

# Contrast-enhanced spectral mammography for breast cancer

Medtech innovation briefing

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## Summary

- The **technologies** described in this briefing are 4 systems for contrast-enhanced spectral mammography (CESM). They are used for enhanced mammography imaging where certain types of breast cancer may be easier to see, compared with standard mammography. These technologies can be useful in people with dense breast tissue.
- The **innovative aspects** are that a contrast agent is used, and 2 X-ray images of different energy are taken. The system software produces a final image, which enhances areas of the mammography image that can indicate cancer.
- The intended **place in therapy** would be in clinics for people with suspected breast cancer, or to help plan treatment in people with confirmed breast cancer. It could be used instead of, or alongside, other types of imaging, such as contrast-enhanced MRI, ultrasound, full-field digital mammography or digital breast tomosynthesis.

- The **main points from the evidence** summarised in this briefing are from 7 diagnostic accuracy studies (including 1 from the UK), and 3 cohort studies, including a total of 1,809 women with known or suspected breast cancer. Indirect comparisons with histopathology show that the performance of CESM is comparable with other imaging techniques in women with known or suspected breast cancer.
- **Key uncertainties** around the evidence or technology are that diagnostic accuracy studies compare imaging with histopathology, and not directly with other imaging techniques. There is also a lack of prospective, comparative studies reporting on longer-term patient outcomes.
- Six **clinical experts** advised that the technology could replace MRI, and people are likely to benefit from fewer hospital appointments, a more comfortable experience, shorter waiting times and quicker diagnosis.
- Two **patient and public involvement organisations** advised that a quicker diagnosis could reduce patient stress and anxiety. They advised that people may be concerned about side effects from contrast injection or increased radiation exposure, and should have the option of other imaging techniques. They also noted an increased radiation dose and possible kidney complications with the contrast agent, concerns around lack of long-term follow up for surgical treatment planning, and potential overtreatment based on CESM results.
- The **cost** to upgrade an existing mammography machine to use CESM software varies between £40,000 and £90,000. Servicing and maintenance are included in either the initial upgrade cost or existing service contract, or cost up to £19,000 per year. Potential barriers to adoption include workforce shortages (additional staff time needed for contrast injection and providing patient information) and capital cost, which could lead to varied provision across the NHS.

## The technology

Contrast-enhanced spectral mammography (CESM) is a technique that combines mammography with contrast enhancement to show breast cancers that may not be visible on standard mammography. An iodine-based contrast agent is injected through a vein in the arm. After allowing the contrast to travel to the person's breast, the breast is compressed to hold it still. Two images are then taken using low- and high-energy X-rays. The low-energy image is identical to a full-field digital mammography (FFDM) image. However, in the high-energy image, the higher-energy X-rays are absorbed more strongly

by the iodine, and areas with more contrast agent will be enhanced. The system software processes the 2 images to remove non-enhanced areas. The radiologist, or trained radiographer interpreting the image, will use the enhanced areas associated with abnormal blood vessels to identify potential cancers.

This briefing focuses on 4 technologies capable of CEM: Senographe Pristina (GE Healthcare), 3Dimensions (Hologic), AMULET Innovality (Fujifilm) and MAMMOMAT Revelation (Siemens). Other technologies may be available but are not included in this briefing. Reasons for this include not being commercially available to the NHS at the time of horizon scanning, or the company choosing not to take part.

All of the included technologies produce X-rays for the high-energy image with a maximum tube voltage of 49 kV. Senographe Pristina, 3Dimensions and AMULET Innovality use a copper filter to remove lower-energy X-rays. MAMMOMAT Revelation uses a titanium filter for this, and is referred to as titanium contrast-enhanced mammography (TiCEM), but is equivalent to the other CEM technologies. All technologies offer both automatic and manual exposure control. All technologies are also capable of 2D FFDM and 3D digital breast tomosynthesis (DBT).

Each technology has its own software for CEM, such that it is not compatible, or available for use, with other CEM mammography machines:

- Senographe Pristina: SenoBright, current version: CEM HD (2017)
- 3Dimensions: I-View, current version: 2.0 (2019)
- AMULET Innovality: CEDM Software, current version: available within system software version 9.2 and above (2019)
- MAMMOMAT Revelation: VC20, current version: VC20D (2021), from October 2022 VC20F.

CEM would be contraindicated in people with an allergy to iodinated contrast media. There are no further contraindications for use specifically relating to CEM for 3Dimensions or AMULET Innovality. Senographe Pristina and MAMMOMAT Revelation are not recommended for CEM in people with breast implants.

## Innovations

The innovative aspect of CESM is that it may be easier to spot cancer, because there is better contrast between suspicious areas, with increased blood flow, and normal breast tissue. For people who might have otherwise had an MRI scan, imaging with these technologies will be quicker and may be completed at the breast clinic, instead of in the radiology department ([Cancer Research UK, 2020](#)). This could release time and resources for MRI in other areas.

## Current care pathway

People with suspected breast cancer are usually invited to a breast clinic, where more tests can be done. These might include standard mammography imaging, ultrasound, biopsy and clinical examination. People with symptoms who are referred by their GP may have different tests than those people referred through the NHS breast screening programme, because they will have already had recent 2-view mammography of both breasts. MRI might also be used as a further test, but this usually takes place in a radiology department, and so might not be available at the same time or in the same location. One of the experts commented that some people may also need a further visit to the breast clinic after MRI, for more investigations or biopsies. CESM could also be used to help plan treatment, or assess response to treatment, in people with confirmed breast cancer.

The following publications have been identified as relevant to this care pathway, providing guidance on breast imaging:

- The [Royal College of Radiologists guidance on screening and symptomatic breast imaging](#) refers to a 'triple assessment' including clinical assessment, imaging and needle biopsy, for people with symptoms of breast cancer. The guidance states that DBT or CESM can be used as an option for diagnostic imaging, instead of mammography, in those with suspicious findings on clinical examination. This may include younger women, who are more likely to have dense breasts, in which mammography has a decreased sensitivity ([Sogani et al. 2021](#)).
- The [Association of Breast Surgery guidelines for the management of symptomatic breast disease](#) includes the 'triple assessment' and makes recommendations for imaging, including that imaging standards should meet the same standards as for breast screening.

- The [Royal College of Pathologists guidelines for non-operative diagnostic procedures and reporting in breast cancer screening](#) give guidance on the use of image-guided biopsies.

## Population, setting and intended user

CESM would be used in clinics for people with suspected breast cancer. This may include people who have been referred by their GP with symptoms, or people who have been recalled after screening. Two experts have stated that CESM is not currently approved by the NHS breast screening programme. The technologies could also be used to assess the extent of disease, or to help plan treatment in people with confirmed breast cancer. Four of 6 experts noted the likely setting of CESM to be district general hospitals. The CESM examination can be done by any radiographer trained in mammography, but a healthcare professional trained to insert the cannula and recognise contrast reactions is also needed. This may be the radiographer or a doctor.

## Costs

### Technology costs

The cost to upgrade an existing mammography machine for CESM ranges between £40,000 and £90,000. This does not include the initial purchase of the mammography machine, which can be used for standard mammography without CESM enabled. Each company provides training on its CESM technology free of charge. Servicing and maintenance are included in either the initial upgrade cost or existing service contract, or cost up to £19,000 per year.

The contrast can be injected by hand or powered pump, but the former might be more time consuming. There will be additional costs for the contrast agents used, and for equipment and consumables used for the injection. These are not provided with the CESM technology, and would also require separate training, maintenance and calibration.

One clinical expert estimated the cost of using CESM to be £82.88 per patient, which includes £64.62 for a standard mammogram, £9.37 for a single-use syringe and lines, and £8.89 for the contrast agent and cannulation. This does not include the software upgrade cost, or the cost of a powered contrast pump.

## Costs of standard care

People with symptoms may have breast ultrasound, FFDM or MRI depending on the referral route, clinical indication or suspicion of breast cancer. The use of unbundled healthcare resource group (HRG) codes, variations in setting and the use of contrast agent, make it difficult to establish total imaging costs per patient. Unbundled HRG codes for ultrasound, FFDM and MRI range between £32.82 (RD40Z: ultrasound scan without contrast, with a duration of less than 20 minutes) and £211.33 (RD03Z: MRI scan of 1 area, with pre- and post-contrast). Based on clinical experience, a clinical expert estimated the cost of a standard mammogram to be £64.62 per patient, and the cost of MRI to be £150 per patient.

One clinical expert considered that most people with symptoms attending a breast clinic would have an ultrasound scan, people older than 40 years would also have mammography, and less than 1% would have breast MRI. People recalled from screening would have further mammography, with either additional views or DBT. The external assessment group (EAG) was unable to identify an unbundled HRG code specific to DBT; however, 1 clinical expert noted that the cost of CESM is comparable with DBT. Three experts noted that CESM is likely to be cheaper than dynamic contrast-enhanced imaging (MRI, tomosynthesis or mammography) and 4 experts also noted CESM is likely to be less costly or more cost effective than MRI.

## Resource consequences

The CESM technologies are used in the NHS to help diagnose suspected or confirmed breast cancer. Senographe Pristina (GE Healthcare) is currently used for CESM in 11 NHS trusts. 3Dimensions (Hologic) is currently used in 9 NHS trusts. AMULET Innovality (Fujifilm) is currently used in 1 NHS trust. MAMMOMAT Revelation (Siemens) is currently used in 6 NHS trusts.

Other trusts have mammography machines with CESM technology enabled, but are not using it routinely, including 28 with the Senographe Pristina. More NHS trusts are likely to have the mammography machines available, and could upgrade them to use CESM. One clinical expert noted that most newly purchased machines have the dual-energy capability needed to conduct CESM.

NHS trusts may train existing staff conducting mammography services to use the technology; however, training and ongoing support may be needed. All 6 experts noted

the additional staff training needed to handle contrast agents, cannulate people or use a powered injection pump. Although allergic reactions to iodinated contrast agents are rare (occurring in less than 1% of cases as estimated by 2 clinical experts), medical staff would also need to be available to treat the patient if a reaction did happen.

CESM will also take more time and resources than FFDM to collect the images. Patient and public involvement groups have advised that adoption of CESM may need additional appointment time to inform people of the steps involved and the benefits of CESM compared with standard care. However, all 6 clinical experts noted that CESM had the potential to reduce the need for, and waiting times related to, MRI. One expert also commented that CESM-guided biopsy could potentially be an alternative to MRI-guided biopsy, which could release additional MRI resources.

## Regulatory information

Senographe Pristina is a CE-marked class IIb medical device regulated under the EU medical devices directive (MDD). One [Medicines and Healthcare products Regulatory Agency \(MHRA\) field safety notice \(2019/006/006/291/001\)](#) was identified but this related to the use of the device to take biopsies, and did not affect the safety of the device for contrast-enhanced spectral mammography (CESM).

3Dimensions Mammography System is a CE-marked class IIb medical device regulated under the EU MDD. Two MHRA field safety notices were identified: one ([2018/012/010/601/008](#)) related to issues visualising contrast uptake and needed recalibration of the I-View software. The other ([2020/001/022/601/003](#)) related to abnormal wear of components which could cause mechanical failure.

Fujifilm digital mammography system AMULET Innovality is a CE-marked class IIb medical device regulated under the EU MDD. One MHRA field safety notice was identified ([2017/007/025/291/004](#)) and related to mechanical failure.

MAMMOMAT Revelation is a CE-marked class IIb medical device regulated under the EU MDD. No MHRA field safety notices were identified.

One patient and public involvement group raised concerns relating to the long-term effects of radiation exposure associated with CESM, especially in people also exposed to radiation for treatment. In addition to the safety notices identified above, 5 studies ([Avramova-Cholakova et al. 2021](#), [Bicchierai et al. 2022](#), [Fusco et al. 2020](#), [James et al. 2017](#) and

[Jeukens et al. 2014](#)), including 1,040 people, were identified that compared radiation doses between CESH and other mammography technologies (full-field digital mammography [FFDM] or digital breast tomosynthesis [DBT]). Four studies reported that the average glandular dose was higher for CESH than FFDM, which is expected as the breast undergoes a standard 2D (low-energy) exposure and a separate high-energy exposure. Two clinical experts stated that total CESH dose could be between 10% and 80% higher than FFDM, depending on the model of mammography machine and the thickness of the breast. Three studies reported the glandular dose was higher for CESH than DBT; however, 1 study reported the dose for CESH was lower. One of the experts commented that the difference between doses delivered by DBT and CESH will depend on the model of mammography machine. One study ([Gennaro et al. 2022](#)) reported a significant difference in mean glandular dose between the same model of mammography machine in 2 different centres, for low-energy images, and high-energy images. One of the experts commented that this is likely to be an issue with setup and optimisation of the machine. One expert commented that the mean glandular dose of CESH lies below NHS breast screening programme remedial level for 2D mammography and is consistent with published literature ([Fusco et al. 2020](#); [Jeukens et al. 2014](#)). Another expert commented that CESH radiation doses were within UK and EU guidelines.

## Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

The contrast-enhanced spectral mammography (CESM) technologies may be used for men and women of any age, who are suspected of having breast cancer. The technologies may be more useful in people with denser breast tissue, who are usually younger. They are therefore associated with the protected characteristics of sex and age.

The technology is unsuitable for people with an allergy to iodinated contrast media. One patient organisation commented that the use of a contrast agent may be refused by some people on religious grounds.

## Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available

published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting [mibs@nice.org.uk](mailto:mibs@nice.org.uk).

## Published evidence

Ninety-six studies were identified: Senographe Essential (GE Healthcare) was used in 39 studies; Selenia Dimensions (Hologic) was used in 21 studies; Senographe DS (GE Healthcare) was used in 5 studies; Senographe Pristina (GE Healthcare) was used in 4 studies; AMULET Innovality (Fujifilm) and MAMMOMAT Revelation (Siemens) were used in 1 study each. One study reported using Senographe Essential and Senographe Pristina (GE Healthcare), and 1 study reported using Senographe DS and Senographe Essential (GE Healthcare). An unnamed GE Healthcare device was used in 20 studies, and an unnamed Selenia (Hologic) device was used in 3 studies.

The 96 studies included 50 diagnostic accuracy studies, 28 cohort studies, 14 comparative studies (reporting limited patient outcomes), 1 pilot study, 1 case control study, 1 observational study and 1 qualitative study.

Studies in a UK setting were prioritised, followed by diagnostic accuracy studies with a comparator in scope in its own right (that is, not histopathology), followed by the largest (with 100 or more people) diagnostic accuracy studies with a combination of multiple interventions (for example, contrast-enhanced spectral mammography [CESM], MRI, ultrasound, full-field digital mammography [FFDM] compared with histopathology, and then studies focusing on change in patient management). There are 10 studies summarised in this briefing, including a total of 1,809 people, across 7 diagnostic accuracy studies comparing CESM and other imaging techniques to histopathology, and 3 cohort studies assessing the impact of CESM on treatment planning in people with known breast cancer. The 7 diagnostic accuracy studies were in people with suspected breast cancer, and included 2 studies in women recalled from screening and 1 study in women with palpable masses. One study was done in the UK.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

## Overall assessment of the evidence

The evidence base, in terms of the number of studies, is at a level expected for a technology that has been commercially available for more than 10 years, and includes multiple devices. However, the studies are typically small for this clinical area, with the largest reported here including only 465 people. One study included was done in the UK; 2 studies, done in the Netherlands, included people being recalled from the screening programme for further investigations, and other studies focused on symptomatic populations.

It is recognised that faster detection of breast cancer, at the earliest stage of development, will improve patient survival and overall quality of life. However, the current evidence on CESM is limited by a lack of prospective, comparative studies reporting on important patient outcomes. Studies generally report diagnostic accuracy for several interventions (for example, FFDM, digital breast tomosynthesis [DBT], CESM, ultrasound, MRI, and combinations of these). However, there are no direct comparisons of CESM with other imaging techniques, to reflect how the technology would be used in clinical practice in the NHS. More prospective research is needed to directly compare the use of CESM with other imaging modalities. As a close comparator, studies directly comparing CESM with contrast-enhanced MRI (CE-MRI), especially in the UK, would be most useful. Many studies used the CE-MRI BI-RADS (breast imaging reporting and data system) lexicon, as no formal guidance on the classification of CESM images was available at the time. However, the [American College of Radiology \(ACR\) has released a supplement on the classification of contrast-enhanced mammography images \(ACR 2022\)](#), which should be used and evaluated in future studies. One clinical expert highlighted that there is a need for longer-term follow up in people who had surgical planning based on the results of CESM. Two experts stated that additional evidence in the use of CESM in monitoring response to neoadjuvant chemotherapy would be useful.

### Tennant et al. (2016)

#### Study size, design and location

Diagnostic accuracy study in 100 women having CESM examinations in a symptomatic clinic setting in the UK.

## Intervention and comparator(s)

Intervention: SenoBright (GE Healthcare; mammography machine not reported). BI-RADS scores using low-energy CESH images alone, and 3 weeks later using both low-energy and combined (low- and high-energy) CESH images.

Comparators: histopathology (if having biopsy or further surgery); breast MRI at baseline (if having neoadjuvant chemotherapy).

## Key outcomes

The area under the receiver operating characteristic curve (AUROC) was significantly higher when reading the combined CESH image, compared with reading the low-energy image only (0.93 versus 0.83;  $p < 0.025$ ). The overall and individual radiologist, sensitivity and specificity also improved when the entire CESH image was reviewed (significance not reported). The difference in measured lesion size was significantly lower between CESH and MRI, compared with between the low-energy images and MRI ( $p < 0.001$ ). The difference in measured lesion size was also significantly lower between CESH and histology, compared with between the low-energy images alone and histology ( $p < 0.0001$ ). Interpretation of the low-energy images alone led to tumour size being underestimated. Overall, radiologists categorised the CESH images to be a 'useful aid to diagnosis' in 40% of cases, and a 'significant aid to diagnosis' in 35%.

## Strengths and limitations

The majority of people had clinically suspicious abnormalities and therefore larger tumours. The authors note that CESH tends to overestimate the size of larger tumours, when compared with MRI, making the findings of this study less generalisable to those with smaller tumours. Although blinded, the 5 consultant radiologists reviewing the CESH image cases knew that the people had symptoms and knew the site of concern. However, by reading the low-energy, and then low-energy and combined, CESH images in separate sessions, it was possible to determine the sensitivity and specificity of both, with minimal bias.

## Lalji et al. (2016)

### Study size, design and location

Diagnostic accuracy study in 199 women having CEMM after being recalled from the breast cancer screening programme in the Netherlands.

### Intervention and comparator(s)

Intervention: Senographe Essential with SenoBright (GE Healthcare). BI-RADS scores assigned using low-energy CEMM images alone, and then upgraded or downgraded using both low-energy and combined (low- and high-energy) CEMM images.

Comparator: true disease status (histology, further imaging, or discharge according to NHS clinical guidance for breast cancer screening assessment and national guidelines).

### Key outcomes

Overall, diagnostic performance in detecting breast cancer improved when using the combined CEMM image, compared with using just the low-energy CEMM images; mean sensitivity increased from 93.0% to 96.9%, and mean specificity increased from 35.9% to 69.7%. The AUROC increased from 0.645 to 0.833 ( $p < 0.0001$ ). The inter-rater variability was excellent, with a kappa value of 0.89.

### Strengths and limitations

A strength of the study is the use of a panel of 10 readers (7 radiologists and 3 residents) with different skill and experience levels, to demonstrate the ease with which CEMM may be adopted. Some of the included cases were assessed for a previous study, but recall bias was minimised by anonymising the images and having them read over 1 year apart. The authors presented analysis to show that recall bias did not affect the results, and acknowledged that all cases were recalls from the screening programme, where readers were not blinded to the reason for referral. However, these potential limitations reflect clinical practice and the way in which CEMM would be used.

## Travieso-Aja et al. (2019)

### Study size, design and location

Retrospective diagnostic accuracy study in 465 women having CESM in a breast cancer clinic in Spain.

### Intervention and comparator(s)

Interventions: Senographe Essential with SenoBright (GE Healthcare; CESM); Senographe Essential (GE Healthcare; FFDM); LOGIQ E9 (ultrasound). FFDM, FFDM plus ultrasound, and CESM cases were evaluated in separate sessions at least 3 weeks apart.

Comparator: histopathology, or negative imaging over 18 to 24 months.

### Key outcomes

The sensitivity, specificity, positive predictive value (PPV), and accuracy of CESM were all significantly higher than those of FFDM. Sensitivity increased from 82.5% to 92.3% ( $p < 0.001$ ), specificity increased from 68.6% to 86.0% ( $p < 0.001$ ), PPV increased from 65.5% to 93.0% ( $p < 0.0001$ ), and accuracy increased from 74.4% to 90.2% ( $p < 0.005$ ). The sensitivity, specificity, PPV and accuracy of CESM were also higher than those of FFDM plus ultrasound, which had sensitivity of 89.8% ( $p < 0.05$ ), specificity of 82.7% ( $p < 0.05$ ), PPV of 88.7% ( $p < 0.01$ ) and accuracy of 87.0% ( $p < 0.05$ ). Negative predictive value (NPV) improved on CESM, compared with both FFDM and FFDM plus ultrasound, but not significantly so. The AUROC increased significantly to 0.888 (95% confidence interval [CI] 0.855 to 0.917) for CESM, from 0.755 (95% CI 0.711 to 0.799) for FFDM ( $p < 0.001$ ), and from 0.861 (95% CI 0.826 to 0.896) for FFDM plus ultrasound ( $p < 0.05$ ).

### Strengths and limitations

A key strength of this study is its comparatively large sample size and use of 3 radiologists, with discrepancies resolved by consensus of 2 additional radiologists. The majority of subjects had clinically suspicious abnormalities, and therefore larger tumours. The findings may therefore be less generalisable to those with smaller tumours. Selection bias may also be present, as the study was retrospective, with no predefined recruitment criteria. The retrospective nature of the study also limited the comparison of CESM with other prospectively used imaging tools, such as magnified views, DBT and targeted

ultrasound.

## Sorin et al. (2020)

### Study size, design and location

Diagnostic accuracy study in 138 women with palpable breast masses, who had CESM in Israel.

### Intervention and comparator(s)

Interventions: Senographe Essential (GE Healthcare; CESM); Acuson S2000 (Siemens; ultrasound). BI-RADS scores assigned using the low-energy images, and the low-energy plus recombined CESM images.

Comparator: biopsy result or negative follow-up imaging over 12 months.

### Key outcomes

The sensitivity of CESM was 100%, compared with 94.7% for the low-energy images only. The specificity of the low-energy images was 83.5%, and was higher than the recombined CESM images at 73.4% ( $p=0.02$ ). This was slightly higher than that of ultrasound (67.9%); however, this difference was not statistically significant ( $p=0.29$ ). Two cases had their BI-RADS score downgraded from the low-energy images using CESM images. Of 80 cases assigned a BI-RADS score of between 1 and 3, targeted ultrasound identified 13 positive cases, which were all benign on biopsy. Using ultrasound, 7 cases were downgraded from their BI-RADS score on CESM. Two cases of invasive ductal carcinoma were missed on the low-energy images, but detected on both CESM and ultrasound. The NPV for the low-energy images was 97.8%, and for both CESM and ultrasound was 100%. There was a strong correlation of  $r=0.80$  ( $p<0.001$ ) between the contrast-enhanced area on CESM, and the tumour size measured by pathology, in the 22 people who had this data available.

### Strengths and limitations

This was a small, retrospective, single-centre study. The authors report a high prevalence of cancer cases in a population of women with palpable lesions, and note that this may be because a large number of cases with benign imaging were excluded with a lack of appropriate follow up or histopathology. This may have influenced the NPV reported. Most

of the women in the study had dense breast tissue, and the results therefore may not be generalisable to those with less dense breasts. All images were read by a single radiologist, with no blinding between images, so this may have introduced bias.

## **Ferranti et al. (2022)**

### **Study size, design and location**

Diagnostic accuracy study in 118 female patients with unresolved or suspicious findings after FFDM plus ultrasound, having CESM and 3T MRI, in a radiology department in Italy.

### **Intervention and comparator(s)**

Intervention: Senographe Essential with SenoBright (GE Healthcare; CESM); Discovery MR750w (GE Healthcare; MRI). BI-RADS score assigned for FFDM plus ultrasound, and MRI images, followed by all images including CESM, 1 month later.

Comparator: Histopathology or cytology.

### **Key outcomes**

The overall reported diagnostic accuracy of CESM was the same as that of FFDM, at 93%. Its sensitivity was 100%, the highest reported, and specificity was 50% (only MRI was lower at 47%). The PPV of CESM was second highest at 92%, with FFDM at 94%, and NPV was the highest overall at 100%. On a per-lesion basis, the authors reported a concordance between CESM and the reference standard of 63% ( $p < 0.001$ ). Concordance between both FFDM and CESM, and FFDM plus ultrasound and CESM was 81% ( $p < 0.001$ ). Concordance between MRI and CESM was 73% ( $p < 0.001$ ). Concordance between the 2 radiologists for CESM, MRI and ultrasound images was 100% ( $p < 0.001$ ), and for FFDM images alone was 53% ( $p = 0.024$ ).

### **Strengths and limitations**

The 2 radiologists reading the images were experienced, but not with CESM, and received training on this beforehand. Although image readings were separated by about a month, the authors note that recall bias was still possible. Authors acknowledge that background parenchymal enhancement is known to contribute to false-positive results, but did not study it. The prospective nature of the study decreases the likelihood of selection bias,

and results were reported transparently as per patient, and per lesion.

## **Petrillo et al. (2020)**

### **Study size, design and location**

Diagnostic accuracy study in 100 consecutive patients having CESM, with breast lesions identified by clinical examination, mammography or ultrasound, in Italy.

### **Intervention and comparator(s)**

Intervention: Selenia mammography system (Hologic; CESM, DBT, and FFDM synthesised from DBT); MAGNETOM Symphony (Siemens; MRI).

Comparator: pathology from surgical specimen or core needle biopsy.

### **Key outcomes**

The sensitivity of CESM plus DBT was the highest of all mammography techniques, at 93.2%, followed by CESM alone at 87.4%. CESM plus DBT, and CESM alone, had the lowest specificity, at 76.5% and 80.9% respectively. The highest specificity was 83.8% for DBT alone. The AUROC for CESM plus DBT was highest, at 0.905, followed by CESM alone, at 0.883. The accuracies of CESM plus DBT and CESM alone were also highest at 86.5% and 84.8% respectively. Diagnostic accuracy was also reported including contrast-enhanced MRI, and dynamic contrast-enhanced MRI (DCE-MRI), in a subset of people. Sensitivity and specificity were comparable across individual imaging techniques, but statistically different between DCE-MRI and CESM ( $p=0.035$ ). The highest correlation between imaging lesion size and pathologic size was obtained by DCE-MRI ( $r=0.811$ ), and was lower for CESM ( $r=0.722$ ) and DBT ( $r=0.684$ ). Both CESM and MRI techniques overestimated lesion size when compared with pathology.

### **Strengths and limitations**

Images were interpreted as a consensus by 2 radiologists (from a pool of 8) who were blinded to results of other imaging techniques. However, as the FFDM images were synthesised from the DBT images, the study was limited by these 2 techniques not being independent. The authors also acknowledged that there is no dedicated BI-RADS lexicon or other classification system for CESM images, but that the use of the existing BI-RADS system is common. It was not clearly reported why the diagnostic performances of MRI

techniques were reported in a subgroup, or how many people were in the subgroup.

## **Bicchierai et al. (2020)**

### **Study size, design and location**

Retrospective cohort study of 326 patients with biopsy proven breast cancer, having CESM for preoperative staging, in Italy.

### **Intervention and comparator(s)**

Interventions: Selenia Dimensions (Hologic; CESM, FFDM, DBT); ESAOTE 70XVG (MyLab; ultrasound).

Comparator: histopathology.

### **Key outcomes**

Results of CESM changed the type of surgery planned in 60 of 326 (18.4%) people: more extensive breast-conserving surgery (BCS) was planned in 19 people, mastectomy was used instead of BCS in 30 people, mastectomy was downgraded to BCS in 2 people, and 9 people had either BCS or mastectomy on the other breast. None of the conversions to mastectomy were because of false-positive CESM findings. However, there were 6 false-positive cases. In 3 cases, the CESM revealed a multifocal tumour, which histology confirmed to be a single lesion. These people had more extensive BCS than was originally planned. Three people had BCS on the other breast, for B3 lesions (for example, atypical ductal hyperplasia). There were 4 false-negative cases, with positive tumour margins, who were operated on again. Two had more extensive BCS, and 2 had mastectomy. Overall, the accuracy of CESM for preoperative staging was 97%. Sensitivity was 93%, specificity was 98%, PPV was 90% and NPV was 98%. The diagnostic accuracy of CESM was significantly better in people with palpable lesions compared with those with non-palpable lesions.

### **Strengths and limitations**

CESM images were reviewed by 2 radiologists and all other imaging reviewed by 2 different radiologists. A fifth radiologist compared reports to determine whether CESM changed the type of surgery planned. As the study included only biopsy-proven breast cancer cases, it may not reflect true clinical use of CESM, and results may not be

generalisable to other populations. The retrospective nature of the study also limits the available data. The authors also note that comparing CESM with MRI would have been useful, to understand which subgroups of people would benefit from having preoperative CESM rather than MRI.

## Houben et al. (2019)

### Study size, design and location

Retrospective cohort, and diagnostic accuracy, study of 147 patients having CESM for suspicious calcifications, after being recalled from the national breast cancer screening programme in the Netherlands.

### Intervention and comparator(s)

Intervention: Senographe Essential with SenoBright (GE Healthcare; CESM). BI-RADS score and measurement of lesions assigned using low-energy CESM images, followed by using recombined CESM images to change their assessment if needed.

Comparator: histopathology.

### Key outcomes

CESM had higher sensitivity, 93.8% (95% CI 85.0% to 98.3%), than the low-energy images alone, 90.8% (95% CI 81.0% to 96.6%). NPV was also higher for CESM: 88.2% (95% CI 73.6% to 95.3%), compared with low-energy images, 84.2% (95% CI 70.4% to 92.3%). The low-energy images had slightly higher specificity of 39.0% (95% CI 28.4% to 50.4%), and PPV of 54.1% (95% CI 49.4% to 58.8%). Specificity for CESM was 36.6% (95% CI 26.2% to 48.0%), and PPV was 54.0% (95% CI 49.6% to 58.3%). In 51 of 65 (78.4%) cases, the diameter of the lesion was incorrectly assessed by CESM, with a mean difference of 4.23 mm (95% limit of agreement -32 mm to 60 mm). Using only the low-energy images, and clinical information, the surgeons recommended BCS in 58 of 65 (89.2%) cases, and primary mastectomy in 7 of 65 (10.8%) cases. Using the CESM images, BCS was recommended in 55 of 65 (84.6%) cases. Decisions were discordant in 7 of 65 (10.8%) cases, and differences were not statistically significant ( $p=0.453$ ). Of these discordant cases, 5 were upgraded from BCS to mastectomy, and 2 were downgraded from mastectomy to BCS.

## Strengths and limitations

Two breast surgeons recommended surgery using the low-energy images and reports, then by using recombined CESM images and reports 8 weeks later. Because of the retrospective design, the surgeons planning treatment were not able to examine the patient or explore their preferences, and treatment decisions were made in a simulated environment with no follow-up data. Using only a single radiologist, it was not possible to determine inter-observer variation.

## Kim et al. (2018)

### Study size, design and location

Diagnostic accuracy study in 84 patients diagnosed with invasive carcinoma or ductal carcinoma in situ, having CESM and CE-MRI for preoperative evaluation, in South Korea.

### Intervention and comparator(s)

Interventions: Selenia Dimensions with I-View (Hologic; CESM); Lorad Selenia (Hologic; FFDM); Achieva (Philips; CE-MRI); iU22 (Philips; ultrasound, unexpected suspicious CE-MRI or CESM findings only).

Comparator: histological findings on biopsy.

### Key outcomes

The sensitivity in detecting secondary cancer (83.9%) and detecting occult cancer (83.3%) were identical for CESM and CE-MRI. Specificity, PPV, NPV, and accuracy were all higher for CESM than CE-MRI, in both secondary and occult cancers, although this was not statistically significant. Six index cancers, and 6 secondary cancers were missed on CESM. Three of these were detected on CE-MRI, 2 were detected on ultrasound, and 1 had been detected on initial FFDM. CE-MRI missed 4 index cancers, 2 of which were not enhanced on CESM either. The third lesion was a multifocal invasive lobular carcinoma, described as background parenchymal enhancement on CE-MRI, and an enhancing lesion on CESM. The fourth lesion was not detected on either CESM or CE-MRI, but had been detected on ultrasound and initial FFDM.

Surgical management was changed in 26 of 84 people because of CE-MRI findings, and in

25 of 84 people because of CESM findings ( $p=0.610$ ). There was no significant difference between changes to surgical management as a result of false-positive findings, with 9 of 26 having excisional biopsy as a result of CESM findings, and 11 of 25 having excisional biopsy as a result of CE-MRI findings ( $p=0.782$ ).

## Strengths and limitations

Selection bias is likely as this is a small study, in people with known cancer. This may also limit the generalisability of the results to people without known cancer, who have CESM for diagnosis. BI-RADS-like score (on a scale of 1 to 5) was assigned to CE-MRI images by 2 radiologists, and to CESM images by 2 different radiologists. Seven lesions were classified as benign on ultrasound, and no biopsy was taken. This may have influenced the diagnostic accuracies reported; however, the authors note that no lesions were upgraded to suspicious within 1 year of imaging follow up. Most of the false-negative results came from cases of ductal carcinoma in situ, or invasive lobular carcinoma, suggesting further investigation is needed in these subgroups.

## Montrognon et al. (2022)

### Study size, design and location

Retrospective cohort study in 132 patients having preoperative staging using CESM, ultrasound and clinical examination, in a cancer centre in France.

### Intervention and comparator(s)

Interventions: Selenia Dimensions with I-View (Hologic; CESM); Logiq (GE Healthcare; ultrasound).

Comparator: histology (only in those having biopsy).

### Key outcomes

CESM revealed additional image enhancement in 44 of 132 people, and 42 had a further biopsy (2 refused). Overall, 24 of 42 biopsies were positive, and histology results found them to be related to the same primary tumour. For 24 people (18.5%, [95% CI 12.2% to 26.2%]), planned surgery was changed because of CESM results alone. Overall, including changes not because of CESM alone, 8 people had surgery cancelled for neoadjuvant

chemotherapy, 13 people (with 14 lesions) had mastectomy instead of lumpectomy, 1 person had oncoplasty instead of lumpectomy, and 2 people had a contralateral procedure. Excellent agreement was found between lesion size measured on CESM and histology, with an intraclass correlation index of 0.82 (95% CI 0.75 to 0.88). However, CESM overestimated lesion size by a mean difference of 4.25 mm, which was statistically significant ( $p < 0.001$ ).

## Strengths and limitations

As the study was retrospective and non-comparative, the true clinical benefit of preoperative staging may not be known. The authors note that the size measurements may not be comparable, because the axis on which they were taken was not predefined. The correlation index may also have been altered because the measurements focused only on infiltrating tumours. Low-energy images were assessed as FFDM images, and an MRI BI-RADS score was assigned to combined CESM images by 2 radiologists. Discordant results were reviewed by a breast radiology board. Diagnostic accuracy was therefore not assessed for tumours combining infiltrating, and in situ, tumours. Primary radiological investigations were conducted outside of the study centre, so quality of referrals cannot be guaranteed. However, this reflects clinical practice.

One additional study was also identified which explored patient preference and tolerance for CESM and contrast-enhanced MRI (CE-MRI) in 49 people having both imaging techniques for breast cancer staging ([Hobbs et al. 2015](#)). CESM was preferred to CE-MRI ( $p < 0.001$ ), and CE-MRI was associated with higher rates of anxiety during the procedure than CESM ( $p = 0.009$ ). People preferred CE-MRI for the contrast injection ( $p = 0.003$ ), and found the breast compression for CE-MRI more tolerable ( $p = 0.001$ ). However, most people reported these factors as being 'comfortable' or 'neutral' during both CESM and CE-MRI. The most common reasons for favouring CESM were the speed of the investigation, comfort (standing or lying), and the noise of the procedure.

## Sustainability

No sustainability claims have been made by the companies. Potential sustainability benefits include reduced travel to hospitals if CESM is used in a breast clinic instead of MRI.

## Recent and ongoing studies

The external assessment group (EAG) identified 1 recruiting study (Hologic) which included imaging with CESM:

[A prospective, multi-site clinical study to collect user feedback using Affirm Contrast Biopsy](#). ClinicalTrials.gov identifier: NCT04671329. Status: recruiting. Indication: women aged 40 or over recommended for biopsy who have had a suspicious finding on previous contrast-enhanced imaging or have lesions that may be occult under other modalities. Devices: Selenia Dimensions and 3Dimensions. Estimated completion date: December 2021. Country: USA.

## Expert comments

Comments on this technology were invited from 6 clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

Five of the 6 experts were familiar with the technology; 3 had used it routinely, 1 had experience of carrying out tests on some of the included mammography machines, and 1 expert was in the process of adopting it in their department. Three experts had done research or audits using the technology.

## Level of innovation

Three experts considered the technology to be well established in practice and no longer new; 2 experts believed contrast-enhanced spectral mammography (CESM) to be already available in at least 10 UK centres. Three experts considered the technology to be a minor variation on an existing procedure, which is unlikely to alter the procedure safety and efficacy.

## Potential patient impact

Three experts said that CESM could support quicker diagnosis or earlier treatment, and 3 experts mentioned existing long waiting times for MRI. One expert said that CESM is more sensitive than standard mammography, and 1 expert said that CESM is more accurate than standard mammography, and could guide more accurate surgical planning. Two clinical experts said that CESM could help to improve detection of certain types of

breast cancer (lobular breast cancer and multifocal disease). Four clinical experts stated particular benefits in people with dense breast tissue. One expert noted that CESM could be offered to women aged over 40 with a symptomatic, clinically classified cancer, or women aged under 40 with a potentially malignant abnormality detected by ultrasound. Three clinical experts and both patient groups noted that these technologies may be used in people who are contraindicated for MRI (for example, because of a pacemaker or metal implant) or are unable to have MRI because of claustrophobia. One of the patient groups noted CESM could be used when MRI is contraindicated in patients with a high body mass index (BMI) or certain body habitus.

Three experts commented on the patient experience of CESM compared with MRI, with 1 saying CESM is more tolerable, 1 saying CESM has greater patient acceptability, and 2 saying CESM is a more pleasant experience. Three experts said CESM could reduce hospital visits, by avoiding a separate visit for MRI. One expert added that CESM images are easier to explain to people than MRI images.

## Potential system impact

Four experts thought that the technology had the potential to replace MRI or reduce its use, with 3 experts commenting that clinical indications for CESM and MRI are similar. Three experts thought that it would be used in addition to standard care, and 1 considered it a significant variation from the current standard of care. One expert said the technology would be unlikely to replace standard mammography or digital breast tomosynthesis (DBT). Three experts said that CESM is also quicker than MRI, with 1 expert estimating the times to be approximately 25 minutes for CESM, compared with 45 minutes for MRI. One expert said that CESM would improve the workflow and shorten the diagnostic pathway. Two experts also said that MRI can produce false-positive results, which can lead to extra unnecessary visits, investigations and biopsies. One expert mentioned CESM-guided biopsy is now commercially available, and may further reduce MRI waiting times. Two experts thought that using CESM could speed up the patient journey along the diagnostic pathway with potentially fewer clinic visits, because of fewer false-positive results when compared with MRI.

## General comments

Three experts said that the CESM technology would be used in addition to standard care. The other 3 experts thought that CESM has the potential to replace breast MRI scanning.

One expert cited a lack of good quality comparative evidence from the UK to support the accuracy and efficacy of CESM. They noted concerns around lack of long-term follow up for surgical treatment planning and overtreatment based on CESM result. One expert also mentioned accuracy, lesion size, extent and multi-focality assessment, and post-operative and long-term outcomes in terms of extent and recurrence.

One clinical expert estimated that their centre did approximately 150 CESM examinations per year when used in a symptomatic setting. Another estimated that the same number of patients would need CESM as currently have MRI, which was 150 per year in their hospital. Two experts also suggested that CESM exams would replace MRI pending additional evaluation; 1 expert suggested that CESM could replace MRI, and estimated between 6,000 and 10,000 CESM exams across the UK each year. One expert estimated that between 10,000 and 20,000 people across the UK would be eligible for CESM, if used in selected breast cancer patients. One clinical expert stated that people eligible for dynamic contrast-enhanced MRI would also be eligible for CESM, however reported that the number of patients would vary depending on the individual breast unit.

All 6 experts noted the additional staff training needed to handle contrast agents, cannulate patients or use a powered injection pump. One referred to a learning curve, but noted that staff can adapt quickly. All 6 experts highlighted a risk of adverse events, including allergic reaction to the contrast agent. Five experts commented on the increased radiation dose, with 1 stating it is similar to that delivered by DBT. Two experts mentioned the risk of kidney injury in people with impaired renal function. One expert stated that availability of contrast and consumables, maintenance on machines, and delays from waiting for kidney function test results in those at risk of kidney damage from the contrast injection, may present as practical issues when implementing CESM in the NHS. One expert stated that cost may be a barrier to implementation.

## Patient organisation comments

Two patient groups (Breast Cancer Now and Lobular Breast Cancer UK) reviewed the draft briefing and completed questionnaires asking for their opinions on contrast-enhanced spectral mammography (CESM) as part of the breast cancer diagnosis process.

Both patient groups agreed that CESM could lead to faster breast cancer diagnosis. One said that this would reduce patient stress and anxiety, and the other thought this may lead to earlier intervention and potentially less invasive surgery. One patient group mentioned that provision of further imaging in breast clinics would improve access to breast care

nurses and information and support available to patients. They also noted system benefits, including an overall reduction in length and number of appointments, which may improve accessibility to other diagnostic imaging services. Both patient groups mentioned that younger women and those with dense breasts would be likely to benefit from CESM, with 1 highlighting worse survival rates in those under 45 years, compared with those aged between 45 and 74 years. One patient group also thought there was potential benefit in patients with lobular tumours (for which there is no palpable lump, and can be undetected on standard mammography) and those being monitored for recurrence. However, they raised concerns on whether CESM would be equally effective across all types of breast cancer, in particular those which do not form a solid tumour or exhibit single or branched blood flow which may limit contrast uptake. Both patient groups mentioned the use of contrast agent, with 1 stating that this may cause anxiety in patients, and the other noting pain associated with the injection and potential allergic reactions. Both patient groups felt that other imaging modalities should be available for patients who do not wish to have CESM. Both patient groups mentioned potential barriers to adoption, including cost, with 1 stating that this could lead to varied provision of care across the NHS. Both groups also cited staff training as a potential barrier, and 1 noted that specialist breast clinics currently have significant workforce and resource shortages. Both patient groups felt that more evidence was needed, including comparing CESM with other imaging modalities. One group felt that more evidence would demonstrate the benefit of CESM and reassure patients of its use. The other group felt that without this evidence, confirmatory testing should be immediately available for all positive CESM results, as an unexpected diagnosis could cause distress. Both patient groups highlighted that there may be issues in describing or using CESM in patients with a learning disability, mental health issues (including panic and anxiety disorders) or communication difficulties. Both groups also noted that the accessibility of CESM for patients with physical disabilities should be considered. The benefit of CESM when compared with contrast-enhanced MRI in patients with smaller, non-solid or mixed tumours, or when compared to hormone-derived tracers with positron emission tomography (PET) imaging, in hormone-positive cancers, was unclear.

## Expert commentators

The following clinicians contributed to this briefing:

- Andrew John Gash, consultant radiologist, Betsi Cadwaladr University Health Board, did not declare any interests.

- Eman Hafez, consultant radiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust, did not declare any interests.
- Jonathan James, consultant radiologist, Nottingham Breast Institute, did not declare any interests.
- Simon Lowes, consultant breast radiologist and honorary clinical senior lecturer, Gateshead Health NHS Foundation Trust and Newcastle University, did not declare any interests.
- Caroline Osborne, consultant oncoplastic breast surgeon, Yeovil District Hospital NHS Foundation Trust, did not declare any interests.
- Kevin Robson, head of diagnostic radiology physics, Newcastle upon Tyne Hospitals NHS Foundation Trust, did not declare any interests.

Representatives from the following patient organisations contributed to this briefing:

- Breast Cancer Now
- Lobular Breast Cancer UK.

## Development of this briefing

This briefing was developed for NICE by Newcastle External Assessment Group. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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