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Abstract. The objective is to optimize low-energy (LE) and high-energy (HE) exposure parameters of contrast-enhanced spectral mammography (CESM) examinations in four different clinical applications for which different levels of average glandular dose (AGD) and ratios between LE and total doses are required. The optimization was performed on a Senographe DS with a SenoBright® upgrade. Simulations were performed to find the optima by maximizing the contrast-to-noise ratio (CNR) on the recombined CESM image using different targeted doses and LE image quality. The linearity between iodine concentration and CNR as well as the minimal detectable iodine concentration was assessed. The image quality of the LE image was assessed on the CDMAM contrast-detail phantom. Experiments confirmed the optima found on simulation. The CNR was higher for each clinical indication than for SenoBright®, including the screening indication for which the total AGD was 22% lower. Minimal iodine concentrations detectable in the case of a 3-mm-diameter round tumor were 12.5% lower than those obtained for the same dose in the clinical routine. LE image quality satisfied EUREF acceptable limits for threshold contrast. This newly optimized set of acquisition parameters allows increased contrast detectability compared to parameters currently used without a significant loss in LE image quality. © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.1.3.033506](https://doi.org/10.1117/1.JMI.1.3.033506)]

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1 Introduction

Contrast-enhanced spectral mammography (CESM) is a new breast imaging technique that has been developed to visualize iodinated contrast agent uptake in the breast. Several clinical studies have shown a significantly higher sensitivity for the detection of invasive breast cancers for CESM (93%) than mammography (78%), the ability of CESM to accurately assess the size of the lesion compared to histology and high sensitivity of CESM for the detection of multifocal disease.^{1–4} Moreover, prospective data comparing CESM to MRI has shown that CESM has similar sensitivity and better specificity than MRI for the detection of index cancer.^{3,4}

This technique is based on dual energy exposure acquisitions using spectra with energies predominantly below [low energy (LE)] and above [high energy (HE)] the iodine K-edge at 33.2 keV.^{5,6} By appropriately selecting the X-ray spectra, both morphological and functional images can be obtained. A breast morphology image, similar to a standard mammogram, can be provided by the LE image. An image of iodine contrast agent uptake (hereafter, referred to as recombined image) can be obtained by applying an appropriate recombination algorithm to the LE and HE images.⁷ In the recombined image, the background tissue is suppressed and the signal intensities are proportional to the surface iodine concentration. SenoBright®, the CESM product introduced by GE Healthcare, operates with an automatic exposure mode enabling one to acquire an LE and HE image pair with a total average glandular dose (AGD)

that is on average 20% higher than that of a screening mammogram acquired with the automated optimization of parameters (AOP) contrast mode present on the same mammography equipment. This AGD is still lower than European reference frame (EUREF) dose guidelines for screening mammography in the range of 3 to 8 cm polymethylmethacrylate (PMMA) equivalent thickness and for all fibroglandular/adipose compositions.^{8,9} To ensure a comparable diagnostic performance between the LE CESM image and a standard mammogram, the LE image acquisition parameters are equivalent to those of a standard mammogram with an AGD ranging between the one delivered with the standard AOP mode and the one delivered with the contrast AOP mode of a Senographe DS® (GE Healthcare, Chalfont St Giles, UK). SenoBright® has been 510(k) cleared by the food and drug administration as an adjunct to mammography and ultrasound exams for breast cancer diagnosis to help localize and determine contrast enhancement of a known or suspected lesion. However, other potential clinical indications of SenoBright® are being considered and these may require different AGD levels and acquisition parameters depending on the acceptable total AGD and desired LE image quality for the respective indications.⁴

The goal of this study was to optimize the LE and HE acquisition parameters for four clinical indications including: (1) assessment of extent of disease, (2) problem solving after nonconclusive mammography and ultrasonography, (3) screening of high-risk women, and (4) CESM-guided biopsy in case of a contrast enhancement depicted on CESM with no associated suspicious finding visible in mammography and ultrasonography. For each indication, a target total AGD level and image

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quality criteria for the LE image were set. Theoretical modeling of the X-ray mammographic image chain was used to optimize the LE and HE target/filter combinations, the tube voltages, and the AGD allocation between the LE and HE images, while accounting for the limitations of accessible mAs values. Experimental validation of our theoretical model was obtained through phantom experiments. Contrast-to-noise ratio (CNR) in the recombined image and contrast-detail detectability in the LE CESM image were compared to those obtained using SenoBright®, which was considered our reference.

2 Methods

2.1 Four Clinical Indications with Different AGD Levels

Four clinical indications for CESM were identified with different needs in terms of AGD delivered to the patient and different acceptable levels of image quality for the morphological information as present in the LE image.

The first indication is the assessment of extent of disease in a patient with a known breast cancer or the assessment of response after neoadjuvant chemotherapy. For this indication, the patient has already been diagnosed with breast cancer. The patient underwent a previous mammography exam for the detection and diagnosis of a breast tumor and the goal of the CESM examination in this context is to make an accurate extent of disease assessment based on the visualization of contrast agent enhancement in the recombined image. We believe that a total AGD (i.e., the sum of the AGD of a LE and HE image pair) superior to the AGD of a screening mammogram is acceptable.

The image quality of the LE morphology CESM image is not required to be as high as the initial diagnostic image quality, but it should be high enough to allow for visual correlation between morphological information in the LE image and contrast enhancement in the recombined CESM image. For this indication, the target total AGD was set equivalent to twice the AGD delivered by a mammogram acquired in standard AOP mode and the target LE image quality was set to be noninferior to the acceptable values (indicating minimal performance limits) for threshold contrast visibility of gold disks of varying diameters and thicknesses in a CDMAM phantom,¹⁰ as defined in the EUREF guidelines.¹¹

The second indication is problem solving after nonconclusive mammography and ultrasonography with lesions classified breast imaging reporting and data system (BI-RADS) 0 or 3.¹² In this indication, similarly to the assessment of the extent of disease, the patient also underwent a previous standard mammography exam, therefore, the morphological information present in the LE CESM image has limited additional value. However, the image quality of the LE image must be sufficient to enable visual

correlation between LE CESM and recombined CESM images as well as between LE CESM and standard mammography images. Moreover, the radiation dose must be restricted because BI-RADS three lesions correspond to probably benign findings with less than 2% chance of malignancy.^{13,14} Therefore, in this indication, the target total AGD was set equivalent to the one delivered by SenoBright® and the target LE image quality was set to achieve the acceptable values for threshold contrast visibility as described in the EUREF guidelines.

The third clinical indication is screening of high-risk women for whom the current recommendation, in our institution as well as in many other institutions, is to perform a mammography and a breast MRI every year.¹⁵ In this indication, the LE CESM images could replace the conventional mammograms whose main interest is to look for microcalcifications suggestive of a ductal carcinoma *in situ* tumor. For this indication, the LE CESM images must have the same image quality as the standard mammograms. The magnitude of the total AGD is critical since patients with BRCA1 and BRCA2 gene mutations are likely to be more sensitive to ionizing radiations and consequently may present more radioinduced cancers than the general population.^{16,17} Therefore, for this indication, the target total AGD was set equivalent to the one delivered by a standard mammogram, and the target LE image quality was set to the achievable values (indicating limits that are achievable) of threshold contrast visibility defined by the EUREF guidelines.

Finally, the last indication is CESM-guided biopsy in case of a contrast enhancement depicted on CESM with no associated suspicious finding visible in mammography and ultrasonography. Such a biopsy could be based on a stereotactic technique with two angulated exposures (−15 and +15 deg). In this indication, the target total AGD was set equivalent to the one delivered by a standard stereotactic-guided examination. No target was defined for the LE image quality in this indication because the recombined CESM image is the only useful required image. Thus, we only focus on the contrast uptakes of abnormal findings that cannot be depicted on the unenhanced mammography (LE image).

A summary of target total AGD and LE image quality levels for the four identified clinical indications can be found in Table 1.

2.2 Imaging System

The Senographe DS® upgraded with SenoBright® application has an X-ray tube with Mo and Rh targets and Mo, Rh, and Cu filters. Three target-filter combinations are allowed for LE image acquisition: Mo–Mo, Mo–Rh, and Rh–Rh, and two target-filter combinations are allowed for HE image acquisition: Mo–Cu and Rh–Cu. The LE images can be acquired with voltages between 22 and 40 kVp. The HE images can be acquired with voltages between 40 and 49 kVp. Depending on the target,

Table 1 Target dose and LE image quality for each clinical indication (5 cm thick, 50% glandular breast).

	Extent of disease	Problem solving	Screening	Stereo-guided biopsy
Target AGD	2× AGD delivered by a mammography in AOP standard mode = $2 \times 1.2 = 2.4$ mGy	AGD delivered by SenoBright® = 1.7 mGy	AGD delivered by a mammography in AOP standard mode = 1.2 mGy	AGD delivered by a stereotaxic-guided examination = 2.2 mGy
Target LE image quality (EUREF)	Acceptable	Acceptable	Achievable	Not assessed

filter and kVp combination, a limited range of mAs values is accessible to the user.

The Senographe DS® X-ray detector consists of a CsI(Tl) phosphor coupled to an array of a-Si photodiodes and thin-film transistors arranged as a matrix on a flat panel. The detector pitch is 100 μm , and 14 bit images are produced. The source-to-detector distance is 66 cm and the distance between the tabletop and the surface of the detector is ~ 1.5 cm.

2.3 Optimization of Acquisition Parameters

To optimize the acquisition parameters for the four above mentioned clinical indications of CESM, speXim, a validated simulator of the Senographe DS® X-ray mammographic image chain was used.⁷ Specific details of SpeXim are proprietary to GE Healthcare and cannot be disclosed. SpeXim is based on a deterministic model of the differential attenuation of x-rays and estimates the per-pixel signal intensity and noise (quantum and electronic). X-ray spectra are computed based on the Bremsstrahlung only spectra of Birch and Marshall and characteristic rays are modeled using tabulated values.^{18,19} X-ray scatter in the imaged object is modeled as an additive term using experimentally obtained scatter-to-noise ratios. In addition, speXim allows calculating the AGD. For LE images, simulated values of the AGD were found in good agreement with published data from Wu et al.²⁰ with a mean difference of 3%. For HE images, simulated values of the AGD were found in good agreement with published data from Boone,²¹ with a mean difference lower than 5%.

Optimization of acquisition parameters was performed for a 5-cm thick compressed phantom, corresponding to the median breast thickness in routine mammograms, and an intermediate glandularity of 50%.^{22,23} The contrast-to-noise ratio per pixel ($\text{CNR}_{\text{pixel}}$) normalized to the square root of the total AGD was used as the figure of merit for the detectability of iodine in the recombined CESM image. $\text{CNR}_{\text{pixel}}$ was defined as

$$\text{CNR}_{\text{pixel}} = \frac{(\text{SI}_{\text{recomb,iodine}} - \text{SI}_{\text{recomb,background}})}{\sigma_{\text{recomb,background}}} \quad (1)$$

where $\text{SI}_{\text{recomb,iodine}}$ and $\text{SI}_{\text{recomb,background}}$ are the mean per-pixel signal intensities in a region of interest in an iodine insert and in

the background, and $\sigma_{\text{recomb,background}}$ is the standard deviation of the signal intensity level in the background.

The ratio of the AGD allocated to the LE image to the total AGD was varied between 0 and 1 to maximize $\text{CNR}_{\text{pixel}}$. Simulations were repeated using all practically available LE and HE tube voltages and anode/filter combinations. $\text{CNR}^2/\text{AGD}_{\text{total}}$ values were evaluated for configurations without constraining the mAs and with constraining the mAs using values available on the Senographe DS®. The maximum reachable mAs was defined so that the exposure time is below a maximum value of 6 s depending on the anode material and kVp value. The upper limit of 6 s corresponds to the maximum exposure time allowed by the Senographe DS® and was selected to limit the thermal load of the X-ray tube and the exposure time reducing the probability of patient motion artifacts. The simulations were performed with an attenuation of iodine corresponding to a surface concentration of 0.5 mg/cm^2 of iodine.

An experimental validation of the theoretically optimized spectra was performed through phantom experiments imaged on a Senographe DS®. Our phantom consists of two parts, stacked to correspond approximately to a 5-cm thick compressed breast with 50% glandularity (Fig. 1). The first part consists of a 1-cm-thick homogenous PMMA section containing 1 cm^2 inserts with iodine concentrations of 0.25, 0.50, 1.00, 2.00 and 4.00 mg/cm^2 . The second part consists of one 2-cm thick BR100 (100% glandular tissue equivalent) homogenous section and one 2-cm thick BR0 (0% glandular tissue equivalent) homogenous section (CIRS, Norfolk, VA). The PMMA section with the iodine inserts was padded with 1-cm thick tissue equivalent sections to obtain a uniform primary plus scatter signal across the iodine inserts. For all clinical indications, except for CESM-guided biopsy, acquisitions were performed with the standard mammography clinical compression paddle and a standard Potter-Bucky containing an antiscatter grid. Acquisitions for the CESM-guided biopsy indication were performed without antiscatter grid and with a compression paddle dedicated to stereotactic procedures (Fig. 1).

For each clinical indication, the acquisitions were repeated five times to assess the accuracy of the measurements. To reduce the potential effect of image lag, a time delay of 2 min was respected between consecutive acquisitions. LE and HE images were acquired with a total AGD equal to the target total AGD while varying the ratio of the LE AGD to the total AGD. The

Fig. 1 Pictures of the iodine phantom acquired on standard mammography and stereotactic mode. The first part consists of a 1-cm-thick homogenous PMMA section containing 1 cm^2 inserts with iodine concentrations of 0.25, 0.50, 1.00, 2.00 and 4.00 mg/cm^2 . The second part consists of two 2-cm-thick homogenous sections of 50% glandular tissue-equivalent material (CIRS, Norfolk, VA).

manufacturer's gain, offset, and defective pixel corrections were applied to the LE and HE images and they were then recombined to obtain CESM images. CNR_{pixel} measurements in the recombined CESM images were performed at all iodine concentrations. The signal intensities measured in experimentally acquired LE and HE images were used to match the simulated gray levels provided by speXim. The Spearman rho test was used to compare the CNR values obtained through simulation and measured CNR values obtained through phantom experiments.

2.4 Impact of Optimized Acquisition Parameters on CNR in Recombined CESM Images

Using optimized acquisition parameters for each clinical indication and associated total AGD level, we assessed the CNR_{pixel} as a function of iodine surface concentration in the recombined CESM images of the phantom containing iodine inserts. This assessment was repeated for SenoBright® acquisition parameters. To gain some insights into lesion detectability in recombined images, we derived from this relationship the minimal detectable surface iodine concentration using the Rose criterion.^{24,25} Following Rose, we assumed the threshold lesion CNR for visibility, $CNR_{\text{lesion-min}}$, to be equal to 4.

We considered the case of a round contrast enhancement with a diameter of 3 mm intending to simulate an invasive breast cancer enhancement with the minimal size that we expect to see in clinical cases.

The pixel CNR is related to the lesion CNR through the following equation:

$$CNR_{\text{lesion}} = CNR_{\text{pixel}} \times \sqrt{\text{Area}_{\text{pixel}}}. \quad (2)$$

With a detector pitch equal to 0.1 mm, the minimum pixel CNR ($CNR_{\text{pixel-min}}$) to detect this 3 mm round contrast enhancement is equal to 0.15.

2.5 Assessment of image quality of low energy images

The quality of LE images was determined from the threshold contrast for detectability in the CDMAM contrast-detail phantom (CDMAM v3.4, serial number 1006, Artinis, Zetten, Netherlands), which contains gold discs of various sizes and thicknesses. CDMAM consists of an aluminum base (0.5 mm thick) attached to a PMMA cover (3 mm) having together an equivalent PMMA thickness of 10 mm. The phantom was imaged on top of a 4-cm-thick PMMA section, approximating a 5-cm thick breast of 50% glandularity.

Images of the CDMAM phantom were acquired using the optimized LE acquisition parameters for each clinical indication and the standard mammography acquisition parameters obtained with the three automatized optimization of parameters (AOP) modes available on the Senographe DS® (dose, standard and contrast). For each analysis, we assessed three sets of 16 acquisitions. The phantom was slightly shifted between each acquisition to account for small geometrical imperfections and partial volume effects in the analysis.

The images were analyzed using the automatic scoring software CDMAM analyzer V1.2 (Artinis, Zetten, Netherlands). Contrast-detail curves were obtained using a detection rate of 62.5%.²⁶⁻²⁸

For extent of disease and problem solving indications, we compared the contrast-detail curves of the optimized LE images

and of standard mammography images acquired in AOP standard and contrast modes, the two AOP settings currently used in our clinical practice for these indications. For the screening indication, we compared the contrast-detail curve of the optimized LE images and of standard mammography images acquired in AOP standard and dose modes, currently used in our clinical practice for this indication. For each experimental condition, we also compared threshold detectable gold thickness with the acceptable and achievable values defined in EUREF guidelines for screening mammography (limits specified for five gold discs diameters: 0.1, 0.25, 0.5, 1 and 2 mm).¹¹ This comparison was made by the calculation of the Image Quality Figure (IQF) taking into account the five gold discs diameters specified in EUREF guidelines. Based on the IQF calculation method,²⁶⁻²⁸ the equivalent IQF for Euref comparison (IQF_{eq}) was defined by

$$IQF_{\text{eq}} = 5 / \sum_{i=1}^5 C_i \cdot D_{i,\text{min}}, \quad (3)$$

where $D_{i,\text{min}}$ is the smallest diameter perceived in column corresponding to a gold thickness C_i .

3 Results

3.1 Exposure Parameters Optimization

Acquisition of images on phantoms has confirmed, for each clinical indication and dose level, the optima found by speXim simulation. The maximum CNR as a function of the dose ratio between LE glandular dose to total glandular dose matches between simulations ran with speXim and acquisitions performed on Senographe DS®. This confirms that optimization can be performed from simulated data. To account for observed differences between LE and HE signal intensities simulated by speXim and LE and HE signal intensities in experimentally acquired images with the Senographe DS®, a gain calibration was performed. A gain (G) ratio was calculated as

$$G = SI_{\text{measured}} / SI_{\text{speXim}}, \quad (4)$$

where SI_{measured} and SI_{speXim} are experimental and theoretical average signal intensities. This calibration process was repeated for a 2.5-cm thick PMMA phantom at all practically available target/filter combinations. A single kVp and mAs values were used for each target/filter combination. While consistent gray levels between simulated and acquired images were expected after calibration, we observed small differences between the intensity of the CNR obtained from simulations and from acquisitions, revealing an imperfect residual match between simulated and acquired values of signal and noise levels. However, there was a linear relationship between simulated and measured CNR with a coefficient of determination R^2 estimated to 0.98 (Fig. 2).

The mean difference in CNR between simulated and real data was 7.8%, and the maximum difference was inferior to 16% for all experimental conditions. Moreover, the shape of the CNR curves as a function of the AGD allocation ratio is similar between curves drawn from simulated data and from real acquisitions (without mAs constraint in Fig. 3 and with mAs constraint in Fig. 4). Overall, the CNR values obtained through simulation are well correlated with the CNR values obtained with our experimental setting, with Rho values ranging between 0.917 and 1 as shown in Table 2.

Fig. 2 Linear relationship between simulated and experimental CNR_{pixel} for 0.5 mg/cm² iodine and for each clinical indication.

The optimal LE and HE acquisition parameters, determining the X-ray spectra used in CESM, obtained by speXim simulations for each dose level are summarized in Table 3.

3.2 Impact of Optimized Acquisition Parameters on CNR in Recombined CESM Images

The difference of CNR_{pixel} measured in inserts with different iodine concentrations for the four clinical indications compared to SenoBright® is displayed in Fig. 5. The CNR_{pixel} was higher for each clinical indication than for SenoBright®, including the screening indication for which the total AGD was 22% lower than the SenoBright® AGD (1.32 versus 1.69 mGy).

Figure 6 shows experimental CNR_{pixel} values as a function of iodine concentration on recombined CESM images for the four clinical indications of CESM and for SenoBright®. A linear relationship was observed for each clinical indication and for SenoBright®. A linear regression was performed to estimate this linear relationship: $CNR_{pixel} = a \cdot Conc_{iodine}$. It was found that the linear fit to the experimental CNR_{pixel} values results in R^2 values superior to 0.99 in all cases. This result suggests that CNR_{pixel} values in the recombined images can be used to accurately estimate the surface iodine concentration when the appropriate linear transformation is known. This linear fit was used to compute the minimal surface iodine concentration required to detect a 3-mm diameter round lesion according to the Rose criteria.

Comparisons of the minimal iodine concentrations detectable according to Rose criterion for each optimized clinical indication and for SenoBright® are summarized in Table 4. The minimal detectable concentration was lower for each optimized clinical indication compared to SenoBright® suggesting the possibility to detect more subtle contrast enhancement and to decrease the number of false negative lesions found in clinical CESM examinations.

3.3 Measures of Image Quality of LE Image

The optimal AGD repartitioning between the LE and HE images affects the image quality of the LE image. Contrast-detail curves for LE images in each optimized clinical indication and for standard mammography with different AOP modes are shown in Fig. 7.

Fig. 3 Comparison of measured and simulated CNR_{pixel} for 0.5 mg/cm² iodine insert as a function of the ratio of the AGD allocated to the LE image to the total AGD without mAs constraint. Results are shown for each of the four clinical indications.

Fig. 4 Comparison of measured and simulated CNR_{pixel} for 0.5 mg/cm^2 iodine insert as a function of the ratio of the AGD allocated to the LE image to the total AGD with mAs constraint. Results are shown for each of the four clinical indications.

The image quality factor (IQF) is used as a global indicator of performance with the highest values related to the highest scores. The comparison of the IQF_{eq} between optimization and EUREF guidelines is showed in Table 5 and illustrated in Figs. 8 and 9.

The use of optimized parameters for the extent of disease, without and with mAs constraint, and for problem solving without mAs constraint satisfied EUREF achievable limits.

The use of optimized parameters for problem solving with mAs constraint and for high-risk screening satisfied EUREF acceptable limits.

Table 2 Correlation of measured and simulated CNR_{pixel} for 0.5 mg/cm^2 iodine insert as a function of the ratio of the AGD allocated to the LE image to the total AGD with and without mAs constraint using the Spearman test.

	mAs constraint	Rho	p-value
Extension of disease	Without	1.000	0.1
	With	1.000	<0.001
Problem solving	Without	1.000	<0.02
	With	0.976	<0.001
High risk screening	With and without	1.000	<0.005
CESM-guided biopsies	Without	1.000	<0.002
	With	0.917	<0.005

4 Discussion

The purpose of this investigation was to optimize the LE and HE acquisition parameters of CESM examinations for four different clinical indications requiring different acceptable total AGD and desired LE image quality. To assess the impact of this optimization, we compared the recombined image CNR obtained after our optimization with the one of the only commercially available CESM products, SenoBright®.

The optimization of LE and HE exposure parameters (anode/filter, kVp, mAs) for different levels of AGD and different ratios between the LE dose and the total dose was based through theoretical modeling of the X-ray mammographic image chain and then validated using experimental measurements on phantoms containing inserts with different iodine concentrations imaged on a Senographe DS®. Optima found by speXim simulation for the four different clinical indications with resulting CNR_{pixel} and $CNR_{pixel}^2/AGD_{total}$ were confirmed through real acquisition of images on the phantom. Our results indicate that the CNR per pixel in recombined CESM images was increased in all of the four clinical indications compared to recombined images obtained using SenoBright®. Moreover, the impact of the variability of the exposure parameters on phantom images CNR measurements was extremely low ranging from 0.02 to 0.05 for an iodine concentration of 0.5 mg/ml . As a result, the minimal detectable concentration was lower for each optimized clinical indication compared to SenoBright®, suggesting the possibility to detect more subtle contrast enhancement and to decrease the number of false negative lesions found in clinical CESM examinations. However, this increased sensitivity for

Table 3 Simulated optimal acquisition parameters and AGD_{LE}, AGD_{HE}, AGD_{TOTAL} for acquisitions with and without mAs constraints.

	LE spectrum	HE spectrum	CNR _{pixel}	AGD _{LE} (mGy)	AGD _{HE} (mGy)	AGD _{TOTAL} (mGy)	CNR _{pixel} ² / AGD _{TOTAL}
Extent of disease							
Without mAs constraint	Rh/Rh 29 kVp 60 mAs	Rh/Cu 46 kVp 440 mAs	1.68	1.05	1.42	2.47	1.14
With mAs constraint	Mo/Rh 24 kVp 140 mAs	Mo/Cu 49 kVp 320 mAs	1.62	1.05	1.42	2.47	1.06
Problem solving							
Without mAs constraint	Rh/Rh 27 kVp 60 mAs	Rh/Cu 46 kVp 320 mAs	1.41	0.76	1.03	1.79	1.11
With mAs constraint	Mo/Rh 27 kVp 50 mAs	Mo/Cu 47 kVp, 320 mAs	1.37	0.67	1.10	1.77	1.06
Screening							
With mAs constraint	Rh/Rh 29 kVp 30 mAs	Rh/Cu 48 kVp 190 mAs	1.21	0.52	0.80	1.32	1.11
Without mAs constraint	Rh/Rh 30 kVp 28 mAs	Rh/Cu 48 kVp 180 mAs	1.21	0.56	0.76	1.32	1.11
CESM-guided biopsy							
Without mAs constraint	Rh/Rh 27 kVp 70 mAs	Rh/Cu 46 kVp 450 mAs	1.09	0.88	1.45	2.33	0.51
With mAs constraint	Mo/Rh 26 kVp 80 mAs	Mo/Cu 49 kVp 320 mAs	0.99	0.91	1.42	2.33	0.42
SenoBright®	Rh/Rh 29 kVp 63 mAs	Rh/Cu 45 kVp 160 mAs	1.08	1.2	0.49	1.69	0.69

iodine detection could also lead to a significant increase in the number of false positives. Further clinical studies are needed to assess the impact of optimization on both sensitivity and specificity of CESM examination.

Fig. 5 Difference of CNR_{pixel} measured in inserts with different iodine concentration for the four different clinical indications versus CNR from SenoBright (mean values and standard deviation for the five repeated acquisitions).

For screening indication, for which the average dose was lowered to the one of SenoBright® (1.32 versus 1.67 mGy) and equal to the one of a routine screening mammography, the modification of the dose allocation for the LE and HE acquisition allowed an increased CNR per pixel, in particular, for low iodine concentrations of 0.5 mg/ml, and a decrease of 6% of the minimal detectable iodine concentration compare to SenoBright®. The possibility to perform CESM examination with a dose equal to the dose used in screening mammography and without the loss of CNR on the recombined images offers new possibilities for CESM in clinical practice, in particular, in women with specific mutations who may be more sensitive to the effects of radiation.

In the diagnostic workup, problem solving using CESM is an indication for nonconclusive mammography and ultrasonography with lesions classified BI-RADS 0 or 3. The assessment of the extent of disease is another indication for which CESM has the potential to provide a more accurate definition of the extent of a known cancer and to allow the detection of additional foci of cancer in the affected breast as well as the detection of otherwise occult cancer in the contralateral breast. This assessment is essential for the planning of an appropriate treatment. Our results show that the CNR per pixel in particular for low surface iodine concentration were not significantly superior using optimized exposure parameters for the extent of disease than using optimized exposure parameters for problem solving

Fig. 6 Experimental CNR_{pixel} as a function of surface iodine concentration for SenoBright® and for the optimized acquisition techniques of each of the four clinical indications.

Table 4 Comparison of AGD and minimal iodine concentration detectable and LE image quality between optimization for each clinical indication and SenoBright®.

	Extent of disease	Problem solving	Screening	CESM-guided biopsy	SenoBright®
AGD (mGy)	2.47	1,69	1.23	2.24	1.69
Minimal iodine conc. compared to SenoBright®	-13.33%	-12.5%	-5.83%	-9.17%	0%
LE image quality (EUREF)	Achievable	Achievable	Acceptable	NA	Achievable

Note: AGD, average glandular dose; LE, low energy; NA, non-assessed.

Fig. 7 Contrast detail analysis on CDMAM phantom: comparison of contrast detail curve of optimized low energy images and standard mammograms.

despite a 28% higher total AGD and despite a very close allocation of the dose between the LE and the HE acquisition, $AGD_{HE}/AGD_{total} = 0.57$ and 0.62 for extent of disease and problem solving, respectively (Table 2 and Fig. 5). These results are not surprising if we consider that when the quantic fluctuation of X-rays follows the Poisson distribution, the CNR is proportional to the square root of the number of photons and the dose increases as the square of the CNR. So, if the dose increases from 1.77 to 2.47 mGy, ($\times 1.4$), the CNR is increased by $\sqrt{1.4} = 1.18$. Our results perfectly confirm this relationship between the dose and the CNR as we observed a CNR of 1.37 for problem solving and 1.62 for extent of disease corresponding to a multiplication factor of 1.18 . Moreover, both extent of disease and problem solving indications lead to a very close minimal detectable iodine concentration. These results suggest that problem solving optimization could provide the best compromise between CNR in the recombined CESM image and the dose delivered to the patient compared to extent of disease optimization. However, it would be useful to know what gain in detectability we can expect for an 18% increase in CNR. Further clinical studies are necessary to determine the clinical impact of an increase in CNR of less than 20% knowing that the detectability depends on other factors such as the shape of the object, its size and the recombined image background.

In CESM-guided biopsies, our optimization leads to similar CNR per pixel at 0.5 mg/ml iodine concentration and to the detection of a similar minimal iodine concentration as obtained in a diagnostic protocol, such as optimized problem solving. This result suggests the possibility to have a similar contrast

uptake visibility for the lesion targeting during a CESM-guided biopsy procedure, compared to the contrast uptake visibility observed during the diagnostic workup.

These results remain valid for higher iodine concentrations, more frequently observed in clinical routine on invasive malignant breast tumors.

The impact of a new allocation of dose between LE and HE exposures was also evaluated on LE image quality. Results of contrast-detail experiments indicate that the optimized parameter provides similar or acceptable detection as the standard mammography for each clinical indication with the exception of the screening indication. For the extent of disease, it resulted in a similar contrast-detail curve than for standard mammography in AOP standard mode with a Senographe DS® and values of IQF_{eq} (for both, without and with mAs constraint optimizations) were superior to EUREF achievable limits for the five gold discs' diameters.

For problem solving indication, our results show a decrease of the LE image quality which is slightly more important in the case of optimization with a constraint on available mAs. Nevertheless, as expected, values of IQF_{eq} were equivalent to those defined as acceptable by EUREF for optimizations without mAs constraint and superior to those defined as achievable by EUREF for mAs constraint optimization (Table 5, Figs. 8 and 9). The degradation of the LE image quality is not problematic in this clinical indication where the CESM examination is performed in addition to a nonconclusive initial standard mammography. This minimal image quality degradation does not preclude carrying out an arguably easy correlation between the contrast uptake information provided on the recombined CESM image and the morphological information provided on the LE CESM image, a very important capability in CESM-based diagnostic.

Optimization for screening of high-risk women shows contrast-detail curves inferior to those of mammography in AOP standard mode and AOP dose mode with a Senographe DS®. IQF_{eq} values were inferior to achievable EUREF limits but superior to acceptable EUREF limits (Table 5). Indeed, the threshold gold thickness satisfied the EUREF achievable limits for gold discs diameters of 0.25 , 0.5 , and 1 mm and satisfied the EUREF acceptable limits for gold discs diameters of 0.1 and 2 mm representative of good quality mammography for screening (Figs. 8 and 9). The degradation of LE image quality compared to the standard mammography AOP modes is more problematic in this clinical indication because the LE image

Table 5 Comparison of IQF_{eq} calculated for optimized low energy images and EUREF limits.

IQF _{eq}	Without mAs constraint	With mAs constraint	EUREF achievable	EUREF acceptable
Extent of disease	22.2	19.9	18	11.8
Problem solving	18.9	16.2	18	11.8
High risk screening	15.9	15.9	18	11.8

Values are IQF_{eq} calculated for the five gold discs diameters specified in EUREF guidelines.

Fig. 8 Contrast detail analysis on CDMAM phantom: comparison of values obtained for each optimization with those of standard mammogram and limiting values determined for five gold discs diameters (0.1, 0.25, 0.5, 1, and 2 mm) as specified as achievable and acceptable in the EUREF guideline. Optimization performed without mAs constraint.

Fig. 9 Contrast detail analysis on CDMAM phantom: comparison of values obtained for each optimization with those of standard mammogram and limiting values determined for 5 gold discs diameters (0.1, 0.25, 0.5, 1, and 2 mm) as specified as achievable and acceptable in the EUREF guideline. Optimization performed with mAs constraint.

should be performed not in addition but in substitution to the standard mammogram. Therefore, LE image has to deliver the same clinical information as a standard mammogram in order to depict masses, architectural distortions, and microcalcifications with the same clinical accuracy. However, the threshold gold thickness satisfied the achievable limits defined in EUREF guidelines for gold disc diameters of 0.25, 0.5 and 1 mm and satisfied the acceptable limits defined in EUREF guidelines for gold disc diameters of 0.1 and 2 mm. Therefore, we can anticipate that the diagnostic accuracy of such optimized LE images should be representative of good quality mammography as expected by EUREF for screening.

Our study has several limitations. First, the optimization (both simulated and experimental) was only performed for a 5-cm-thick breast assuming 50% of glandularity. While we expect to observe the same trends, this optimization should be extended to a clinically relevant range of breast thicknesses and breast glandularity before being used in clinical routine. We may also extend this work to virtual phantoms with structured background²⁹ in order to take into account the impact of fibroglandular texture encountered in clinical images on the detectability of contrast uptake. More realistic morphology of contrast uptake in the lesions as well as contrast uptake in normal parenchyma should be modeled to derive results closer to what is observed in clinical practice.

5 Conclusion

The results of our investigation suggest that a problem solving optimized protocol gives the best compromise between the CNR in the recombined CESM image, the dose delivered to the gland, and the image quality of the low energy image. This newly optimized set of acquisition parameters may eventually replace the current SenoBright® protocol of acquisition for clinical routine CESM examination. Moreover, our proposed screening optimized protocol gives a new opportunity to perform CESM examinations with a similar dose as is used in regular mammography. While we observed a small degradation of the LE image quality due to the new allocation of the dose between the LE and the HE images, in comparison to Senographe DS® images, it remains within the achievable limits defined in EUREF guidelines for screening.

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