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The feasibility of contrast-enhanced spectral mammography immediately after contrast-enhanced CT

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Abstract
Contrast-enhanced spectral mammography (CESM) is a digital mammography method that requires an intravenous injection of iodinated contrast material to detect hypervascular lesions. In patients undergoing evaluation for metastases before breast tumor surgery, a contrast material must be injected for computed tomography (CT) and CESM studies. The purpose of our study was to investigate the feasibility of performing CESM immediately after contrast-enhanced CT, without injecting additional contrast material. We enrolled 77 women with 88 breast carcinomas. Immediately after contrast-enhanced CT, we performed CESM without injecting additional contrast material. The patients were divided into two groups based on the length of the interval between contrast material injection and the start of mammography. In group A ($n=51$), it was less, and in group B ($n=26$) it was more than 7 min. We measured the tumor gland contrast of each tumor on the CESM images and recorded the tumor opacification on a 4-point visual scale. The mean interval between the start of contrast material injection for CT and the acquisition of mammograms in groups A and B was 5.41 and 10.40 min, respectively. All lesions were detectable on the CESM images. There was no significant difference in the visual evaluation between the two groups ($p=0.21$). CESM immediately after contrast-enhanced CT without the injection of additional contrast material is feasible and cost-effective.

Keywords Contrast-enhanced spectral mammography · Digital mammography · Contrast-enhanced computed tomography · Iodinated contrast

1 Introduction

Breast contrast-enhanced magnetic resonance imaging (MRI) is currently considered the most sensitive technique for the detection of breast lesions. The American Cancer Society recommends MRI screening for high-risk women. However, MRI examinations are expensive, and women with claustrophobia cannot be examined this way. As an alternative, contrast-enhanced spectral mammography (CESM) has been suggested [1, 2].

CESM is a digital mammography method that requires an intravenous injection of iodinated contrast material for the detection of hypervascular lesions [1, 2]. It uses a pair of low- and high-energy images to subtract the normal mammary gland and to highlight tumor vascularization [3]. The technique is reported to yield a higher positive predictive value and fewer false-positive findings than contrast-enhanced MRI [4].

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In patients undergoing evaluation for metastases before breast tumor surgery, contrast material must be injected for computed tomography (CT) and for mammography studies. For CESM, contrast material with an iodine concentration between 300 and 370 mg I/ml is used; the injection volume (1.5–2.0 ml/kg of body weight) is similar to that delivered for abdominal CT [5]. A high-dose contrast material is expensive and inadvisable in patients with renal failure.

We investigated whether CESM performed immediately after contrast-enhanced CT (CECT) can detect tumors without the need for injection of additional contrast material.

2 Materials and methods

2.1 Patients

Our study was approved by the ethics review committee in our institution, and all patients provided written informed consent for their inclusion. The study population comprised 77 consecutive women (median age 59 years; range 36–92 years) with 88 breast carcinomas who were referred to our hospital between August 2015 and March 2017. All patients underwent breast ultrasonography, mammography, and contrast-enhanced MRI, followed by a histological confirmation of the breast carcinoma. Next, we performed CECT to evaluate for metastases, as well as accurately measure the size and location of the breast carcinomas to help in planning the treatment. At the same time, bilateral CESM without additional contrast material was also performed. Patients with renal insufficiency (estimated glomerular filtration rate < 30 ml/min per 1.73 m^2), allergy to contrast agents, and pregnant or possibly pregnant women were excluded.

2.2 CT scanning

Unenhanced and contrast-enhanced helical CT scans were performed using a 128-detector-row CT scanner (Brilliance iCT, Philips Electronics, Netherlands) or a 64-detector-row CT scanner (Bright Speed Elite, GE Healthcare, Milwaukee, WI). We delivered 500 mg I/kg of nonionic contrast material (Iopamidol, Iopamiron 300 mg I/ml) at a flow rate of 2.0 ml/s to all patients. Whole-body CT scans were acquired 90 s after the start of contrast material injection. The scan parameters included: collimation, 128×0.625 mm or 64×0.625 mm; rotation time 0.5 s; tube voltage, 120 kV; and tube current, 120–480 mA. Axial images were reconstructed; the slice thickness and reconstruction interval were 5.0 and 5.0 mm, respectively.

2.3 CESM imaging

Immediately after CECT, the patients moved to the mammography suite; the distance was approximately 5 m. CESM was performed on a Senograph Essential CESM instrument (GE Healthcare, Solingen, Germany). Without injecting additional contrast material, low- and high-energy CESM images were acquired under automated parameters during one breast compression. Depending on the breast density and compression thickness, molybdenum (Mo) or rhodium (Rh) target and Mo or Rh filters were used [2]. For low-energy mammography, the kVp ranged from 26 to 31; it ranged from 45 to 49 for high-energy mammograms [2]. After mediolateral oblique (MLO) and craniocaudal (CC) views of the affected breast were acquired, we obtained the same views of the unaffected breast. We recorded the interval between the start of contrast material injection for CT and the start of mammography, and then divided the patients into two groups [group A, interval less than 7 min (51 patients with 57 carcinomas); group B, interval more than 7 min (26 patients with 31 carcinomas)].

2.4 Quantitative analysis

One reader with 20 years of experience in mammography performed measurements on a high-resolution workstation (Barco Inc, Duluth, GA). The tumor gland contrast (TGC) was recorded as previously described [6]. Three regions of interest (ROIs) were marked on a peripheral site in the tumor and their mean value was calculated. Then, three ROIs (mean area 3.0 mm^2) were placed on the adipose tissue, and their mean value was calculated. TGC was standardized to the enhancement of the adipose tissue and defined as:

$$\mathrm{TGC} = \mathrm{ROI}_{\mathrm{L}} - \mathrm{ROI}_{\mathrm{A}},$$

where L and A represent the lesion and adipose tissue density, respectively. The TGC on MLO and CC views of the affected breast was recorded and the mean TGC values were calculated using the equation:

$$\mathrm{TGC}_{\mathrm{mean}} = (\mathrm{TGC}_{\mathrm{MLO}} + \mathrm{TGC}_{\mathrm{CC}})/2.$$

2.5 Qualitative analysis

All patients enrolled in this study underwent contrast-enhanced MRI, and we used the MRI images as a reference for CESM. Anonymized images were visually evaluated on a high-resolution workstation (Barco Inc, Duluth, GA) by a radiologist and a mammary surgeon with 15 and 3 years of experience, respectively, in reading mammograms and breast MRI scans. Both had undergone basic training in reading CESM images. The readers were blinded to any clinical and histologic information. If their analysis did not match, a final decision was reached by consensus. Tumor visualization on the CESM images was rated as 4 (good: tumor strongly enhanced, good tumor opacification), 3 (acceptable: tumor moderately enhanced, fair tumor opacification), 2 (poor: tumor enhancement weak, poor tumor opacification, but detectable), and 1 (not detectable) (Fig. 1).

2.6 Statistical analyses

The image quality scores for the two groups were compared using the Wilcoxon signed-rank test. Interobserver agreement in the qualitative evaluation was assessed using the Cohen kappa κ coefficient, rated as follows: κ value less than 0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and 0.81–1.00 = near-perfect agreement. We performed all statistical tests using Excel Statistics (version 1.12; Social Survey Research Information, Tokyo, Japan). Differences were considered to be statistically significant at $p < 0.05$.

3 Results

The CT and CESM images were acquired without complications in all patients. We examined 77 women with 88 breast carcinomas; 68 had one, 8 had two, and one had four carcinomas. Of the 88 carcinomas, 70 (79.5%) harbored an invasive carcinoma (IC), and 18 (20.4%) were ductal carcinomas in situ (DCIS). The mean interval between the start of contrast material injection for CT and the acquisition of mammograms in groups A and B was 5.41 min (range 3.30–6.58 min) and 10.40 min (range 7.00–15.39 min), respectively.

The TGC_{mean} was higher in patients with an IC than in those with a DCIS [82.2 ± 46.3 HU (range 17.0–272.7 HU) and 54.5 ± 29.0 HU (range 24.5–138.4 HU), respectively]. All lesions were visually detectable on the CESM images (Table 1); image-quality score was higher for the ICs than the DCISs. The number of carcinomas for score 1, 2, 3, and 4 were 0, 9, 20, and 28 in group A, and 0, 10, 7, and 14 in group B; the rate of the number scored 3 or 4 in group A (84%) was higher than that in group B (68%). However, there was no significant difference between the two groups ($p = 0.21$, Fig. 2). There was substantial interobserver agreement with respect to the overall image quality ($\kappa = 0.77$). A representative patient with an invasive ductal carcinoma is shown in Fig. 3.

Table 1 Visual evaluation results

	Good (%)	Acceptable (%)	Poor (%)	Not detectable (%)
IC ($n = 70$)	37 (52.9)	25 (35.7)	8 (11.4)	0 (0)
DCIS ($n = 18$)	2 (11.1)	5 (27.8)	11 (61.1)	0 (0)

IC invasive carcinoma, *DCIS* ductal carcinoma in situ

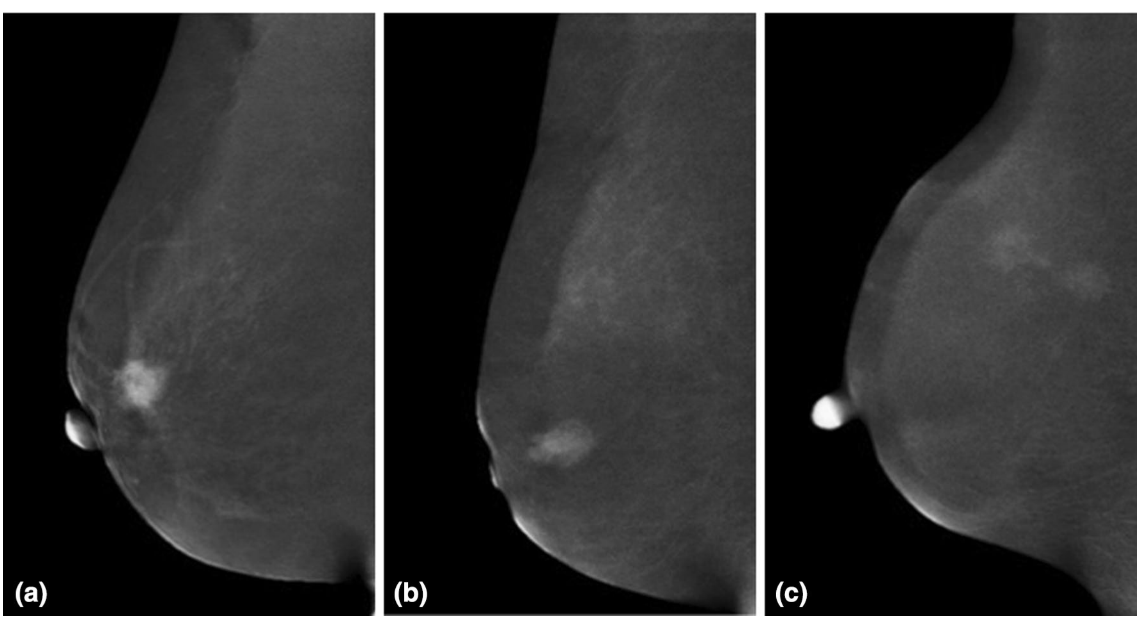

Fig. 1 Examples of the degree of enhancement of lesions on CESM images. **a** Good image quality (score = 4), **b** acceptable image quality (score = 3), **c** poor image quality (score = 2)

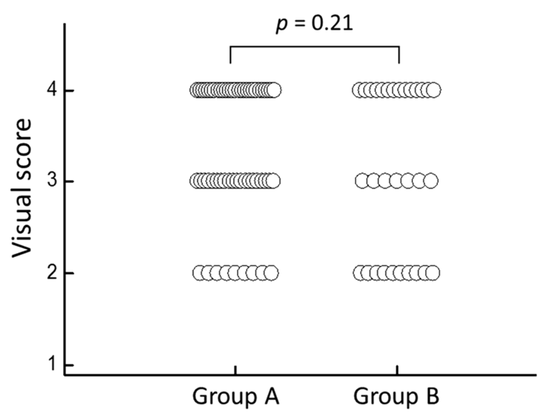

Fig. 2 Visual evaluation showed no significant difference between groups A and B ($p=0.21$)

4 Discussion

To the best of our knowledge, this is the first study to investigate the feasibility of CESM performed immediately after CECT without the injection of additional contrast material.

For CESM, an iodinated contrast agent is injected and then dual-energy subtraction images are acquired [1, 7]. The two source images are combined to render an image that minimizes the appearance of breast tissue and increases the conspicuity of the contrast material [7, 8]. According to Lobbes et al. [9], the sensitivity and negative predictive value of CESM are 100%, suggesting that a negative CESM finding generally excludes any kind of breast cancer. In our series, all lesions were visualized on the CESM images.

Other researchers [1, 10, 11] have suggested that the acquisition of CESM images be started approximately 2 min after, and no later than 7 min after a contrast material injection. Our patients moved from the CT to the mammography suite immediately after the CT scanning. As it was possible that the interval between contrast material injection and the start of mammography exceeds 7 min, we conjectured whether this would result in deterioration of the tumor detectability. Therefore, we visually compared the tumor opacification in group A (interval < 7 min) and group B (interval > 7 min). Although the rate of the number scored 3 or 4 in group A (84%) was higher than that in group B (68%), there was no significant difference between the two groups.

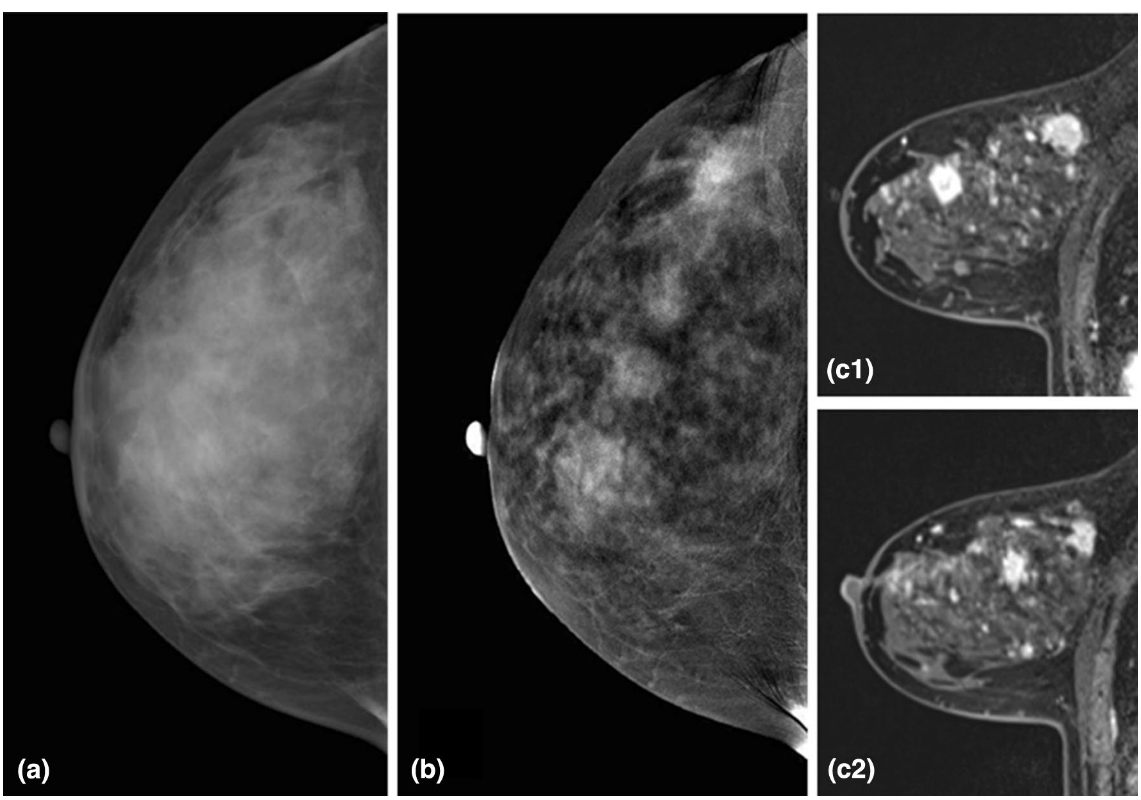

Fig. 3 A 50-year-old woman with four invasive ductal carcinomas in the right breast. The interval between the injection of contrast material for CT to the acquisition of mammograms was 4 min. Although, tumors were difficult to detect on conventional digital mammogram, they were clearly visible on CESM (score = 4). **a** Conventional digital mammogram, **b** CESM, **c1** and **c2** axial MRI

We found that the TGC and image-quality score were higher in patients with ICs than in those with DCISs. Lewin et al. [12] reported strong enhancement in all 14 IC lesions they studied; DCIS lesions, on the other hand, were not enhanced in their study of dual-energy contrast-enhanced mammograms. Similar findings were made by Dromain et al. [13]. Shiraishi et al. [14] attributed the relatively slow enhancement of DCISs to the presence of fibrocystic changes.

An advantage of our method is its cost-effectiveness. Bar et al. [3] injected 1.5–2.0 ml/kg of contrast material (concentration 300–370 mg I/ml) for CESM. In Japan, contrast material is priced strictly by volume and as we performed CESM immediately after CECT without the additional injection of contrast material, the saving was $100 per patient. In addition, our method decreases the risk of contrast medium-induced nephropathy [15]. Our method would be beneficial for patients who require both CECT and mammography or patients who cannot undergo breast MRI.

Our study has some limitations. Before CESM, all 77 enrolled patients were known to harbor histologically confirmed breast carcinoma. Therefore, the diagnostic accuracy of our method was not evaluated. In addition, as the number of patients with DCIS was relatively small (18 of 88, 20%), the informational value of our findings is limited and additional studies on larger patient populations are needed. Lastly, although the radiation dose was slightly higher in our CESM than it is with conventional mammography studies, we believe that the high lesion detectability on CESM images compensates for this disadvantage.

In conclusion, we investigated the feasibility of performing CESM immediately after CECT without injecting additional contrast material. The tumor opacification was not impaired even when the interval between the start of contrast material injection for CT and the start of mammography was more than 7 min.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board (IRB) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Daniaux M, De Zordo T, Santner W, Amort B, Koppelstatter F, Jaschke W, et al. Dual-energy contrast-enhanced spectral mammography (CESM). Arch Gynecol Obstet. 2015;292(4):739–47. https://doi.org/10.1007/s00404-015-3693-2.
2. Blum KS, Rubbert C, Mathys B, Antoch G, Mohrmann S, Obenauer S. Use of contrast-enhanced spectral mammography for intramammary cancer staging: preliminary results. Acad Radiol. 2014;21(11):1363–9. https://doi.org/10.1016/j.acra.2014.06.012.
3. Badr S, Laurent N, Regis C, Boulanger L, Lemaille S, Poncelet E. Dual-energy contrast-enhanced digital mammography in routine clinical practice in 2013. Diagn Interv Imaging. 2014;95(3):245–58. https://doi.org/10.1016/j.diii.2013.10.002.
4. Lee-Felker SA, Tekchandani L, Thomas M, Gupta E, Andrews-Tang D, Roth A, et al. Newly diagnosed breast cancer: comparison of contrast-enhanced spectral mammography and breast MR imaging in the evaluation of extent of disease. Radiology. 2017;285(2):389–400. https://doi.org/10.1148/radiol.2017161592.
5. Pellerin O, Delorme L, Bellmann L, Sapoval M. Clinical presentation and percutaneous endovascular management of acute left subclavian artery thrombosis: report of two cases. Diagn Interv Imaging. 2014;95(1):95–9. https://doi.org/10.1016/j.diii.2013.07.005.
6. Uhlig J, Fischer U, von Fintel E, Stahnke V, Perske C, Lotz J, et al. Contrast enhancement on cone-beam breast-CT for discrimination of breast cancer immunohistochemical subtypes. Transl Oncol. 2017;10(6):904–10. https://doi.org/10.1016/j.tranon.2017.08.010.
7. Luczynska E, Niemiec J, Hendrick E, Heinze S, Jaszczynski J, Jakubowicz J, et al. Degree of enhancement on contrast enhanced spectral mammography (CESM) and lesion type on mammography (MG): comparison based on histological results. Med Sci Monit Int Med J Exp Clin Res. 2016;22:3886–933.
8. Bhimani C, Matta D, Roth RG, Liao L, Tinney E, Brill K, et al. Contrast-enhanced spectral mammography: technique, indications, and clinical applications. Acad Radiol. 2017;24(1):84–8. https://doi.org/10.1016/j.acra.2016.08.019.
9. Lobbes MB, Lalji U, Houwers J, Nijssen EC, Nelemans PJ, van Roozendaal L, et al. Contrast-enhanced spectral mammography in patients referred from the breast cancer screening programme. Eur Radiol. 2014;24(7):1668–766. https://doi.org/10.1016/j.crad.2013.04.009.
10. Dromain C, Balleyguier C, Muller S, Mathieu MC, Rochard F, Opolon P, et al. Evaluation of tumor angiogenesis of breast carcinoma using contrast-enhanced digital mammography. AJR Am J Roentgenol. 2006;187(5):W528–37. https://doi.org/10.2214/AJR.05.1944.
11. Lobbes MB, Smidt ML, Houwers J, Tjan-Heijnen VC, Wildberger JE. Contrast enhanced mammography: techniques, current results, and potential indications. Clin Radiol. 2013;68(9):935–44. https://doi.org/10.1016/j.crad.2013.04.009.
12. Lewin JM, Isaacs PK, Vance V, Larke FJ. Dual-energy contrast-enhanced digital subtraction mammography: feasibility. Radiology. 2003;229(1):261–8. https://doi.org/10.1148/radiol.2291021276.
13. Dromain C, Thibault F, Muller S, Rimareix F, Delaloge S, Tardivon A, et al. Dual-energy contrast-enhanced digital mammography: initial clinical results. Eur Radiol. 2011;21(3):565–74. https://doi.org/10.1007/s00330-010-1944-y.
14. Shiraishi A, Kurosaki Y, Maehara T, Suzuki M, Kurosumi M. Extension of ductal carcinoma in situ: histopathological

association with MR imaging and mammography. Magn Reson Med Sci. 2003;2(4):159–63.

15. Nyman U, Bjork J, Aspelin P, Marenzi G. Contrast medium dose-to-GFR ratio: a measure of systemic exposure to predict contrast-induced nephropathy after percutaneous coronary intervention. Acta Radiol. 2008;49(6):658–67. https://doi.org/10.1080/02841850802050762.