Editorial Commentary

Dual-energy contrast-enhanced spectral mammography (CESM) for breast cancer screening

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Dual-energy contrast-enhanced spectral mammography (CESM) is a novel imaging modality. It enables anatomical and functional imaging of the breast (1). At CESM two images of each view are obtained, at two energy levels. The first is a low-energy image depicting breast morphology. This image is equivalent to standard 2D mammography. The second image is a subtracted image highlighting areas of contrast uptake that can indicate malignant neovascularization (2).

First introduced in 2003 by Lewin *et al.* (3) CESM has gained increasing interest in the literature with promising results (4). In 2011 the Food and Drug Administration approved CESM as a supplemental imaging tool for diagnostic purposes, to localize known or suspected breast lesions (5). CESM has since been implemented in clinical care mainly in the diagnostic setting, as a problem-solving tool for inconclusive findings (6), for evaluation of disease extent and for breast cancer staging (7-9). A few recent publications have also assessed CESM for breast cancer screening (10-13).

In a retrospective study published recently in Radiology (2019), Sung *et al.* assessed CESM as an alternative to standard mammography for breast cancer screening (13). The authors compared between the whole CESM examination (both low energy and subtracted images) and the low energy images alone. In their analysis, they included 858 baseline CESM examinations, which is the largest published cohort for CESM screening to date. Their study population had increased risk for breast cancer, including a majority of women with dense breasts and a large proportion of women with family or personal history of breast cancer. Sung *et al.* used biopsies or imaging follow up of one year as their standard reference. There were a total of 15 cancers in 14 women detected at the time of screening. Those included six ductal carcinomas *in situ* (DCIS), six invasive ductal carcinomas (IDC), two invasive lobular carcinomas and one invasive adenosquamous carcinoma. Three additional interval cancers (two DCIS and one IDC) in two women were detected at the first year of follow-up.

There are several key results to the Sung *et al.* study (13). The addition of contrast-enhanced images depicted seven malignant lesions that were not detected at the low energy images. The sensitivity as compared to standard mammography significantly increased from 50% to 87.5% (P=0.03). Respectively, the negative predictive value also increased from 99.0% for standard mammography to 99.7% at CESM (P=0.02). Specificity on the other hand decreased from 97.1% at standard mammography to 93.7% at CESM (P<0.001). As a consequence, there was an increase in false positive findings from CESM and a resultant increase in the number of benign biopsies performed.

Looking at the characteristics of cancers from the Sung *et al.* study (13), the lesions detected only at CESM include two DCIS, three IDC and two invasive lobular carcinomas (ILC). As previously reported by Kuhl *et al.* breast MRI

could improve DCIS diagnosis, and specifically high-grade DCIS lesions (14). Theoretically, this could also be the case for CESM, as it can depict areas of increased contrast uptake at the subtracted images and calcifications at the low-energy images. CESM can therefore depict DCIS even in the absence of calcifications at 2D mammography. There are two published studies that assess CESM utility for calcifications (15,16), but none yet to assess DCIS lesions that do not calcify.

It is interesting to note that the two ILCs in this study were depicted only at contrast-enhanced images (13). ILC can be challenging for diagnosis both clinically and radiologically. That is because these lesions often do not form a palpable mass, and they can be elusive or have atypical appearance at standard mammography (17). Breast MRI and US perform better when imaging ILC and are used as supplemental modalities (18). The reported sensitivity of MRI for ILC is around 93% (19). MRI is the preferable imaging modality for preoperative disease extent assessment of ILC due to the frequent incidence of multifocal and bilateral disease (20). As CESM also provides functional imaging and highlights areas of hypervascularity, it may be suitable for ILC imaging. One recent study by Patel *et al.* examined CESM for the assessment of disease extent in women with known ILC lesions (21). They reported the superiority of CESM over standard mammography at this task. We can only speculate that CESM may outperform standard mammography at ILC detection in screening as well. It remains to be a topic of interest for future studies and we hope that those are soon to come.

Another parameter we would like to highlight from the Sung *et al.* study is their reported incremental cancer detection rate for CESM, which was 6.6/1,000 (13). In a different study assessing CESM for screening, incremental cancer detection rate was as high as 13.1/1000 (11). Using CESM over standard 2D mammography therefore has the potential to detect about 6-13 additional cancers in every 1,000 women. These numbers exceed what was previously reported for the addition of whole breast US as a supplement to screening mammography, which is in the range of 1.7–7.7/1,000 (22). They also exceed the numbers reported for digital breast tomosynthesis. Breast tomosynthesis is another fairly recent technological advance that enables a type of "three-dimensional" mammographic image when multiple thin image slices are acquired. The incremental rate for tomosynthesis was reported to be around 1.2–2/1,000, with no increase in detection of DCIS (23-25).

It is important to keep in mind that Sung *et al.* in their study, evaluated women with dense breasts and increased risk for breast cancer, a population for which screening with standard mammography has limited sensitivity. Women at intermediate breast cancer risk (15–20% lifetime risk) fall in a gap in which there are no conclusive guidelines for breast cancer screening. There is however increased interest into personalized screening, adjusted for risk. Recently "density notification" laws were established in the United States (26). These laws require informing women of their breast density, and some require informing that additional imaging modalities can detect cancers not visible at standard mammography. The basis for these regulations is that diagnosis of cancers before their clinical presentation is more likely to result in successful intervention. With these new legislative requirements, there is an increase in supplemental breast US and MRI, as well as an increase in confusion among physicians regarding the preferable imaging work-up for these women. We certainly believe that as Sung *et al.* suggest there may be an important role for CESM in breast cancer screening of certain women. CESM imaging however needs to be standardized with guidelines that are still astonishingly lacking. Unfortunately, CESM is yet to be included in the latest BI-RADS atlas. There is a consequent lack of standardization for reporting, and it is customary to report the low energy images according to standard mammography guidelines, and the subtracted images according to guidelines for MRI (27).

The question therefore arises, should women with dense breasts and increased risk for breast cancer be referred to CESM? Possibly. Screening standard 2D mammography currently remains the only imaging modality proved to reduce breast cancer mortality (28). Although CESM increases cancer detection over standard mammography, as of today there are no studies to assess whether the cost of CESM screening is in balance with mortality benefit. As Sung *et al.* showed CESM results in an increased rate of false positive outcomes and overdiagnosis of clinically insignificant lesions (13). These may not only lead to an increase in benign biopsies, but also increase stressful situations for healthy women. CESM requires an increased radiation dose (29) and the administration of intravenous iodinated contrast agent. These human costs remain to be assessed in an equation with the benefits of CESM as a substitute to mammography screening in different populations.

The study by Sung *et al.* contains clinically relevant results that are in one line with the results of other

studies published on this subject. With the Breast Cancer Awareness Month behind us, we are hopeful that findings from this study will help clinical management of women at increased risk for breast cancer. It is also time to establish guidelines regarding the use of CESM in general and in screening in particular, and include CESM in the BI-RADS lexicon.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Dromain C, Balleyguier C, Adler G, Garbay JR, Delaloge S. Contrast-enhanced digital mammography. Eur J Radiol 2009;69:34-42.
2. Jochelson MS, Dershaw DD, Sung JS, Heerdt AS, Thornton C, Moskowitz CS, Ferrara J, Morris EA. Bilateral Contrast-enhanced Dual-Energy Digital Mammography: Feasibility and Comparison with Conventional Digital Mammography and MR Imaging in Women with Known Breast Carcinoma. Radiology 2013;266:743-51.
3. Lewin JM, Isaacs PK, Vance V, Larke FJ. Dual-Energy Contrast-enhanced Digital Subtraction Mammography: Feasibility. Radiology 2003;229:261-8.
4. James JJ, Tennant SL. Contrast-enhanced spectral mammography (CESM). Clin Radiol 2018;73:715-23.
5. FDA 510(k) clearance for GE Contrast Enhanced Spectral Mammography (CESM). Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf10/K103485.pdf
6. Lobbes MBI, Lalji U, Houwers J, Nijssen EC, Nelemans PJ, van Roozendaal L, Smidt ML, Heuts E, Wildberger JE. Contrast-enhanced spectral mammography in patients referred from the breast cancer screening programme. Eur Radiol 2014;24:1668-76
7. Lobbes MBI, Lalji UC, Nelemans PJ, Houben I, Smidt ML, Heuts E, de Vries B, Wildberger JE, Beets-Tan RG. The Quality of Tumor Size Assessment by Contrast-Enhanced Spectral Mammography and the Benefit of Additional Breast MRI. J Cancer 2015;6:144-50.
8. Iotti V, Ravaioli S, Vacondio R, Coriani C, Caffarri S, Sghedoni R, Nitrosi A, Ragazzi M, Gasparini E, Masini C, Bisagni G, Falco G, Ferrari G, Braglia L, Del Prato A, Malavolti I, Ginocchi V, Pattacini P. Contrast-enhanced spectral mammography in neoadjuvant chemotherapy monitoring: a comparison with breast magnetic resonance imaging. Breast Cancer Res 2017;19:106.
9. Helal MH, Mansour SM, Ahmed HA, Abdel Ghany AF, Kamel OF, Elkholy NG. The role of contrast-enhanced spectral mammography in the evaluation of the postoperative breast cancer. Clin Radiol 2019;74:771-81.
10. Jochelson MS, Pinker K, Dershaw DD, Hughes M, Gibbons GF, Rahbar K, Robson ME, Mangino DA, Goldman D, Moskowitz CS, Morris EA, Sung JS. Comparison of screening CEDM and MRI for women at increased risk for breast cancer: A pilot study. Eur J Radiol 2017;97:37-43.
11. Sorin V, Yagil Y, Yosepovich A, Shalmon A, Gotlieb M, Neiman OH, Sklair-Levy M. Contrast-Enhanced Spectral Mammography in Women With Intermediate Breast Cancer Risk and Dense Breasts. AJR Am J Roentgenol 2018;211:W267-W274.
12. Kim G, Phillips J, Cole E, Brook A, Mehta T, Slanetz P, Fishman MDC, Karimova E, Mehta R, Lotfi P, Resteghini N, Raj S, Dialani V. Comparison of Contrast-Enhanced Mammography With Conventional Digital Mammography in Breast Cancer Screening: A Pilot Study. J Am Coll Radiol 2019;16:1456-63.
13. Sung JS, Lebron L, Keating D, D'Alessio D, Comstock CE, Lee CH, Pike MC, Ayhan M, Moskowitz CS, Morris EA, Jochelson MS. Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer. Radiology 2019;293:81-8.
14. Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, Kuhn W, Schild HH. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet 2007;370:485-92.
15. Cheung Y-C, Tsai H-P, Lo Y-F, Ueng S-H, Huang P-C, Chen S-C. Clinical utility of dual-energy contrast-enhanced spectral mammography for breast microcalcifications without associated mass: a preliminary analysis. Eur Radiol 2016;26:1082-9.
16. Houben IPL, Vanwetswinkel S, Kalia V, Thywissen T, Nelemans PJ, Heuts EM, Smidt ML, Meyer-Baese A, Wildberger JE, Lobbes MBI. Contrast-enhanced spectral mammography in the evaluation of breast suspicious calcifications: diagnostic accuracy and impact on surgical management. Acta Radiologica 2019;60:1110-7.
17. Lopez JK, Bassett LW. Invasive Lobular Carcinoma of

the Breast: Spectrum of Mammographic, US, and MR Imaging Findings. Radiographics 2009;29:165-76.
18. Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, Ioffe OB. Diagnostic Accuracy of Mammography, Clinical Examination, US, and MR Imaging in Preoperative Assessment of Breast Cancer. Radiology 2004;233:830-49.
19. Mann RM, Hoogeveen YL, Blickman JG, Boetes C. MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat 2008;107:1-14.
20. Weinstein SP, Orel SG, Heller R, Reynolds C, Czerniecki B, Solin LJ, Schnall M. MR Imaging of the Breast in Patients with Invasive Lobular Carcinoma. AJR Am J Roentgenol 2001;176:399-406.
21. Patel BK, Davis J, Ferraro C, Kosiorek H, Hasselbach K, Ocal T, Pockaj B. Value Added of Preoperative Contrast-Enhanced Digital Mammography in Patients With Invasive Lobular Carcinoma of the Breast. Clin Breast Cancer 2018;18:e1339-e1345.
22. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, Böhm-Vélez M, Mahoney MC, Evans WP, Larsen LH. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 2012;307:1394-404.
23. Rose SL, Tidwell AL, Bujnoch LJ, Kushwaha AC, Nordmann AS, Sexton R. Implementation of Breast Tomosynthesis in a Routine Screening Practice: An Observational Study. AJR Am J Roentgenol 2013;200:1401-8.
24. Friedewald SM, Rafferty EA, Rose SL, Durand MA, Plecha DM, Greenberg JS, Hayes MK, Copit DS, Carlson KL, Cink TM, Barke LD, Greer LN, Miller DP, Conant EF. Breast Cancer Screening Using Tomosynthesis in Combination With Digital Mammography. JAMA 2014;311:2499.
25. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, Izadi M, Jebsen IN, Jahr G, Krager M, Niklason LT, Hofvind S, Gur D. Comparison of Digital Mammography Alone and Digital Mammography Plus Tomosynthesis in a Population-based Screening Program. Radiology 2013;267:47-56.
26. ACOG. State Laws on Breast Cancer Screening & Breast Density 2018. Available online: https://www.acog.org/-/media/Departments/State-Legislative-Activities/2017BreastDensityTally.pdf?dmc=1&ts=20191022T0819190187
27. Perry H, Phillips J, Dialani V, Slanetz PJ, Fein-Zachary VJ, Karimova EJ, Mehta TS. Contrast-Enhanced Mammography: A Systematic Guide to Interpretation and Reporting. AJR Am J Roentgenol 2019;212:222-31.
28. Kalager M, Zelen M, Langmark F, Adami H-O. Effect of Screening Mammography on Breast-Cancer Mortality in Norway. N Engl J Med 2010;363:1203-10.
29. Phillips J, Mihai G, Hassonjee SE, Raj SD, Palmer MR, Brook A, Zhang D. Comparative Dose of Contrast-Enhanced Spectral Mammography (CESM), Digital Mammography, and Digital Breast Tomosynthesis. AJR Am J Roentgenol 2018;211:839-46.

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