identified any additional observations that were made during the exams solely on the basis of CESM information ('CESM-only lesions'). In addition, the radiologist reviewed whether the CESM-only lesions were retrospectively visible on either the low-energy CESM images or the screening FFDM, scoring lesion conspicuity on a three-point-scale: (0) occult (*i.e.* no abnormality visible), (1) 'minimal sign' (*i.e.* an abnormality is visible in retrospect but the radiologic appearance did not justify a recall), and (2) visible lesion (*i.e.* a clear abnormality is visible and should have been recalled or annotated by the screening radiologists).

The detection of additional benign lesions based on CESM was considered as disadvantage, since it would result in (unnecessary) supplementary procedures without any patient benefit. The detection of additional tumour foci by CESM alone, it being either additional foci next to a unifocal recalled lesion or the detection of an occult cancer, was considered to be an advantage of CESM-based work up of recalled patients (Fig. 1).

Breast density classification was collected from the radiology report and was assessed using the definitions provided in the BI-RADS lexicon by visual inspection and classified as follows: (1) the breasts are almost entirely fatty, (2) there are scattered areas of fibroglandular density, (3) the breasts are heterogeneously dense and (4) the breasts are extremely dense [16].

2.3. Histopathological analysis

For all additional (CESM-only) lesions, pathological examination after core needle biopsy (in benign lesions) or surgical excision (in malignant or benign excised lesions) served as the gold standard.

Core biopsies were routinely processed and were immediately fixed with formalin and stained with haematoxylin and eosin (HE) according to current national guidelines [17]. Pathology samples were routinely processed. Excisions were freshly lamellated for optimal formalin fixation, and afterwards grossed. Tumour size was measured with representative slides being taken, and subsequently paraffin embedded. 3 µm HE stained slides were obtained after which initial pathological analysis occurred. If necessary, additional immunohistochemical stains were performed for completing diagnosis. For invasive breast cancers, tumour grade (Nottingham Histologic Score system; the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) [18–21] and the final estrogen (ER), progesterone (PR) or human epithelial growth factor receptor-2 (HER2) receptor status were determined according to national guidelines. For ductal carcinoma *in situ* (DCIS), receptor status was not assessed [22]. All diagnostics were done by a single breast pathologist.

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