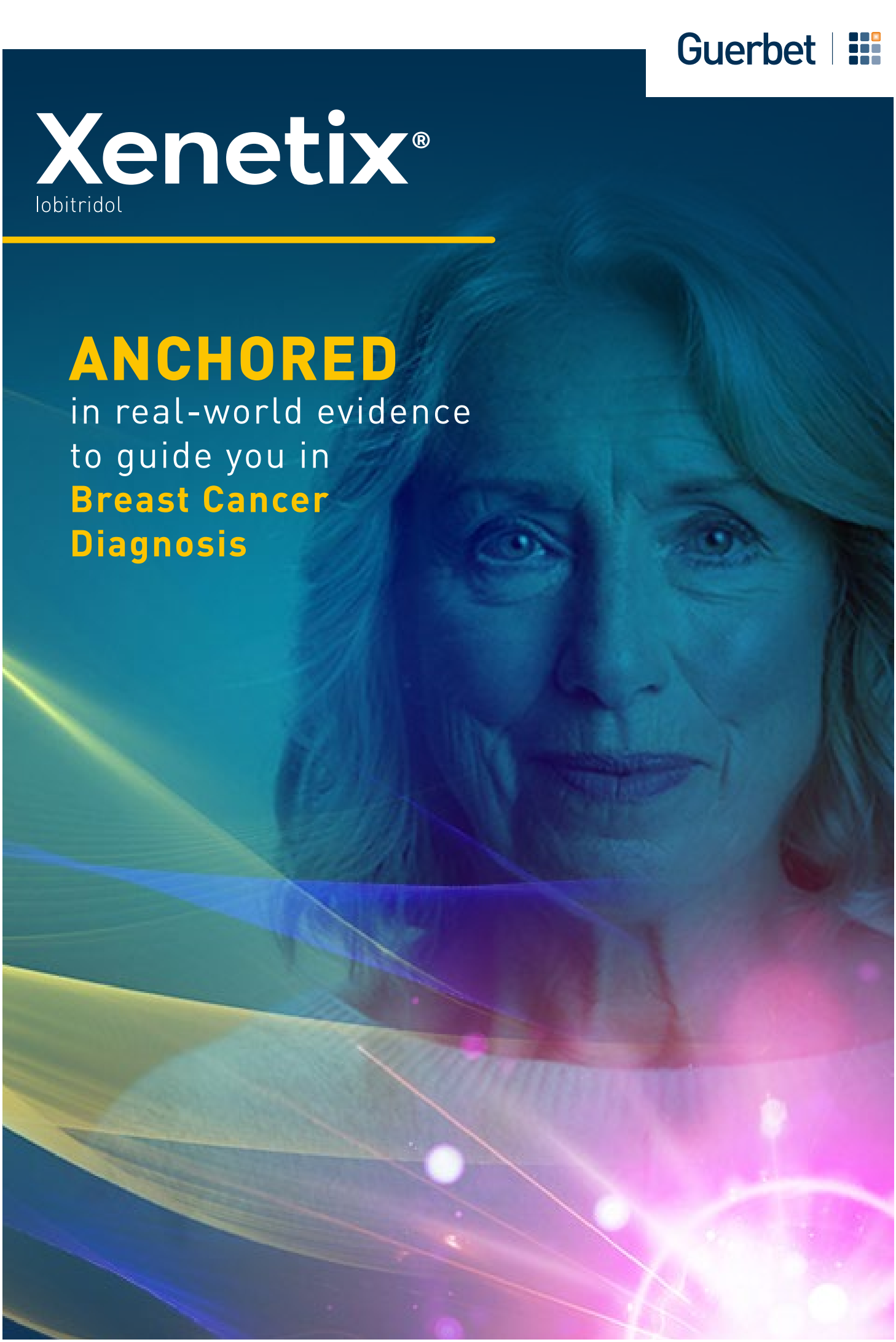
Guerbet

Xenetix®

Iobitridol



ANCHORED

in real-world evidence
to guide you in
Breast Cancer Diagnosis

CONTEXT AND EVOLUTION OF BREAST CANCER WORLDWIDE

Breast cancer remains a worldwide public health issue and is currently the most common cancer across the globe. About one in twenty women will be diagnosed with breast cancer over the course of their lifetime [1]. In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally [2].

From 2013 to 2018, the death rate went down by 1% per year. This decrease is believed to be the result of finding breast cancer earlier through screening and increased awareness, as well as finding better treatments [3].

Currently, approximately 90% of women with breast cancer survive 5 years or more after diagnosis [4].

BREAST CANCER PATHWAY

Two imaging techniques, mammography (MG) and ultrasound (US) [5] are currently used as a routine clinical practice for breast imaging. Mammography is the gold standard imaging technique for breast cancer screening, follow-up or in case of clinical signs. [6-10]

However, in some cases, mammography has limited sensitivity such as for the study of high-density breasts [11,12], which requires additional examinations such as MRI [13-16].

In recent years, new imaging techniques have been developed, which are less costly and more accessible than MRI, including contrast-enhanced spectral mammography (CESM) [17]. This technique improves the sensitivity and the specificity of breast cancer detection as it provides higher contrast and better lesion delineation than mammography alone. [17-20]

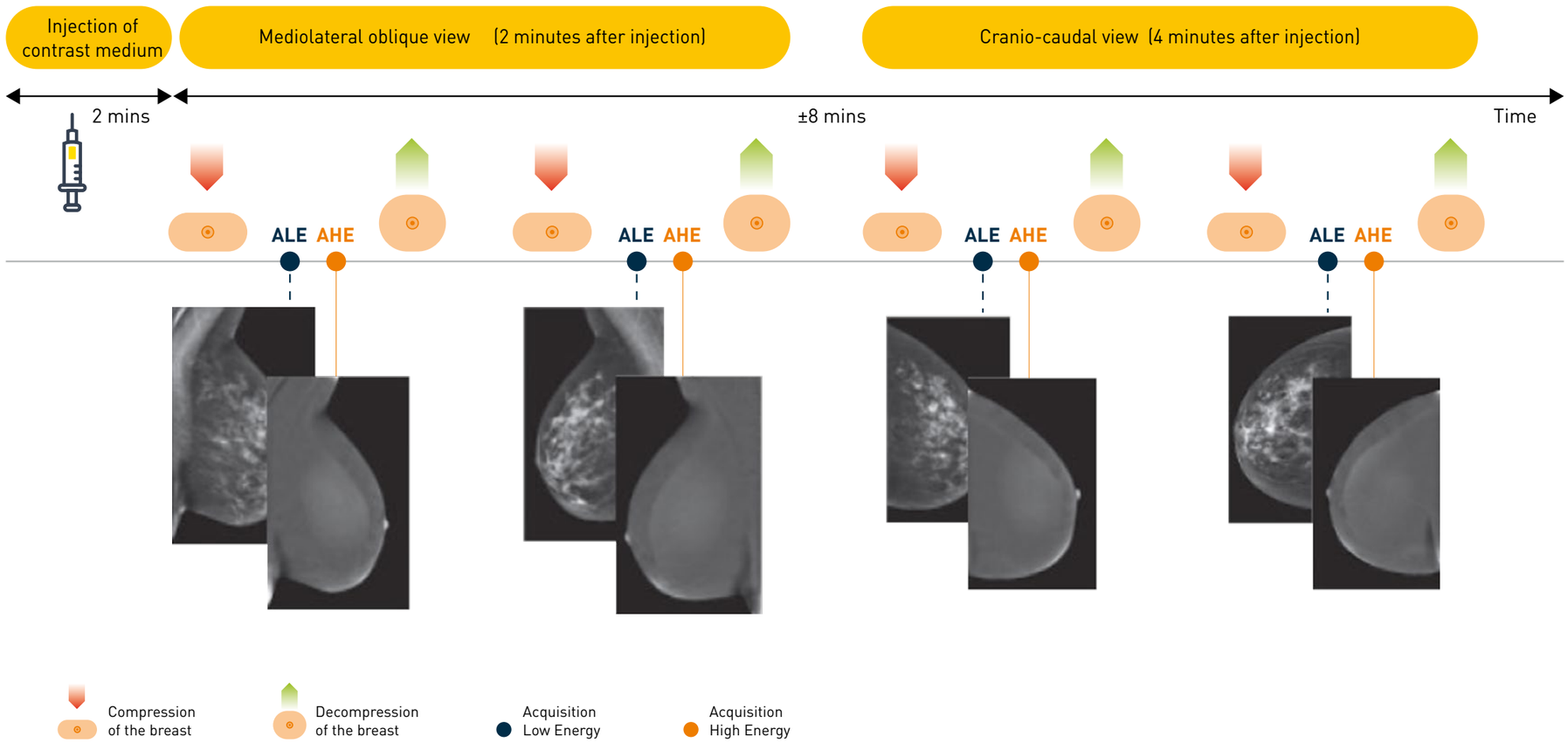
Contrast-enhanced mammography (CEM), contrast-enhanced spectral mammography (CESM), contrast-enhanced digital mammography (CEDM) or angiomammography describe the same procedure. The terms were harmonised as “CESM” in this document.

CONTRAST-ENHANCED SPECTRAL MAMMOGRAPHY TECHNIQUE

CESM is a recent development of mammography combining X-ray imaging of the breast and the use of intravenous iodinated contrast agents. CESM is performed by using standard mammography equipment that has been upgraded to include copper filtration and additional software that make the unit capable of performing dual energy imaging [21]

- This technique uses the energy dependence of X-ray attenuation through materials of different compositions in the breast [22].
- Two images are taken: a low energy exposure (comparable to that of a standard mammography) for morphological information, and a high energy exposure, beyond the iodine attenuation coefficient (33.2 KeV), providing information on vascular structures (iodine uptake) [23,24]
- The low- and high-energy images are automatically postprocessed. The resulting recombined image highlights areas of contrast enhancement while the signal from background breast tissue has been suppressed [24]
- Contrast injection allows better tissue differentiation to improve lesion detection and obtain information on tumour neoangiogenesis [18-23]

Diagram of contrast-enhanced spectral mammography technique



Images courtesy of Dr. M. Lobbes, MD, PhD; Zuyderland Medical Center and Maastricht University Medical Center, the Netherlands

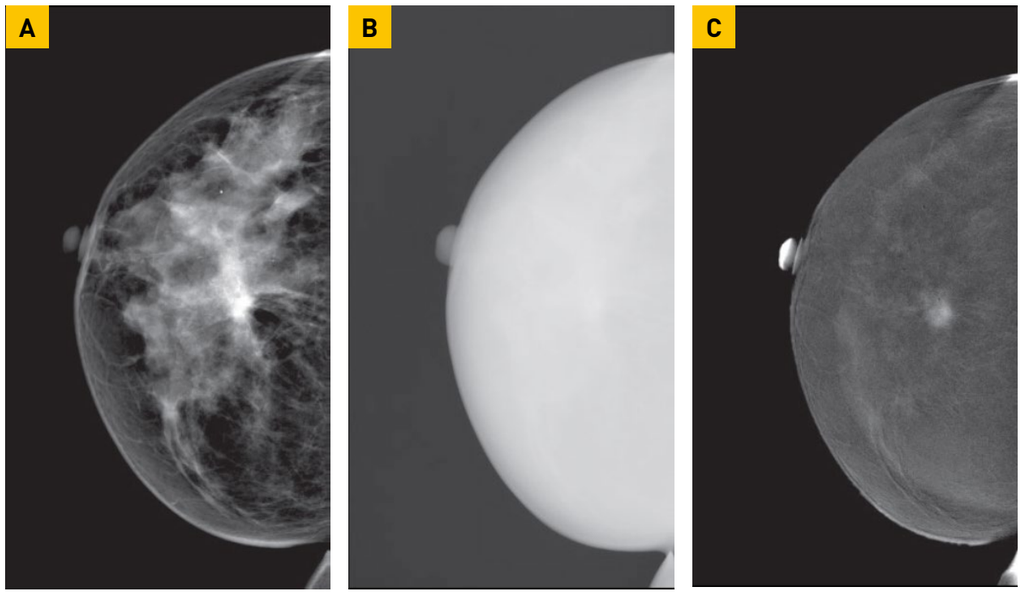
This diagram illustrates the various steps of a CESM examination (acquisition of low and high energy images in cranio-caudal and oblique views) for both the left and right breast of a patient, with timing of breast compression in between image acquisitions.

CESM IMAGING PROTOCOL

Two minutes before image acquisition, an iodine-based contrast medium is intravenously injected at a standard dose of 1.5 mL/kg and a rate of 2-3 mL/s [23]. Next, at minimum, both breasts are imaged in craniocaudal (CC) and mediolateral oblique (MLO) views. In each step, compression is applied followed by rapid acquisition of low- and high-energy images.

Low and high energy images are processed to generate recombined images. After each exposure, compression is released. Images are considered to be of diagnostic value if they are acquired within 10 minutes after contrast material administration.

Illustration of CESM case [25]



Images courtesy of Dr. M. Lobbes, MD, PhD; Zuyderland Medical Center and Maastricht University Medical Center, the Netherlands.

Typical example of CESM images

First, a low-energy image is acquired (A, comparable to a standard mammography), immediately followed by the high-energy image (B), which is used in post-processing to create the recombinant image (C), in which a lesion is clearly visible.

RECOMMENDATIONS OF MEDICAL SOCIETIES

The 2019 European Society for Medical Oncology (ESMO) recommendation [10,21] for management of early breast cancers cites the CESM technique as a new technique with a potential to increase diagnostic accuracy, especially in dense breasts.

The 2017 EUSOBI recommendation specified that CESM may be useful in the detection of breast cancer, in the characterization of lesions, particularly in dense breasts and as an alternative to MRI [9], particularly in cases of contraindications or difficulty in accessing this examination. [26]

APPLICATIONS AND BENEFITS OF CONTRAST-ENHANCED SPECTRAL MAMMOGRAPHY

In comparison with mammography, CESM presents:

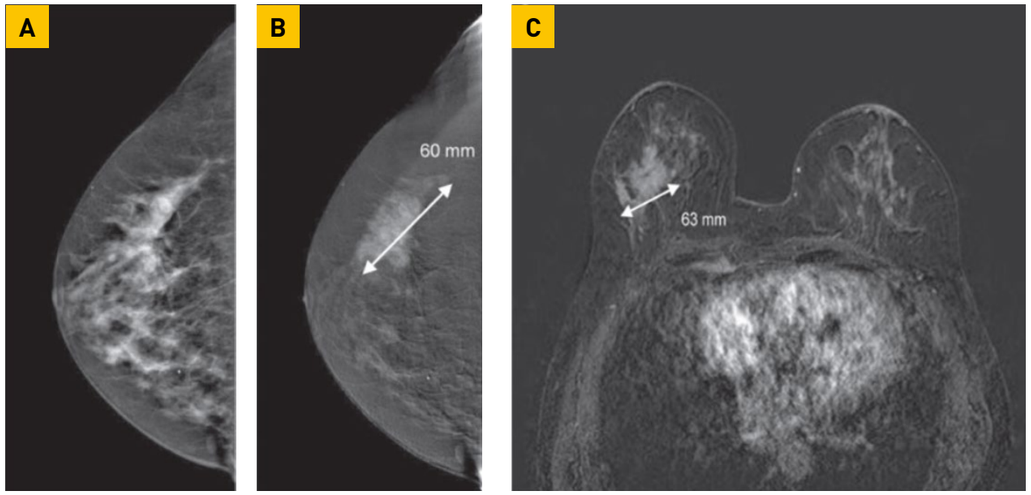
- Superior diagnostic performance (both sensitivity and specificity) to mammography alone [19,27,28]
- CESM showed that it detects more malignancies than mammography alone [19,20,27,29,30]

The main applications of contrast enhanced mammography are abnormal screenings, symptomatic patients, preoperative staging of breast cancer, evaluation of response to neoadjuvant chemotherapy, screening women with dense breasts, and screening women at an increased risk of developing breast cancer [23].

The advantages of CESM compared to breast MRI are:

- High sensitivity and better specificity (fewer false positives) [31]
- A shorter exam time (10 min instead of 30 min)
- The ability to perform the examination immediately after the mammography and thus allow for an overall view of the case
- Easy and rapid image analysis, rapid learning curve
- An alternative for patients who are claustrophobic, pacemaker wearers or cannot adopt the moderately uncomfortable position of medium duration for MRI
- An imaging technique considered to be less anxiogenic [32,33]

Illustration of a breast tumour diameter measurement case using CESM and MRI [25]



Images courtesy of Dr. M. Lobbes, MD, PhD; Zuyderland Medical Center and Maastricht University Medical Center, the Netherlands

Image example of good agreement between tumour diameter measurements using CESM and breast MRI. The cancer is ill-defined on the low-energy CESM image (A) and can be measured more confidently on the recombined image (B, 60 mm). Subtracted contrast enhanced T1w MRI image (C) showed a similar irregular mass (63 mm). Final pathological results showed a 60mm invasive ductal carcinoma [25].

ADVANTAGES OF THE CONTRAST-ENHANCED SPECTRAL MAMMOGRAPHY

- **Superior performance to mammography for breast cancer detection [19, 27, 29]**
- **CESM indications are largely similar to breast MRI indications and could be an alternative to breast MRI in cases of contraindications (obesity, presence of ferromagnetic materials, claustrophobia, etc.) [9, 23]**
- **High sensitivity for delineation of malignant findings, particularly masses, architectural distortion, and microcalcifications [24].**

Just like all other imaging techniques, CESM has some limits. They are described in references 21, 23 and 24.

ABOUT XENETIX®

Xenetix® is well tolerated and safe for use in patients of a wide range of ages and conditions, although local clinical guidelines and the local Summary of Product Characteristics (SmPC) should always be taken into account. Its good safety profile has been demonstrated in the general population, including patients with risk factors, based on five post marketing surveillance studies totalling more than 400,000 patients [34-38].

THERAPEUTIC INDICATIONS [39]

Xenetix® is approved for use in adults and children in a wide range of indications and can be used via several routes of administration; local prescribing information should be consulted.
To complete this wide range of indications, **Xenetix®** is now approved in IV administration for contrast enhanced spectral mammography.

XENETIX IN CONTRAST-ENHANCED SPECTRAL MAMMOGRAPHY

Dose

Legal statements: Average dose 1.5 mL/kg Total volume (min-max) 50 to 150 mL.

In practice, the iodinated contrast medium is injected intravenously by automated bolus system using an injector with a flow rate of 2-3mL/s. Image acquisition begins 2-3 minutes after injection [17,40].

		Xenetix® 250 [1]	Xenetix® 300 [2]	Xenetix® 350 [3]
NEW	Intravascular administration	• Phlebography • Whole body computed tomography	**Intravenous route** • Intravenous urography • Head and whole body computed tomography • Intravenous digital subtraction angiography • Herniography	**Intravenous route** • Intravenous urography • Head and whole body computed tomography • Intravenous digital subtraction angiography • Sialography • Endoscopic retrograde cholangiopancreatography
			Intravenous administration in **adult women for contrast-enhanced spectral mammography** to identify known or suspicious lesions of the breast	
		• Intra-arterial digital subtraction angiography • Arteriography	**Intra-arterial route** • Arteriography of all regions • Angio-cardiography	**Intra-arterial route** • Arteriography of all regions • Angio-cardiography
	Local administration	• Endoscopic retrograde cholangiopancreatography	• Endoscopic retrograde cholangiopancreatography • Arthrography • Hysterosalpingography	

*Not all the indications may be available in your country. Please check with your local Guerbet representative for more information. Indications may differ from children to adult population

EFFICACY OF XENETIX IN CESM

- In a first study including 120 women with suspect findings on mammography (MG) and/or ultrasound (US), *Dromain et al* showed a better diagnostic accuracy for CESM with Xenetix® 300 in addition to MG compared to MG alone and MG + US. The lesion size was closer to the histological size for CESM compared to MG and US. The sensitivity was higher for CESM + MG than for MG alone (93% vs. 78%; p<0.001) with no loss in specificity [19].
- These results were confirmed in a second study with multiple readers assessing images from 110 women. Diagnostic accuracy was improved when CESM with Xenetix® 300 was used in addition to MG ± US, with an average sensitivity across all readers significantly higher for MG ± US + CESM than for MG ± US (78% vs. 71% using BIRADS, p = 0.006) [20]. Addition of CESM with Xenetix® 300 to MG facilitates the visualization of breast lesions [20].
- In three studies including women with histologically proven breast cancer, *Fallenberg et al* compared MG, CESM with Xenetix® 300, and magnetic resonance imaging (MRI) in the detection and size estimation of breast cancers using postoperative histology as the gold standard. They provided the following results:
  - *CESM showed better sensitivity in breast cancer detection than MG and good correlation with postoperative histology in size assessment. The sensitivities for the detection of the index tumour were 82.5% for MG (66/80), 100 % for CESM (80/80), and 97.4 % for MRI (76/78)* [17]
  - *CESM alone had the same sensitivity and better size assessment as CESM + MG and was significantly better than MG with only 6.2 % increase in average glandular dose (AGD). Sensitivity across readers (3 independent blinded radiologists) was 77.9 % for MG alone, 94.7 % for CESM, and 95 % for CESM + MG. The increase in sensitivity was much greater in dense versus non-dense breasts and in pre- versus postmenopausal women* [41].
  - *CESM alone and in combination with MG is as accurate as MRI but is superior to MG for lesion detection. Patients with dense breasts benefited most from CESM with the smallest additional radiation dose compared to MG. In this larger prospective two-centre, multi-reader study, the mean sensitivity for index lesions was 94% for CESM and for CESM + MG 81% for MG and 95% for MRI. Considering all lesions (index plus additional), the mean sensitivity and specificity were 72% and 94% for CESM, 70% and 92% for CESM + MG, 55% and 95% for MG and 76% and 88% for MRI* [42].
- In a study including 195 women with suspicious or undetermined findings on MG and/or US, *Tardivel et al* showed that CESM can be performed easily in a clinical assessment after positive breast cancer screening and may impact significantly patient's management through breast cancer staging [43]. CESM changed diagnostic and treatment strategy in 41 women (21%), leading to more extensive surgery (n = 20) or neo-adjuvant chemotherapy (n = 1) or avoiding further biopsy for 20 patients with negative CESM. The sensitivity of CESM was 94% (CI: 90–96%) and the specificity was 77% (CI: 66–86%).
- In a study comparing low dose CESM with Xenetix 350 and contrast-enhanced MRI, *Clauser et al* showed a high sensitivity and accuracy in women with suspicious findings on conventional imaging. CESM had the potential to increase the specificity and might help to reduce false positive biopsies while obtaining sensitivity comparable to that of CE-MRI [44].

CLINICAL SAFETY OF XENETIX IN CESM

In the context of CESM, the publications reported a very good safety profile for Xenetix® with only two mild skin reactions among the 550 women included in these studies [17, 19, 20, 41-44].

OVERALL CONCLUSIONS FROM THESE STUDIES

- **The use of CESM with Xenetix® 300 increased the diagnostic accuracy compared to mammography alone or mammography + ultrasound.**
- **The sensitivity of CESM was comparable to the one of MRI and there was a trend for better specificity.**
- **The estimation of lesion size was better with CESM compared to MG.**
- **The added value of CESM is particularly important for young women and women with dense breasts.**

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