Propagation-based X-ray phase-contrast tomography of mastectomy samples using synchrotron radiation

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Purpose: Propagation-based phase-contrast computed tomography (PB-CT) is a method for three-dimensional X-ray imaging that utilizes refraction, as well as absorption, of X-rays in the tissues to increase the signal-to-noise ratio (SNR) in the resultant images, in comparison with equivalent conventional absorption-only X-ray tomography (CT). Importantly, the higher SNR is achieved without sacrificing spatial resolution or increasing the radiation dose

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delivered to the imaged tissues. The present work has been carried out in the context of the current development of a breast CT imaging facility at the Australian Synchrotron.

Methods: Seven unfixed complete mastectomy samples with and without breast cancer lesions have been imaged using absorption-only CT and PB-CT techniques under controlled experimental conditions. The radiation doses delivered to the mastectomy samples during the scans were comparable to those approved for mammographic screening. Physical characteristics of the reconstructed images, such as spatial resolution and SNR, have been measured and compared with the results of the radiological quality assessment of the complete absorption CT and PB-CT image stacks.

Results: Despite the presence of some image artefacts, the PB-CT images have outperformed comparable absorption CT images collected at the same radiation dose, in terms of both the measured objective image characteristics and the radiological image scores. The outcomes of these experiments are shown to be consistent with predictions of the theory of PB-CT imaging and previous reported experimental studies of this imaging modality.

Conclusions: The results presented in this paper demonstrate that PB-CT holds a high potential for improving on the quality and diagnostic value of images obtained using existing medical X-ray technologies, such as mammography and digital breast tomosynthesis (DBT). If implemented at suitable synchrotron imaging facilities, PB-CT can be used to complement existing imaging modalities, leading to more accurate breast cancer diagnosis.

1. INTRODUCTION

Breast cancer is the leading cause of cancer fatalities for women [1]. Despite some recent controversy about the efficacy of the procedure, regular mammographic screening is recommended by health authorities in most developed countries as an optimal strategy for detecting the first signs of breast cancer, since early detection is crucial for successful treatment of this common type of cancer, before it spreads to vital organs [2]. Even though considerable progress in the development of alternative methods for breast imaging (ultrasound, magnetic resonance imaging (MRI), terahertz radiation, photoacoustic tomography and others) has been achieved in recent years, X-ray mammography remains the mainstream method for mass breast screening. Notwithstanding a considerable improvement in the performance of X-ray mammographic systems in recent years, the technique still demonstrates relatively high rates of both false negatives and false positive diagnoses. According to the National Cancer Institute, mammography misses about 20% of cancers [2],

indicating that the potential for better performance of X-ray mammography is still high. There remains a considerable incentive for the development of improved mammographic techniques which would lead to a reduction in false positives and false negatives diagnoses, deliver reduced X-ray dose to the patient and, preferably, would also reduce or remove physical discomfort experienced by many patients during conventional breast screening procedures [3-11].

Among the newer techniques, digital breast tomosynthesis (DBT) has become the leading approach to 3D mammography. Publications (including recent studies performed by members of our team) confirm that X-ray DBT is capable of an improvement in the sensitivity and specificity of breast cancer diagnosis compared to conventional 2D mammography [12,13]. Sensitivity and specificity still remain, however, below optimal levels. It is well-accepted that computed tomography (CT) is generally superior to DBT in terms of the fidelity of 3D reconstruction, but radiation dose with CT is a major issue. If the dose could be kept at a level comparable with that in the present-day clinical 2D two-view mammography or DBT, while ensuring sufficient spatial resolution and signal-to-noise ratio (SNR), mammographic CT could outperform all other X-ray imaging techniques. In this context, phase-contrast X-ray CT, which utilises refraction as well as absorption, of X-rays in tissue, shows particular promise due to its superior sensitivity to soft-tissue tumours. This enables better-quality images to be obtained at lower radiation doses compared to conventional absorption-based CT [6,7,9,14,15,16].

Up to 76% of women experience pain or discomfort during a mammographic procedure with moderate levels of pain persisting for up to four days post-examination [17]. A recent Cochrane review demonstrated that current interventions had not effectively reduced pain and that further innovations are still required [18]. Since CT imaging does not rely on the uniformity of breast tissue thickness, strong compression is not required with that technique [19]. The reduction in physical discomfort associated with the procedure, combined with the reduced radiation dose in phase-contrast CT, has the potential to increase the participation rate of women in regular breast screening. This would most likely deliver improvements in early cancer detection leading to more successful treatment and, ultimately, decrease the mortality and morbidity associated with breast cancer.

In recent years, several different modalities of phase-contrast CT have been studied in conjunction with breast imaging. The main modalities are the propagation-based (also known as in-line) CT (PB-CT) [20], edge illumination CT [21], grating-based CT [22] and analyser-based CT [8,23]. Among these techniques, only PB-CT does not require any specialized X-

ray optical elements in order to render the phase-contrast visible. As a consequence, this technique is the easiest to implement in principle, although it requires a highly spatially coherent X-ray illumination to work effectively [24,25]. Therefore, PB-CT is typically implemented either with highly-parallel X-ray beams at synchrotron facilities or with microfocus laboratory X-ray sources that produce quasi-spherical incident X-ray waves. The microfocus X-ray source technology is currently at a stage where it still cannot deliver X-ray illumination of sufficient spatial coherence with a brightness (X-ray flux) that would enable CT scans of a full human breast within a clinically acceptable time. Recent work on the development of PB-CT technology for breast cancer imaging of live human patients has been concentrated at synchrotron facilities [26], especially at Elettra synchrotron in Trieste, Italy [27] and at the Australian Synchrotron in Melbourne [20,28]. In the present paper, we describe some of the latest results obtained in the process of development of breast PB-CT imaging facility at the Imaging and Medical Beamline (IMBL) of the Australian Synchrotron [29,30].

2. MATERIALS AND METHODS

2.A. Experimental setup

The experiments described in the present paper have been carried out at the Imaging and Medical beamline (IMBL) of the Australian Synchrotron (Clayton, Victoria, Australia). This beamline is based on a super-conducting wiggler and provides a wide monochromatic and nearly parallel X-ray beam with an area of up to 500 mm × 40 mm (h×v) at a distance of 140 m from the source, at 30 keV energy [29]. A bent double-crystal monochromator is used in the double-Laue configuration to deliver an X-ray beam in an energy range between 20 keV and 120 keV (we have used the X-ray energy of 32 keV in this study) with an energy resolution of $\Delta E/E = 10^{-3}$. The X-ray detector used for the present study was a Hamamatsu CMOS Flat Panel Sensor C9252DK-14, utilized in partial scan mode, with pixel size 100 μm × 100 μm, 2432 × 100 pixels (horizontal × vertical) field of view, 12-bit output and typical resolution of 4.5 lp/mm (at CTF=5%).

For the CT scans, the mastectomy samples were placed in a thin-walled plastic container, with the nipple area of the breast located near the top. The cylindrical container

with the sample inside was then positioned on a rotation stage for CT scans which consisted of 1800 projections each, collected over 180 degrees with the angular step of 0.1 degree. Such an angular step is slightly finer (providing some degree of angular over-sampling) than that corresponding to the optimal Nyquist sampling condition for a CT scan with the 2432 detector pixels in each image row [31].

The PB-CT scans analysed in this paper were collected at two different sample-to-detector distances. The "short" distance of 0.2 m (or 0.7 m in some cases - see details below) represented the minimum practically achievable distance between the sample and the detector, while the "long" distance of approximately 6 m represented the maximum achievable distance. The images collected at the "short" propagation distance were intended to approximate the conventional absorption-only CT, while the scans at the "long" distance allowed us to maximize the gain in reconstructed image quality due to in-line phase-contrast effects (see details in Section 3.A below).

The radiation dose delivered to the sample was monitored during each scan with the help of an ionization chamber, with the subsequent calculations of the mean absorbed dose (MAD) taking into account the size of the sample and using the method described in [15,28,32]. The images described in the present paper were selected from the scans collected at two different dose levels: one approximately equal to 4.5 mGy MAD, which is referred to as "std" dose below, and another one close to 2.3 mGy MAD, referred to as "low" dose, for a complete CT scan (see details in Table 1).

The final implementation of the setup for breast PB-CT imaging at IMBL will include an evacuated pipe between the irradiated breast and the X-ray detector, but such a pipe was not installed during the experiments described in the present paper. As a result, the images collected at the sample-to-detector distance of 6 m were negatively affected by X-ray absorption in air, which resulted in a reduction factor of approximately 0.8 (at 32 keV) in the X-ray flux reaching the detector. For example, the X-ray dose of 4.5 mGy used in a PB-CT scan with 6 m propagation distance was equivalent, in terms of the photon statistics in the detector plane, to a dose of $4.5 \times 0.8 = 3.6$ mGy in a similar scan performed at 0.2 m propagation distance, while the dose of 2.4 mGy at 6 m was equivalent to $2.4 \times 0.8 = 1.9$ mGy at 0.2 m. In this sense, "std" doses used in our experiment for the scans at the "long" and "short" propagation distances were approximately equivalent, while the "low" dose used with the scans at the "long" distance was effectively approximately 1.7 times lower than the "std" dose at the "short" distances ($3.3 \text{ mGy} / 1.9 \text{ mGy} \cong 1.7$, see Table 1).

The standard measure of radiation exposure in breast imaging is mean glandular dose (MGD), however its accurate evaluation requires the knowledge of breast glandularity. In this work we measured the air kerma directly and calculated the mean absorbed dose (MAD) following the approach used previously in [15,28,32] and elsewhere, which assumes 50% mixture of glandular and adipose tissue in the breast sample. Both MAD and MGD are proportional to air kerma, but the two could differ by as much as 25% in certain cases. For the purpose of the present study, the exact value of the radiation dose delivered to the sample was not critical, as the reference and the test images in each comparison pair were collected at the same effective air kerma, and hence with the same MGD, as well as MAD. This allows us to objectively estimate the advantage in the image quality achieved in PB-CT imaging, compared to absorption CT images collected at the same absorbed dose.

2.B. Breast tissue samples

Seven complete unfixed mastectomy samples have been used in this study. The main relevant characteristics of the samples and the key X-ray scan parameters are summarized in Table 1.

2.C. CT reconstruction

Each collected CT scan effectively comprised 1800 "full-height" projections, as well as 200 "dark-current" images (X-rays off) and 200 "flat-field" images (X-rays on, no sample in the beam). Half of the flat-field and dark-current images were collected immediately before the sample scan, with the other half collected immediately after the sample scan, in order to compensate for the possible temporal variation of the incident beam intensity. Each "full-height" projection was assembled by "stitching" partial projections which had a height of 10 mm and overlap of 2 mm at each common horizontal edge. For example, in order to obtain a single CT scan of a sample with a height of 60 mm, seven or eight sub-scans with a vertical size of 10 mm had to be collected and subsequently stitched. A sample projection from a single sub-scan and a corresponding flat-field and dark-current corrected full-height stitched projection are shown in Fig. 1.

The full-height projections, corrected for flat and dark fields, were then used as input to the Homogeneous Transport-of-Intensity equation (TIE-Hom) "phase" retrieval method

(also known as Paganin's method) [33,34]. The mathematical procedure corresponding to this method represents an image convolution operation:

$$I_{ret}(x, y) = \int P_{\sigma}(x - x', y - y') I_R(x', y') dx' dy' , \quad (1)$$

where $I_R(x, y)$ is the intensity distribution of a projection collected at the sample-to-detector distance R , which is a function of Cartesian coordinates (x, y) in the object plane (in a corresponding discrete representation of an image, this intensity is a function of pixel indices (i, j)), $I_{ret}(x, y)$ is the TIE-Hom retrieved image intensity distribution, as a function of Cartesian coordinates in the object plane, and $P_{\sigma}(x, y)$ is the TIE-Hom point-spread function (PSF). The latter PSF is equal to

$$P_{\sigma}(x, y) = (2\pi\sigma^2)^{-1} K_0[\sigma^{-1}(x^2 + y^2)^{1/2}] , \quad (2)$$

where K_0 is the zero-order modified Bessel function of the second kind. This PSF represents a low-pass filter, because $K_0(0) = +\infty$, it decreases exponentially, $K_0(z) \sim [\pi / (2z)]^{1/2} \exp(-z)$, when $z \rightarrow +\infty$, and $\sigma = \frac{1}{2}(\gamma\lambda R / \pi)^{1/2}$ represents the standard deviation of the PSF (the integral of this PSF is equal to 1, as expected) [35]. It is also well known that the Fourier transform of this PSF is equal to $\hat{P}_{\sigma}(u, v) = 1 / [1 + \pi\lambda\gamma z(u^2 + v^2)]$ [33, 35]. It can be seen that the width of this PSF is proportional to the square root of the product of the sample-to-detector distance R , the X-ray wavelength λ and the ratio $\gamma = \delta(\mathbf{r}) / \beta(\mathbf{r})$ of the real to imaginary part of the sample's complex refractive index $n(\mathbf{r}) = 1 - \delta(\mathbf{r}) + i\beta(\mathbf{r})$, where $\mathbf{r} = (x, y, z)$ denotes a position inside the sample [35]. Even though in the original theory of TIE-Hom reconstruction [33], the value of γ was assumed to be the same at any point inside the sample, the method described by equations (1)-(2) can in principle be applied to any image, always resulting in an increase of signal-to-noise ratio (SNR), simply because this method represents a low-pass filtering operation. However, if γ varies across the sample, as is generally the case for breast tissues, the application of the TIE-Hom method with $\gamma = \text{constant}$ (as in the present study) to a propagated image may result in incomplete compensation of phase-contrast effects in some areas and excessive blurring in other areas.

As these effects have been studied and explained in detail elsewhere [28,36], we will not discuss them further here.

It has been shown [35] that the application of the TIE-Hom retrieval method, in the form described by eqs.(1)-(2), to CT projections collected at a sample-to-detector distance R , followed by conventional filtered back-projection (FBP) CT reconstruction, leads to a gain in SNR in the reconstructed CT slices, compared to the SNR in the corresponding CT slices reconstructed without phase retrieval from contact ($R = 0$) projections collected at the same X-ray dose. The gain coefficient is approximately equal to

$$G \equiv \frac{SNR_{ret}}{SNR_{contact}} \approx 0.28 A \left(\frac{T_R}{\ln A - 1} \right)^{1/2}, \quad (3)$$

where $A \equiv (\pi/4)\gamma\lambda R/h^2$, h is the detector pixel size and T_R is the transmittance of X-rays in the gap between the sample and detector [35]. Equation (3) is valid under the following assumptions: 1) the modulation transfer function of the detector is equal to one (i.e. there are no correlation of noise in raw projections), 2) the dimensionless parameter A is much greater than one, 3) nearest neighbor interpolation is used in the FBP algorithm, and 4) ramp filter is used in the CT reconstruction from phase-contrast projections, while Hann filter is used in the reconstruction from contact projections. It can be easily verified that, under the conditions employed in the present experiments, i.e. with $\gamma = 550$ representing the relative ratio $(\delta_g - \delta_b)/(\beta_g - \beta_b)$ of glandular breast tissue (g) and blood (b) at the X-ray energy of 32 keV, $\lambda = 0.039$ nm, $R = 6$ m and $h = 100$ μ m, one obtains $\sigma = 101.20$ μ m and $G \approx 2.17$. The estimated gain factor reduces if one takes into account the finite resolution of the detector and uses linear interpolation in the FBP algorithm. Other experimental imperfections can also affect these estimates. In the end, we have not observed a gain factor larger than 1.76 in our experimental images (see Table 2). However, some of the "technical" detrimental experimental factors can be removed or reduced in a future implementation of PB-CT breast imaging, leading to larger values of the gain factor. For example, if an X-ray detector with a pixel size of 50 μ m is utilized, it would push the gain factor to $G = 6.06$ under the same experimental conditions as considered above, increasing further to $G = 6.80$ with the installation of an evacuated pipe between the sample and the detector. Equivalently, the last gain factor can be converted into the reduction of the X-ray dose by a factor of 46 at the same SNR as in the corresponding absorption-only CT images [35].

It is also important to keep in mind that considering SNR without a reference to the corresponding spatial resolution in the image is usually meaningless [37]. Indeed, it is often possible to apply a low-pass filter to an image and increase its SNR that way. Such filtering always leads, however, to a commensurate loss of spatial resolution unless *a priori* information about the sample can be utilized in the process. This trade-off between SNR and spatial resolution can be also employed in reverse. Image resolution can often be improved in post-processing by using, for example, a deconvolution operation, but it inevitably amplifies noise and lowers SNR. As a result, a more physically meaningful measure, termed "intrinsic imaging quality characteristics", is represented by a ratio of SNR to spatial resolution, normalized by the square root of the incident photon fluence (number of photons per unit area) F_{in} [37]:

$$Q = \frac{SNR}{h' F_{in}^{1/2}}, \quad (4)$$

where h' denotes the spatial resolution of the imaging system (which is equal to h in the "ideal" case of a detector with single-pixel PSF). The quantity Q is invariant with respect to linear image filtering, because SNR increases or decreases in exactly the same proportion as the spatial resolution h' [37]. No form of linear image filtering, including the one described by eq.(1), can increase Q .

The PB-CT method, which combines forward free-space propagation of the transmitted coherent X-ray wave from the sample to the detector with "phase" retrieval in accordance with eq.(1), does increase Q , in comparison with that for a contact CT obtained at the same incident fluence (and hence, the same X-ray dose). This increase of Q is only possible because the forward free-space propagation improves spatial resolution (effectively decreasing h') without increasing image noise (see detailed explanation in [38]). Understanding this point is very important in order to appreciate the difference between the PB-CT method employed in the present study and any form of image processing that can be utilized in conjunction with conventional absorption-based CT. While the latter cannot improve SNR in the reconstructed slices without sacrificing the spatial resolution or increasing the X-ray dose, PB-CT is capable of achieving this goal [38], as demonstrated earlier [14,15,16,28] and discussed further below.

2.D. Radiological assessment

Due to the geometry of our CT scans, the standard FBP-reconstructed CT slices corresponded to the so-called coronal sections (considering the breast attached to the patient's body, i.e. before the mastectomy operation). As it is more conventional for radiologists and pathologists to examine sagittal and axial breast tissue sections instead (which correspond to standard mammographic imaging planes), we re-sliced the reconstructed 3D volumes accordingly. When preparing both the sagittal and the axial slices for analysis, we merged them into 1 mm thick slices (corresponding to the DBT standard) using the Maximum Intensity Projection method, while preserving full original transverse resolution (100 μm pixels) within each slice.

The PB-CT ("test") slice stacks were compared with the contact ("reference") slices obtained from CT scans collected with the same sample and same scan conditions (described in the previous section), except for the sample-to-detector distance and the radiation dose. As explained above, the "std" doses were approximately equivalent for the "test" and "reference" scans, while the "low" dose, used only for some of the "test" slices, was about effectively 1.7 times lower compared to the "reference" scan. Nine medical imaging specialists and five practicing radiologists (specializing in breast imaging) were asked to look at 14 pairs of "test" and "reference" slice sets, each pair consisting either of "std" dose PB-CT images and "std" dose absorption CT images, or "low" dose PB-CT images and "std" dose absorption CT images. The assessors were asked to compare the pairs of stacks of images and fill in an assessment table according to the following written instructions: "After examining the quality of the stack of images ("Test" images) prepared in axial and sagittal planes, in comparison with the same stacks of "Reference" images, please, nominate a single overall comparative rating for each of the 7 image attributes by putting a cross mark (X) in exactly one cell in each of the attribute rows in the table above. The meaning of the rating scores is as follows: the fulfilment of the corresponding criteria in the test images is clearly better than (+2); slightly better than (+1); equal to (0); slightly worse than (-1); and clearly worse than (-2) the fulfilment of that criteria in the reference images. The intended meaning of image attributes is as follows. Overall quality: overall radiological quality of the image. Perceptible contrast: difference between low and high radiolucency in various soft tissue regions. Lesion sharpness: clarity of definition of lesions and spiculations. Normal tissue interfaces: clarity of visualisation of interfaces between fatty and fibroglandular tissues. Calcification visibility:

sharpness of micro-calcifications (if any). Image noise: presence of quantum mottle in the image. Artefacts: evidence of any other technical artefacts such as rings or distortions."

3. RESULTS

Figures 2a and 2b show an example of a slice of sample C1 obtained, respectively, from the "absorption-only" projections collected at $R = 0.2$ m and 3.3 mGy dose, and from PB-CT projections collected at $R = 6$ m at an approximately equivalent dose and reconstructed with the help of eqs.(1)-(2). An improvement of image quality can be observed in the PB-CT image compared to the absorption image. This was confirmed by both "subjective" radiological assessment (+1.75 and +1.33 average scores out of 2.0 maximum, assigned by medical imaging experts and radiologists, respectively, in favor of the PB-CT images), and "objective" measurements of SNR (5.38 vs 9.46, respectively) and spatial resolution (166 μ m vs 195 μ m, respectively). The "objective" measurements are described in detail in the next section.

The results of the radiological assessments, averaged separately across the nine imaging experts ("Experts score") and five radiologists ("Radiol. score"), are presented in the last two columns of Table 2. The order in which the image stack pairs were presented to the assessors was randomized. The correspondence between the sample (case) numbers together with the relevant radiation doses, and the successive image stack pairs, numbered from (Ref_1, Test_1) to (Ref_14, Test_14) according to the order in which these pairs were presented to the assessors, is shown in columns 1 and 2 of Table 2. The scores in the last two columns of Table 2 were obtained by comparing the "test" image against the corresponding "reference" image, as explained above.

We have also systematically measured the spatial resolution in two orthogonal directions ("xres" and "yres") of the reconstructed slices corresponding, respectively, to the horizontal and vertical axes of the reconstructed sagittal and axial slices. The SNR and the ratio of the SNR to the average spatial resolution (which corresponded to Q multiplied by the square root of the incident photon fluence) in every tenth sagittal and axial slice of the reconstructed slice stacks have also been measured. The results were then averaged over all analyzed slices (typically, ten per CT slice stack), both sagittal and axial, for a given slice stack. These results can be seen in columns 3-6 of Table 2, with column 7 containing the

pair-wise differences between the SNR-to-resolution ratios of the “test” (PB-CT) and “reference” (“absorption” CT) images.

Note also that the method for spatial resolution measurement that we applied in this study, as implemented in X-TRACT software [34] and described in detail in [15,36], takes into account the PSF of the detector, but not the X-ray source size. However, under the experimental conditions used in this work, the effect of the X-ray source on the spatial resolution was quite small due to the geometrical demagnification factor, which was approximately equal to 0.0014 for the scans at 0.2 m sample-to-detector distance and 0.041 for the scans at 6 m.

Figure 3 summarizes the results presented above. It depicts the overall relative image quality scores averaged across nine medical imaging experts and five radiologists, assigned to PB-CT “test” images in comparison with the corresponding “reference” absorption-only CT images, alongside with the differences of the SNR-to-spatial-resolution ratios for the same pairs of test and reference images.

4. DISCUSSION

It can be noticed in Table 2 that the “xres” and “yres” values in the “reference” images were consistently different, equaling to about 2 pixels and 1.4 pixels (i.e. 200 μm and 140 μm), respectively, in all reference images. It transpired that this difference was caused by the smoothing effect of the Hahn filter used in the FBP CT reconstruction, which affects only the “horizontal” plane of the original FBP-reconstructed slices [31]. The latter plane corresponds to the coronal plane in the standard medical imaging geometry, and hence affects only the “vertical” (“yres”) direction of the sagittal and axial slices. The Hahn filter was not used in the reconstruction of the “test” PB-CT images, because the TIE-Hom filter was applied there instead. The latter filter affects both the horizontal and vertical directions of the original CT projections in equal measure, as can be seen in eqs.(1)-(2), and as a result the “xres” and “yres” values in the resultant PB-CT slices were consistently similar, equaling to about 1.9 pixels (190 μm) in all cases.

Some clear trends can be observed also in Fig. 3.

(1) All PB-CT images obtained at the same radiation dose as in absorption-only images have received higher scores compared to absorption-only reference CT images. This indicates a

clear and consistent advantage achieved by utilizing X-ray phase contrast in the PB-CT method.

(2) All PB-CT images, collected at a lower radiation dose, have received lower scores compared to PB-CT images of the same sample collected at a higher radiation dose. Such behavior, of course, was naturally expected.

(3) The overall assessed quality of low-dose PB-CT images was on average similar to that of standard-dose absorption-based images (it was better for some samples and worse for the others) (Fig 4). We believe that by improving the implementation of PB-CT method and, in particular, using a better detector, as discussed above, it should be possible in the future to make this result more consistent across different samples.

(4) With some exceptions, the general trends were similar between the subjective image quality scores and the differences in SNR-to-spatial-resolution ratios, indicating a correlation between the objective image quality measure (Q) and the results of the subjective image assessment.

However, we also observed some "exceptions" to this trend. The most notable "exceptions" among the datapoints in Fig. 3 were represented by the difference between the average SNR/resolution values for the "test" and "reference" images (blue curve) at points number three and nine, i.e. for samples C2 "std" and C5 "std" (see also Table 2).

A close re-inspection of these particular sets of CT slices have revealed that the corresponding samples had relatively high glandularity and, as a result, they had relatively few "uniform" image areas of adipose tissue of the size sufficient for reliable, reproducible and representative measurement of SNR. As a consequence, the regions where the SNR measurements have been performed inevitably contained some larger-scale "non-uniformities" represented by inclusions of tumours and glandular tissues, as well as smaller-scale non-uniformities seemingly representing genuine variations in the local density of the fatty tissues. These tissue density variations could not be separated from the true image noise in the measurement of SNR used in this work, which led to artificially lower measured values of SNR in PB-CT slices, compared to the subjective appearance of the images, where the "test" images looked noticeably sharper than the "reference" images. For these reasons, in these two cases in particular, the corresponding relatively high scores given by the imaging specialists and radiologists disagreed with the relatively low values of measured image SNR (see Fig.(5)). In our future studies we plan to investigate this issue further and use other objective image quality metrics, such as, for example, local "visibility", represented by the difference between the intensity (grey level) of certain "features of interest" and the intensity

of the "background" within a selected region, divided by the sum of the two intensities. Other possible metrics could be utilized as well, such as the width of the local image histogram, the "universal image quality index" [39] and others.

5. CONCLUSIONS

We have presented the results of PB-CT X-ray phase-contrast imaging of seven full unfixed mastectomy samples performed at Imaging and Medical beamline of the Australian Synchrotron. We have compared the CT reconstructions of the same samples obtained in the conventional absorption-only ("contact") CT regime and in the PB-CT regime at the sample-to-detector distance of 6 m. The radiation dose delivered to the samples during the scans was comparable to that approved for routine mammography or breast tomosynthesis. We have shown that the image quality, as assessed by nine experienced medical imaging specialists and five practicing radiologists was, on average, higher in the PB-CT images compared to absorption-only CT images collected at an equivalent dose. We have argued that further improvement of the X-ray imaging hardware (primarily, the X-ray detector) used in this type of imaging, is expected to bring further substantial gains in the image quality in the PB-CT mode. The assessment results by the imaging experts and radiologists were found to be generally consistent with the objective measurements of SNR and spatial resolution in the reconstructed CT slices of mastectomy samples. These results constitute part of the systematic research that our collaborative team has been conducting with the goal of developing medical breast cancer imaging facilities at the Australian Synchrotron in Melbourne, Australia, and at Elettra Synchrotron in Trieste, Italy [11,15,25,27,40].

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CONFLICT OF INTEREST

The authors have no conflicts to disclose.

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Figure legends

Fig. 1. (a) An example of a single X-ray projection of mastectomy sample C4 collected at sample-to-detector distance of 6 m at "low" X-ray dose (2.4 mGy per complete CT scan), and, (b) the corresponding "stitched" full-height projection corrected for dark current and flat field, and for defective pixels.

Fig. 2. Sagittal slice of sample C1 reconstructed from: (a) contact projections, and (b) projections collected at $R = 6$ m, both obtained in CT scans at "std" dose.

Fig. 3. Average imaging experts comparison score (green, triangles), average radiologists comparison score (red, squares) and difference between average SNR/resolution values for the "test" and "reference" images (blue, circles). The data points 1 to 14 here are in the same order as in Table 2.

Fig. 4. Axial slice of sample C3 reconstructed from: (a) contact projections at "std" dose, and (b) projections collected at $R = 6$ m at "low" dose. The PB-CT image in (b) was assessed as having higher quality, even though the radiation dose at which it was collected was lower. This sample did not contain any cancerous tumours.

593 Fig. 5. Axial slice of sample C5 reconstructed from: (a) contact projections, and (b)
594 projections collected at $R = 6$ m, both obtained in CT scans at "std" dose. A large tumour is
595 clearly visible in both images. The PB-CT image in (b) was assessed as having higher
596 quality, even though the measured SNR and spatial resolution were apparently better in
597 image (a) (see Table 2).

1 Table 1. Main characteristics of mastectomy samples and imaging parameters used in the present study.

Case No.	Prior treatment	Diagnosis	Weight and size (from pathology reports)	X-ray dose (mGy)
C1		A rare focus of atypical lobular hyperplasia. Fibrocystic changes with epithelial hyperplasia and benign / sclerosing adenosis. Benign fibroadenomata. No DCIS or invasive tumour.	Left breast mastectomy weighing 311g and measuring 160mm from lateral to medial, 120mm from superior to inferior and 25mm from anterior to posterior.	6.0m std = 4.5 6.0m low = 2.4 0.2m std = 3.3
C2		Fibrocystic changes with epithelial hyperplasia and benign / sclerosing adenosis. Benign fibroadenomata. No DCIS or invasive tumour.	Right breast skin and nipple sparing mastectomy, weighing 316g and measuring 160mm from medial to lateral, 160mm from superior to inferior, and up to 30mm from anterior to posterior.	6.0m std = 4.3 6.0m low = 2.4 0.2m std = 3.2
C3	Wide local excision +/- mammoplasty + sentinel node biopsy. Re-incision of medial margin.	A 2mm focus of high grade DCIS, margins clear. Changes consistent with previous surgery. An additional 3mm focus of high grade DCIS in the lateral half of the scarred area. There is no invasive tumour seen.	Right mastectomy specimen weighing 336g, measuring 150mm from medial to lateral, 115mm from superior to inferior, 50mm from anterior to posterior.	6.0m std = 4.4 6.0m low = 2.6 0.2m std = 3.1

C4	Breast core biopsy. Chemotherapy for breast Ca	Invasive carcinoma, NST, BRE Grade 3. Number of tumours - multifocal, multicentric. High grade ductal carcinoma in-situ. Intralymphatic/intravascular tumour present. The maximum dimension of tumour bed - more than 100mm. Invasive tumour dimension - multiple tumour foci 0.5mm to 15mm. Circumferential (radial) margins clear.	Right breast mastectomy specimen, weighing 446g, measuring 170mm from lateral to medial, 150mm from superior to inferior, 35mm from anterior to posterior.	6.0m std = 4.3 6.0m low =2.4 0.2m std = 3.2
C5		One invasive carcinoma, NST, BRE grade 3. In-situ tumour: not seen. Maximum tumour dimension: 35mm. Invasive tumour dimension: 35mm. Intralymphatic / intravascular tumour: present. Fibrocystic change; one benign intramammary node.	Right breast mastectomy specimen, weighing 318g, measuring 170mm medial to lateral, 140mm superior to inferior, 35mm anterior to posterior.	6.0m std = 4.3 6.0m low =2.3 0.7m std = 3.4
C6	Chemotherapy for breast Ca	No evidence of an in-situ or invasive malignancy.	Right breast skin and nipple sparing mastectomy weighing 565g, measuring 190mm medial to lateral, 160mm superior to inferior, 35mm anterior to posterior.	6.0m std = 4.5 6.0m low =2.3 0.7m std = 3.4

C7		Invasive carcinoma (NST), modified Bloom-Richardson-Elston grade 3, with a minor component of intermediate-grade DCIS, 30mm in maximum dimension, no lymphovascular invasion was seen, clear of excision margins.	Right breast mastectomy weighing 617g, measuring 200mm medial to lateral, 120mm superior to inferior, 40mm anterior to posterior.	6.0m std = 4.5 6.0m low = 2.3 0.7m std = 3.4
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Table 2. Measured spatial resolution, SNR and related image characteristics, alongside the comparison scores averaged across nine medical imaging specialists and five radiologists.

Sample, dose	Ref./test	xres (pix)	yres (pix)	SNR	SNR/res	$\Delta(\text{SNR/res})$	Gain	Experts score	Radiol. score
C1, std	Ref_1	1.93	1.38	5.38	3.30				
1	Test_1	1.96	1.95	9.46	4.84	1.54	1.76	1.75	1.33
C1, low	Ref_10	1.93	1.38	5.22	3.22				
2	Test_10	1.88	1.90	7.88	4.17	0.96	1.51	-1.00	-0.33
C2, std	Ref_3	1.98	1.40	6.07	3.66				
3	Test_3	1.97	2.00	8.12	4.14	0.48	1.34	1.75	1.17
C2, low	Ref_14	1.96	1.38	5.59	3.39				
4	Test_14	1.90	1.89	7.53	3.98	0.59	1.35	-0.25	-0.33
C3, std	Ref_12	1.92	1.39	5.42	3.33				
5	Test_12	1.87	1.95	9.40	4.92	1.59	1.74	1.50	1.00
C3, low	Ref_2	1.92	1.40	6.13	3.74				
6	Test_2	1.82	1.91	8.18	4.39	0.65	1.33	0.88	0.33
C4, std	Ref_7	1.92	1.42	6.13	3.71				
7	Test_7	1.86	2.00	8.49	4.42	0.71	1.38	1.50	1.33
C4, low	Ref_13	1.93	1.41	5.95	3.62				
8	Test_13	1.82	1.92	6.67	3.58	-0.04	1.12	0.62	0.17
C5, std	Ref_9	1.99	1.42	8.97	5.35				
9	Test_9	1.97	2.00	8.49	4.25	-1.10	0.95	1.13	1.00
C5, low	Ref_4	2.01	1.44	8.49	4.98				
10	Test_4	1.96	1.94	7.65	3.91	-1.07	0.90	-0.50	-0.50
C6, std	Ref_5	1.98	1.40	10.01	6.01				
11	Test_5	1.98	2.01	12.83	6.47	0.46	1.28	1.00	0.50
C6, low	Ref_11	1.98	1.40	10.19	6.06				
12	Test_11	1.92	1.93	9.16	4.76	-1.31	0.90	-0.50	-0.33
C7, std	Ref_8	1.97	1.40	6.55	3.94				
13	Test_8	1.98	1.99	11.40	5.73	1.80	1.74	1.63	1.17
C7, low	Ref_6	1.99	1.40	6.66	3.96				
14	Test_6	1.91	1.93	9.16	4.80	0.84	1.38	0.38	0.17

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