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EXPERIMENTAL

Assessment of grating-based X-ray phase-contrast CT for differentiation of invasive ductal carcinoma and ductal carcinoma in situ in an experimental ex vivo set-up

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Abstract
Objective Limited contrast between healthy and tumour tissue is a limiting factor in mammography and CT of the breast. Phase-contrast computed tomography (PC-CT) provides improved soft-tissue contrast compared with absorption-based techniques. In this study, we assessed the technical feasibility of grating-based PC-CT imaging of the breast for characterisation of ductal carcinoma in situ (DCIS).
Methods Grating-based PC-CT was performed on one breast specimen containing an invasive ductal carcinoma and DCIS using monochromatic radiation of 23 keV. Phase-contrast and absorption-based images were compared qualitatively and quantitatively with histopathology in a blinded fashion.
Results Grating-based PC-CT showed improved differentiation of soft-tissue components. Circular structures of high phase-shift contrast corresponding to the walls of the dilated ductuli of the DCIS were visualised with a contrast-to-noise ratio (CNR) of 9.6 using PC-CT but were not detectable on absorption-based images (CNR=0.27). The high phase-shift structures of the dilated ductuli were identifiable in the PC-CT volume data set allowing for 3D characterisation of DCIS.
Conclusions Our results indicate that unlike conventional CT, grating-based PC-CT may allow the differentiation between invasive carcinoma and intraductal carcinoma and healthy breast tissue and provide 3D visualisation of DCIS.
Key Points
- *Phase-contrast computed tomography (CT) yields improved soft-tissue contrast.*
- *The method can resolve the fine structure of a breast tumour.*
- *Invasive and intraductal carcinoma can be differentiated.*
- *Differentiation is possible by visual inspection and quantification.*
- *The method could improve early breast cancer diagnosis.*

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Keywords X-ray phase-contrast imaging · Computed tomography · Synchrotron radiation · Ductal carcinoma in situ (DCIS) · Invasive ductal carcinoma

Abbreviations and acronyms

PC-CT	phase-contrast computed tomography
DCIS	ductal carcinoma in situ
PHU	phase-contrast Hounsfield unit

Introduction

Important advances in breast imaging have recently been achieved. The performance of X-ray-based methods, such as mammography, tomosynthesis and CT have greatly improved. B-scan ultrasound has been complemented by contrast-enhanced ultrasound and elastography, as well as other novel ultrasound techniques. MRI of the breast has been established as a method of unique sensitivity for the detection of breast malignancies. However, the methods available still have major shortcomings in terms of diagnostic efficiency or cost-effectiveness.

Further improvement of image quality in screening mammography, tomosynthesis and CT of the breast is restricted because of the limited contrast difference between healthy glandular and tumour tissue in X-ray absorption-based imaging. Phase-contrast imaging, a fundamentally different approach to X-ray-based imaging, has recently attracted significant interest in the field of medical diagnostics and has proven to be most promising when the contrast achieved by conventional absorption-based imaging reaches its limits [1, 2]. X-ray phase-contrast imaging exploits the phase shift that occurs when X-ray waves pass through different tissue components. This phase shift can be used to generate improved contrast differences in the image and several methods have been described that detect the phase information, including free propagation, diffraction-enhanced and interferometry-based imaging [3–5]. Among them, grating-based phase-contrast imaging is currently one of the most promising candidates for future clinical implementation of the technique, as it has been shown to be transferrable from highly brilliant synchrotron sources to conventional X-ray tubes [6, 7].

Phase-contrast imaging has previously been applied to both mammography and CT imaging of the breast. Phase-contrast mammography images show improved visualisation of collagen strands and contours between glandular and adipose tissue [8, 9]. Furthermore, phase-contrast mammography allows improved tumour visualisation and detection of skin invasion, and yields improved differentiation of scar tissue, healthy tissue and tumour [10]. Initial clinical trials of phase-contrast mammography have been performed in Italy and Japan, and suggest improved sensitivity and specificity of the technology compared with conventional mammography [11, 12]. Early phase-contrast CT (PC-CT) images suggested that the technique was able to clearly differentiate fibrotic from cancerous tissue [13]. More recently, diffraction-enhanced PC-CT imaging was shown to perform well on both lobular and ductal carcinoma [14, 15]. However, diffraction-enhanced imaging requires a monochromatic, parallel beam and is limited when it comes to quantitative tissue-specific values. Conversely, grating-based X-ray phase-contrast imaging has been shown to be achievable with standard polychromatic laboratory sources and provides quantitative element-specific values that allow establishment of Hounsfield units for phase-contrast imaging [16, 17].

In this technical development, we experimentally assessed the feasibility of grating-based PC-CT imaging of the breast in detecting different histopathological characteristics in an ex vivo human cancerous breast tissue specimen with invasive ductal carcinoma and ductal carcinoma in situ (DCIS) compared with histopathology. The investigation was designed as a proof-of-concept study and was thus performed at a synchrotron radiation source.

Materials and methods

Study subjects and sample preparation

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained before imaging. We analysed one breast sample ($2\times2\times2$ cm^3) from a 65-year-old woman containing an invasive ductal cancer and a DCIS. Following surgical resection, the sample was fixed in 4 % neutral-buffered formaldehyde solution.

Grating-based phase-contrast CT and absorption-based CT

CT measurements were carried out at the beamline ID19, European Synchrotron Radiation Facility (ESRF, Grenoble, France). For a detailed description of the experimental set-up, see "Supplementary methods" and Weitkamp et al. [18]. Briefly, a monochromatic and coherent X-ray beam of 23 keV produced by a wiggler and a fixed-exit double-crystal monochromator was used, as this energy level is close to the mean energy used in mammography. The grating-based imaging set-up consisted of a silicon phase grating (Laboratory for Micro- and Nanotechnology, Paul Scherrer Institut, Villigen, Switzerland) and a gold analyser grating (Institute for Microstructure Technology and Karlsruhe Nano Micro Facility, Karlsruhe Institute of Technology, Germany). For every projection a set of four images at

different positions of the phase grating perpendicular to the beam were recorded. The intensity variation in each pixel during this grating imaging was used to calculate conventional absorption contrast, phase-contrast, and dark field images from each of these sets according to the following equation:

$$I(j,k,\omega,x_g) = \sum_{n=0}^{\infty} a_n(j,k,\omega)\cos\left[\frac{2\pi n}{g_2}x_g - \phi_n(j,k,\omega)\right] \quad (1)$$

where the intensity signal $I(j,k)$ for each pixel with coordinates (j,k) will oscillate as a function of grating position x_g, and where a_n are the amplitude coefficients, φ_n are the corresponding phase coefficients, g_2 is the period of the analyser grating and ω is the rotation angle of the sample around the optical axis. Only absorption- and phase-contrast images were used for analysis. A schematic overview of the experimental set-up is shown in Fig. 1.

The formalin-fixed breast specimen was examined in a plastic container in a water bath. For full tomography, 1,199 projection images were collected while rotating the specimen by 360°. For every projection, four phase steps over one grating period were recorded. Image acquisition was achieved with a CCD camera (ESRF FReLoN E230-42; 2,048×2,048 pixels, dynamic range 13,000:1) using an indirect detection scheme comprising a single-crystal (lutetium aluminium garnet) scintillator screen of 125 μm in thickness and lens optics resulting in an effective pixel size of 30 μm. Ten reference projections without the sample were acquired after every 100th projection for flat-field correction.

Sample postprocessing

After CT data collection, the formaldehyde-fixed sample was cut into 5-mm slices. After macroscopic examination, the region of interest was excised and dehydrated in an ascending alcohol series before embedding in hot paraffin wax. After solidification, the paraffin blocks were cut into 5-μm sections using a standard microtome and sections were stained with haematoxylin and eosin using standard protocols.

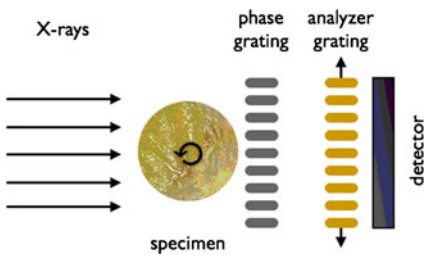

Fig. 1 Simplified schematic of the experimental set-up. The sample is rotated in the monochromatic X-ray beam. After passing through the sample, X-ray waves travel through a silicon phase grating and a gold analyser grating. A set of four images at different positions of the phase grating are recorded for every projection. The detector records the intensity variation in each pixel during this grating imaging. The information is used to calculate conventional absorption-contrast as well as phase-contrast images

Correlation of histological slices and PC-CT data

Absorption- and phase-contrast tomographic data sets are intrinsically co-registered and were manually reorientated to match the histological sections by an independent investigator (JH). No further postprocessing was applied to the data. Upon visual exploration of the tumour by radiologists with experience in clinical mammography (AS, SL, FB), the most representative slices were chosen.

PC image analysis and interpretation

Tomographic reconstruction was performed using the standard filtered back projection algorithm with a Hilbert filter for PC-CT and Ram-Lak filter for standard absorption CT [19]. All images were qualitatively analysed by radiologists (AS, SL, FB and MR) and a pathologist (DM) with experience in mammography for identification of regions of interest and matching with morphological sections of the tissue sample in a blinded fashion. Quantitative analysis was performed by a blinded radiologist placing ten regions of interests in the respective area of the co-registered PC-CT and absorption CT images (invasive carcinoma and DCIS vs. surrounding ductuli) to derive Hounsfield units (HU) and phase-contrast HU (PHU). PHU were derived as described by Herzen et al. and Qi et al. [16, 17]. Also, quantitative analysis included calculation of the contrast-to-noise ratio (CNR), which was defined as $(S_A - S_B)/\sigma$, where S_A and S_B are the measurements between the two histologically defined structures.

Statistical analysis

For this technical development, only descriptive statistics were applied.

Results

Imaging was performed without complications or technical interruptions using the experimental set-up shown in Fig. 1. Overall, the data acquisition time for 1,199 grating-based PC-CT projections, including flat-field projections, was 1.5 h.

Invasive ductal carcinoma and ductal carcinoma in situ

Histological work-up revealed that the breast sample contained an invasive ductal carcinoma and adjacent secondary DCIS (Fig. 2a). Histopathological analysis indicated that the DCIS was surrounded by mammary ducts (Fig. 2b) with intact mammary ducts completely enclosing the cancerous tissue, and showed closely packed, characteristically polymorphic tumour cells within the lumen and hyperchromatic nuclei (insets b.1 and b.2). Conversely, the invasive ductal carcinoma was characterised by irregular shape and high cellularity (see bottom of Fig. 2c) with invasive and intraductal cellular components in immediate proximity (c.1 and c.2).

Co-registered absorption (b.3) and phase-contrast (b.4) CT slices corresponding to histological section b are provided in Fig. 3. In both absorption- and phase-contrast images, adipose tissue appears with low attenuation and phase-shift effect. Fibrous parenchyma, ductal wall and intraductal carcinoma provide similar density on the absorption-based image, with no or only very limited internal contrast differences (Fig. 3b.3). Conversely, the phase-contrast image visualises differences in phase shift within these areas, similar to histopathology (Fig. 3b.4). In particular, structures with a high phase-shift effect distinctly coincide with the ductal wall and basement membrane (compare with Figs. 3b and 2b.1, b.2), which are distinguishable from the light grey areas with low phase-shift effect corresponding to the intraductal carcinoma (see Figs. 3b, b.4 and 2b.1, b.2) and extend throughout the slices of the CT data set (Supplementary Movies 1 and 2). These structures cannot be differentiated in the corresponding absorption-based CT slices (Supplementary Movies 3 and 4).

In quantitative analysis, the difference observed between invasive carcinoma and DCIS and the surrounding ductuli was low for absorption-based images (63±26 vs. 70±26 HU for invasive carcinoma/DCIS vs. surrounding ductuli, respectively) with low CNR (0.27). Conversely, PC-CT provided significantly different phase-effect values between invasive carcinoma and DCIS and the surrounding ductuli (47±1.7 vs. 72.5±3.6 PHU for invasive carcinoma/DCIS vs. surrounding ductuli, respectively) with high CNR (9.6).

Absorption and PC-CT images corresponding to the histological section depicted in Fig. 2c are shown in Fig. 3c.4 and c.5, respectively. Again, fibrous parenchyma, invasive carcinoma, ductal wall and intraductal carcinoma are of similar absorption densities (Fig. 3c.4) while phase-shift effects differentiate internal structures (Fig. 3c.5). Specifically, the round-shaped invasive ductal tumour with disordered inner sections is visualised. Adjacent to the tumour, several small ring-shaped structures with high phase-contrast effect can be detected, corresponding to the ductal wall surrounding the DCIS. These annular structures contain portions with high phase-shift effects, consistent with the intraductal carcinoma, which can be three-dimensionally visualised (see Supplementary Movies 1 and 2 and Movies 3 and 4 for phase-contrast and absorption-based CT data sets respectively).

Breast tissue without pathological findings

Histological analysis of non-cancerous tissue is shown in Fig. 4. This section is characterised predominantly by

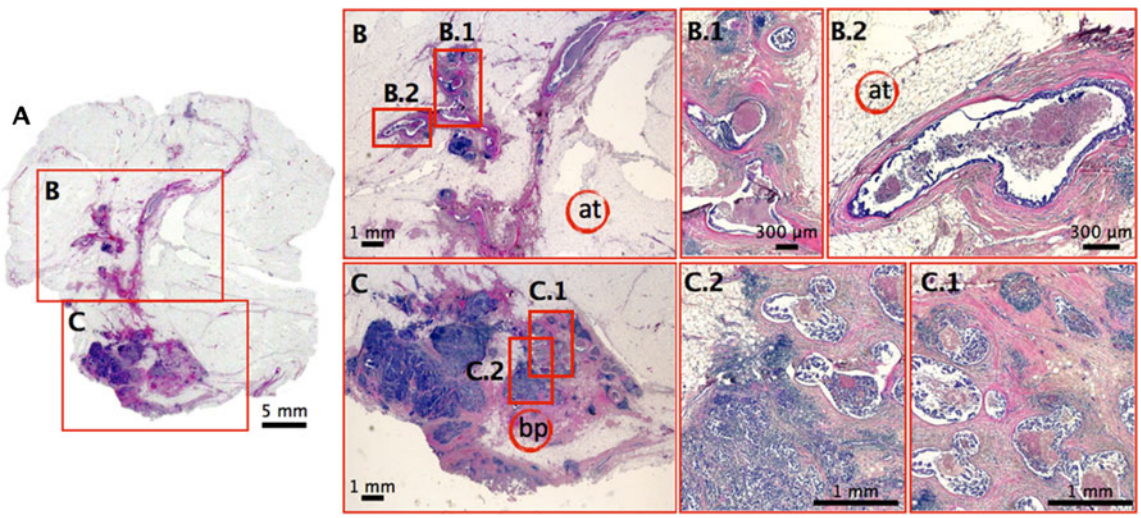

Fig. 2 Histology (H&E staining) of invasive ductal carcinoma and ductal carcinoma in situ. **a** Histological section (×10) showing an invasive ductal carcinoma (*bottom left*) and intraductal carcinoma (*centre*). **b** Close-up view (×20) of the intraductal carcinoma. **c** Close-up view (×20) of the invasive carcinoma (*left*), as well as intraductal carcinoma (*right*). **b.1**, **b.2** Magnification (×100 and ×400) of individual ducts from **b** (*pink*) containing the DCIS (*violet*). **c.1** Magnified section (×100) of **c** showing the DCIS. **c.2** Magnified section (×100) of **c** showing invasive (*bottom left*) and intraductal (*top right*) components. *bp* breast parenchyma, *at* adipose tissue

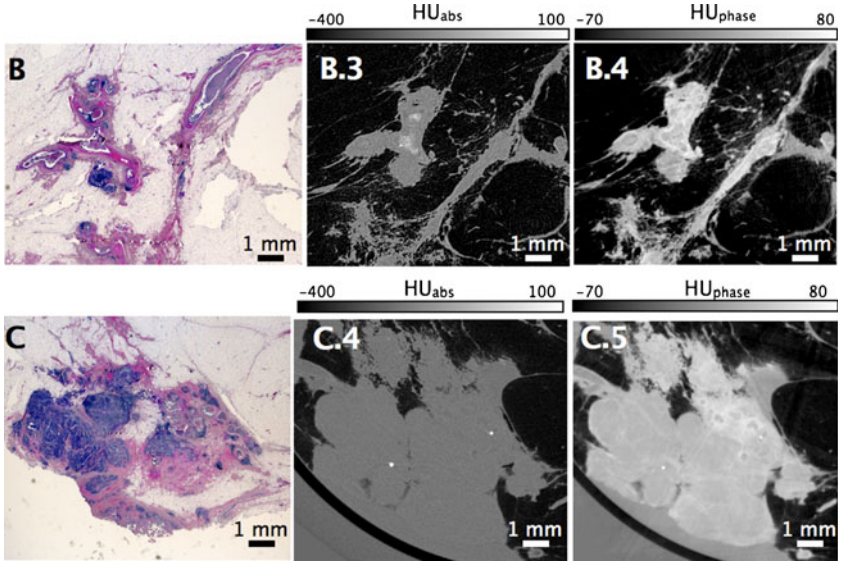

Fig. 3 Comparison of absorption CT and grating-based PC-CT. **b** Histological section as shown in Fig. 2b. **b.3** Absorption CT image corresponding to the histological section shown in **b**. **b.4** Grating-based PC-CT image corresponding to the histological section shown in **b**. **c** Histological section as shown in Fig. 2c. **c.4** Absorption CT image corresponding to the histological section shown in **c**. **c.5** Grating-based PC-CT image corresponding to the histological section shown in **c**

adipose tissue and tumour-free fibrous parenchyma (Fig. 4b), containing some normal ducts (Fig. 4b.1, b.2, b.3). Figure 5 shows the corresponding absorption (b.4) and grating-based PC-CT images (b.5) of the healthy reference section of Fig. 4b. Adipose tissue (low attenuation, low phase shift) can be differentiated from normal breast parenchyma (high attenuation, high phase shift) on both absorption- and grating-based PC-CT images. Consistent with the histopathology, PC-CT does not reveal any further abnormalities (see also Supplementary Movies 5, 6, 7 and 8).

Discussion

Soft-tissue contrast on conventional absorption-based X-ray imaging is intrinsically low and a key limiting factor in mammography and CT of the breast. Phase-contrast X-ray imaging has recently been shown to significantly outperform absorption-based imaging in this respect and has been successfully applied to breast tissue [8–15, 20]. In this study, we aimed to explore the potential of grating-based PC-CT for imaging of a breast sample affected by both a ductal carcinoma in situ and an invasive ductal carcinoma.

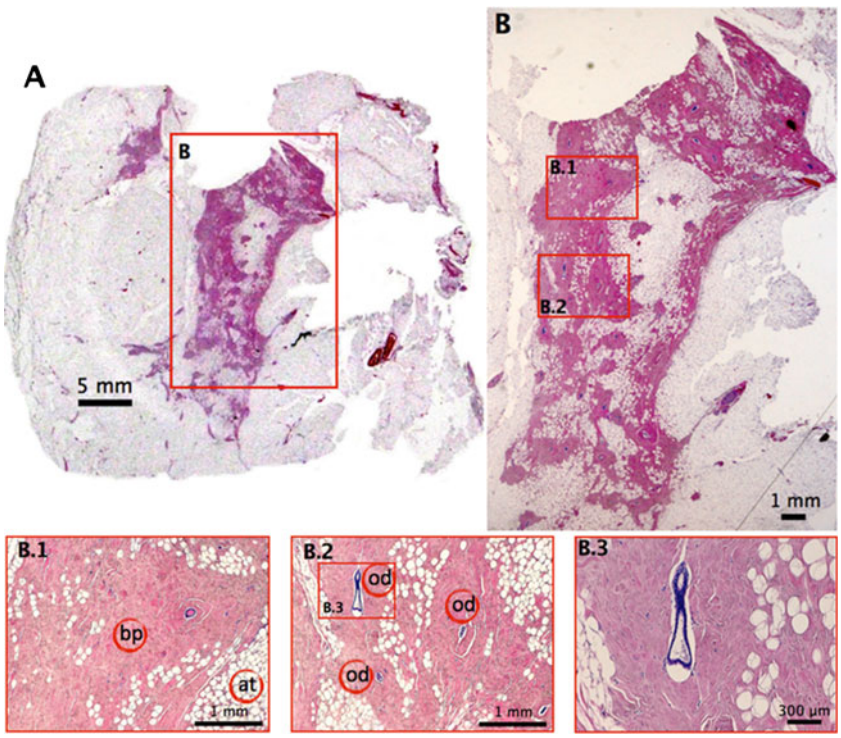

Fig. 4 Histology (H&E staining) of unaffected breast tissue. **a** Section (×10) containing adipose tissue (*grey*) and tumour-free parenchyma (*pink*). **b** Close-up view (×20) of **a**, showing the breast parenchyma. **b.1**, **b.2** Normal ducts (×100), characterised by an epithelial layer (*violet*) and without dilatation. **b.3** Magnified view (×400) of **b.2**. *ap* adipose tissue, *bp* breast parenchyma, *od* normal ducts

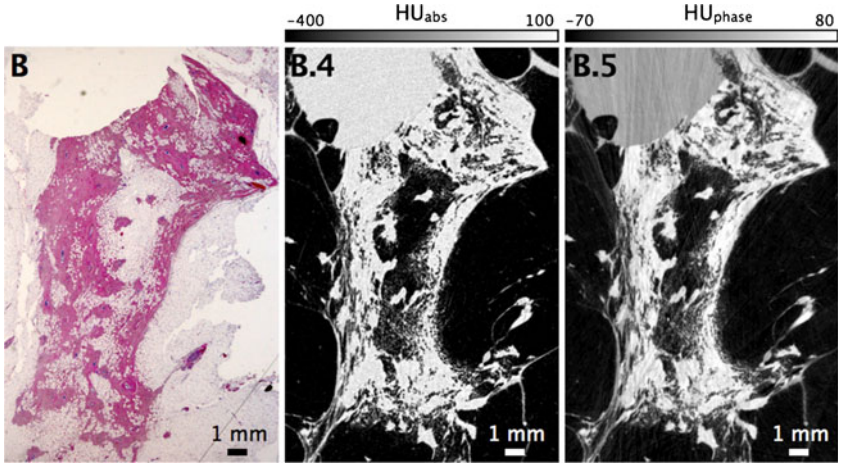

Fig. 5 Comparison of absorption- and grating-based phase-contrast CT of unaffected breast tissue. **b** Histological section as shown in Fig. 4b. **b.4** Absorption CT image corresponding to the histological section shown in **b**. **b.5** Grating-based PC-CT image corresponding to the histological section shown in **b**

Grating-based PC-CT imaging yielded insight into the fine structure of the tissue that was not resolved by absorption-based imaging, including circular structures of high contrast that clearly corresponded to the walls of the dilated ductuli, which are a characteristic feature of a DCIS. This was confirmed by quantitative analysis, which included measurement of differences in HU and PHU as well as CNR. Unaffected ductuli, on the other hand, did not result in a strong PC-CT signal. This suggests that grating-based PC-CT may be able to provide a 3D representation of a DCIS and to differentiate between invasive and intraductal carcinoma. Grating-based PC-CT therefore may be able to provide insight into the integrity of the basement membrane and the delineation of extensive intraductal tumour components before surgery, thus improving accurate breast cancer diagnosis and treatment planning.

In this experimental technical development, we also show that grating-based PC-CT allows a quantitative description of signal strength in the form of phase-contrast Hounsfield units. Confirming visual inspection, ductal components enclosing the DCIS yielded high HUs, significantly different from the much lower values measured for the DCIS inside the affected ducts, or within the invasive carcinoma. The CNR of cancerous tissue and the ductal walls improved from 0.27 measured on the absorption-based images to 9.6 obtained by phase-contrast imaging. We suspect that the high contrast differences in the areas of the DCIS may result from strong phase-shifting effects at the interface between the ductal walls and the tumour cell masses they enclose. These phase effects do not appear to occur at unaffected ductal walls, possibly because they do not enclose cellular (cancerous) material and are typically not dilated.

The early detection of breast cancer remains a great challenge in radiology [21]. Ideally, in order to significantly reduce breast cancer mortality, a cancer should be detected at the stage of a carcinoma in situ. Despite the high sensitivity of magnetic resonance imaging (MRI) of the breast, non-invasive procedures are not sufficient for the reliable diagnosis of a DCIS and biopsies are performed [22, 23]. The grating-based PC-CT images presented in this study clearly picture the walls of the dilated ductuli, which are pathognomonic for a DCIS on histology. Because of this, and its full 3D capability, grating-based PC-CT might be advantageous as a new and complementary diagnostic tool, sparing patients invasive procedures. In this context it is interesting to note that dedicated breast CT is now possible at a reasonable radiation dose [24]. As of now these breast CT set-ups depend on absorption-based imaging only, but it appears feasible to implement grating-based PC-CT technology into the system.

The results described here were carried out using highly brilliant synchrotron radiation and thus demonstrate the best results achievable by PC-CT. In order to be transferred to clinical application, the grating-based phase-contrast set-up must be implemented on conventional tube X-ray sources. This has recently been accomplished and, encouragingly, images recorded on such systems are characterised by good soft-tissue contrast differences, albeit at lower spatial resolution than the images reported here [25]. The images shown in the present study were recorded with an effective pixel size of 30 μm, whereas a typical laboratory set-up today can reach a resolution of about 100–150 μm. However, for absorption-based CT imaging of the breast, this resolution has been shown to yield adequate resolution [24]. Because of the high resolution and use of an experimental set-up not optimised for minimum radiation exposure, the radiation dose applied to our sample was significantly above the maximum acceptable clinical dose. However, it has been shown that a grating-based phase-contrast set-up using a tube X-ray source can be optimised for radiation exposure [10]. It is important to note that our findings were carried out in a highly experimental context and the investigation was designed as proof-of-concept study. The development towards a clinical technique will require substantial resources and at this point it remains unclear what can be expected in

in vivo studies. Future studies in a laboratory set-up and on a higher number of samples are planned in order to confirm the results provided here at lower spatial resolution and reduced radiation doses. Also, future research will need significantly higher sample size in order to evaluate the distribution of findings and may include different phase-contrast imaging approaches, such as free propagation, diffraction-enhanced and interferometry-based imaging.

In conclusion, this ex vivo study demonstrates the potential of grating-based phase-contrast imaging on a human breast sample of an invasive ductal carcinoma and ductal carcinoma in situ (DCIS) and indicates that the technology may eventually be able to provide in vivo 3D representation of the outline of a DCIS.

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